AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

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

American College of Rheumatology
73rd Annual Scientific Meeting

Association of Rheumatology Health Professionals
44th Annual Scientific Meeting

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ACR/ARHP 2009 Annual Scientific Meeting Overall Needs Assessment

Submitted by Joel A. Block, MD, Chair & Brian F. Mandell, MD, PhD, Immediate Past-Chair on behalf of the Annual Meeting Planning Committee.

Rheumatologists need in-depth knowledge of the most recent developments in rheumatology to ensure the highest standards of patient care and safety. They rely heavily on the ACR/ARHP Annual Scientific Meeting to meet this need.

The ACR/ARHP has created a forum for physicians and health professionals to receive the most relevant and timely information at the annual meeting. In addition to the presentation of the latest peer selected clinical and scientific abstracts, invited speakers will provide clinical, practice and quality focused, education delivery, and basic scientific information in various formats including, didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions.

Sessions and topics are chosen for presentation at the annual meeting by the AMPC, a diverse group of individuals with representation from full-time clinical practice, academic, and institutional environments, as well as the international rheumatology community. The selection of the annual program proceeds after a systematic review of feedback provided by the ACR membership and past meeting attendees. Feedback on content needs is solicited annually after the Annual Scientific Meeting. Attendance at individual sessions is recorded, and the content areas of highly attended sessions are offered again the next year. The charge of the AMPC is to produce a meeting that communicates the latest important science, evidence-based clinical recommendations, and experience derived management strategies in the rheumatic diseases.

Clinician representation on the AMPC expressed a need for more discussion of practical management issues, in a forum that could accommodate a larger proportion of the attendees. Several innovations have been added in the last two years to meet those needs. These include the Curbside Consults – Ask the Professors session, and additional Medical Aspects lectures. This year, a series of Clinical Management sessions, such as a Thieves' Market, Radiology Pearls and management of difficult issues, will be added.

Workforce assessment indicates that pediatric expertise is not universally available. Therefore, a specific pediatric rheumatology curriculum is integrated into the annual meeting to provide pediatric updates to adult rheumatologists, in addition to providing a high-level educational program to pediatric rheumatologists.

As new practice guidelines are developed, formal presentations are provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation; similarly, as new technology relevant to musculoskeletal diseases is adopted clinically, such as ultrasound, workshops and talks are provided to facilitate their utilization in attendees' clinical practices. Training program directors are surveyed formally and informally regarding education gaps as they relate to curriculum development. Results of the in-training examination and other evaluations are, and will be increasingly utilized to support content development at the annual meeting. For instance, assessment of competence and skill in synovial fluid analysis of trainees and staff has reinforced the need to offer workshops continuously on synovial fluid analysis at the annual meeting. Workshops are offered on skin score because it was recognized during the conduct of clinical trials in patients with scleroderma that clinicians were not uniformly measuring the progression of the disease, and obtaining a skin score at the time of examination provides a standardized measure for recording progression or response to treatment. Focus groups have been added to our toolbox of approaches to assess the educational needs of our attendees.

The basic science of rheumatology is a rapidly advancing field, and is covered extensively in the schedule. Basic Science Symposia, State-of-the-Art Lectures, a series of Immunology Updates for the Clinicians, and a Basic Science pre-meeting course are offered. The science curriculum is developed by a sub-committee of the AMPC consisting of U.S. and internationally prominent basic scientists.

We will continue to expand our efforts to poll the membership regarding their needs and desires, as well as vigilantly continue to review quality and pay-for-performance initiatives to guarantee that the needs of the rheumatology community and of our patients are consistently met.

About ACR/ARHP Education

ACR/ARHP Program Objectives

The American College of Rheumatology and the Association of Rheumatology Health Professionals, a division of the ACR, are organizations of physicians, health professionals and scientists serving members through programs, including education and research. Through these programs, the ACR and the ARHP foster excellence in the care of people with rheumatic and musculoskeletal diseases.

The 2009 ACR/ARHP Annual Scientific Meeting programs have been independently planned by the ACR Committee on Education, the ACR Annual Meeting Planning Committee, the ARHP Program Committee, the ARHP Advanced Practice Skills Training Course Task Force and the ARHP Clinical Focus Course Task Force.

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

Program Objectives

At the conclusion of the 2009 ACR/ARHP Annual Scientific Meeting, participants should be able to:

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

CME Credit and Certificates of Participation

Physicians

The American College of Rheumatology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. The following activities have been approved for 52.75 *AMA PRA Category 1 Credit(s)™*: the Basic Research Conference, the Clinical Research Conference, the Review Course, the ACR/ABIM MOC Learning Session For Recertification, the ARHP Clinical Focus Course, the ARHP Advanced Practice Skills Training Course, the ACR Scientific Sessions including the ACR Workshops and the ACR Meet the Professor Sessions. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Health Professionals

As a division of the College, the Association of Rheumatology Health Professionals offers a Certificate of Participation.

The ARHP designates the Clinical Focus Course, the ARHP Advanced Practice Skills Training Course, the ACR/ARHP Scientific Sessions, the ACR pre-conference courses, the ACR Meet the Professor and Workshop sessions for hours of participation.

International Physicians

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

Meeting Evaluations

Computers are available on-site for you to complete your CME/ Certificate of Participation application and meeting evaluation form online during the meeting. In addition, you can complete the evaluation and print your certificate after you return home. Paper CME application forms will not be available.

Conflict of Interest/Disclosure Statement

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

None: Nothing to disclose

1. Stock, stock options or bond holdings in a for-profit corporation or self-directed pension plan
2. Research grants
3. Employment (full or part-time)
4. Ownership or partnership
5. Consulting fees or other remuneration (payment)
6. Non-remunerative positions of influence such as officer, board member, trustee or public spokesperson
7. Receipt of royalties
8. Speakers' bureau
9. Other

Speakers, moderators and abstract authors submitted their disclosure online prior to publication. Disclosures for invited speakers are listed in the program book indices and online. These disclosures are listed by presenters' last name in numeric format according to the list above.

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

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ACR Poster Session A

Animal Models 1, Cytokines, T cells, Gene Targeting

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Antibodies against An HSP Epitope Suppress Autoimmune Arthritis by Modulation of Cytokine Regulation. Y. Naparstek, G. Katzavian, R. Meyuhas, A. Hershko, E. Moallem and R. Ulmansky, Hadassah University Hospital, Jerusalem, Israel

Purpose: We have previously shown that resistance to Adjuvant Arthritis (AA) is due to the presence of anti-heat shock protein (HSP) antibodies, directed at peptide 6, a 16 amino-acid surface epitope.

Method: In this work we have studied the effect of antibodies against peptide 6 on various models of autoimmune arthritis and the mechanism of their anti-inflammatory effect.

Results: Active vaccination with peptide 6 as well as passive vaccination with monoclonal anti-peptide 6 murine and chimeric monoclonal antibodies suppressed significantly murine adjuvant and collagen arthritis. Incubation of murine and human mononuclear cells with the protective antibodies induced the secretion of IL-10. The antibodies bound to a surface molecule on human cell membrane and induced upregulation of IL-10 mRNA, via a cAMP associated pathway. The level of anti peptide 6 antibodies in the serum of patients with rheumatoid arthritis was significantly lower than in healthy controls. We have recently developed a humanized anti-peptide 6 antibody devoid of immunogenic epitopes. This antibody has similar immunomodulatory effects as those of the murine and chimeric antibodies.

Conclusion: We conclude that HSP contains protective B-cell epitopes exposed on its surface, and that natural and acquired resistance to autoimmune arthritis is associated with the ability to develop an antibody response to these epitopes. These antibodies cross react with a macrophage surface receptor and modulate cytokine production. Lower levels of anti peptide 6 antibodies in patients with RA suggest that they play a role in protection against human autoimmune diseases as well. The monoclonal humanized anti-peptide 6 antibody, as well as active vaccination with peptide 6, may serve as new therapeutic tools for suppression of human arthritis by skewing the immune system selectively towards an anti-inflammatory response.

Disclosure: Y. Naparstek, ProtAb Ltd., 6 ; **G. Katzavian**, None; **R. Meyuhas**, ProtAb Ltd., 3 ; **A. Hershko**, None; **E. Moallem**, None; **R. Ulmansky**, None.

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A Therapeutic Vaccine Arrests Disease Progression in the Collagen Type II (Bovine) Murine Model for Rheumatoid Arthritis by Altering Cytokine Environment. Daniel Zimmerman[1], Eyal Talor[2], Patricia Taylor[3], Sean O'Neill[4], Alison Bendele[5] and Kenneth Rosenthal[6], [1]CEL SCI Corporation, Vienna, VA, [2]CEL, Vienna, VA, [3]Northeastern Ohio colleges of Medicine, Rootstown, [4]Washington Biotech, Columbia, MD, [5]BolderBiopath, Bolder, CO, [6]Northeastern Ohio colleges of Medicine, Rootstown, OH

Purpose: The collagen type II (bovine) (CIA) induced arthritis murine model is often used to evaluate treatments for rheumatoid arthritis (RA). Following initial induction, the disease progresses into a more classical cell and cytokine mediated pathogenesis. We will use this model to evaluate a new therapeutic vaccine for RA

Method: Male (7-8 week old) DBA/1J mice with CIA induced arthritis were either untreated or treated with the CEL-2000 L.E.A.P.S. experimental therapeutic vaccine or etanercept (Enbrel). CEL-2000 vaccine consists of 2 peptides of human origin, a segment of the beta 2 microglobulin molecule referred to as peptide J and a peptide (254-273) from human collagen Type II. Disease was induced by 2 immunizations of bovine type II collagen on day 0 (in CFA) and day 21 (in ICFA). The mice were scored daily for an Arthritic Index (AI) score. Therapy was initiated when the mice (n=8) had a group mean AI score of 3.5 +/- 0.1 and range of 1-6. CEL-2000 vaccine 33 or 100 nmole was administered on day 0 and 7 of therapy and etanercept 3 mg/kG was administered every other day for the 28 days unless otherwise noted. Mice were evaluated at least 3 times a week for **A**) footpad swelling and **B)** AI score. At the termination of the study, tissue sections were evaluated for **C**) histopathological parameters including 1) inflammation, as evidenced by accumulation of eosinophils, basophils, neutrophils and macrophages, 2) cartilage destruction 3) bone resorption, and 4) pannus membrane formation in the synovial

space. **D)** Sera, collected at the start of therapy and 10 days later, were evaluated for levels of 22 cytokines / chemokines, as measured by the RayBiotech protein array.

Results: By all four parameters there was a statistically significant ($p \leq 0.05$ or better depending on the day of therapy and parameter being considered) benefit of the CEL-2000 vaccine therapy and to a lesser extent for etanercept therapy. CEL-2000 caused an increase in IL-12p70 and IL10 and reduction in disease associated serum levels of TNF-a, IL-17, IL-6, MCP-1 and IL-12p40. A number of cytokine changes were also seen with Enbrel although to a lesser degree

Conclusion: CEL-2000 vaccine administered as a therapy arrested the progression of RA disease and its efficacy was demonstrated by reduction in disease parameters (AI) and in the reduction of serum levels of pro-inflammatory cytokines.

Disclosure: D. Zimmerman, CeL SCI, 9 ; **E. Talor**, CEl sCI Corporation, 9 ; **P. Taylor**, None; **S. O'Neill**, None; **A. Bendele**, None; **K. Rosenthal**, None.

3

Administration of IL-18BP by Gene Therapy Reduces Inflammation in Rat AIA. Hubert Marotte[1], Jeffrey H. Ruth[1], Salahuddin Ahmed[2], Mohammad A. Amin[1], Phillip L. Campbell[1], Jean Dudler[3] and Alisa E. Koch[4], [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Toledo, Toledo, OH, [3]Service de Rhumatologie, Médecine Physique et Rééducation, Epalinges, Switzerland, [4]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Interleukin-18 (IL-18) is a proinflammatory cytokine that is of pivotal importance for the induction of production of T helper (Th)1 cells. Enhanced production of IL-18 has been linked to the pathogenesis of diseases such as rheumatoid arthritis (RA). The natural inhibitor of IL-18 is the IL-18 binding protein (IL-18BP), which appears to be a promising novel therapeutic strategy for RA. This study examined expression of rat IL-18 and IL-18BP at various time points in the rat adjuvant-induced arthritis (AIA) model. Then, the benefit of ankle intra-articular injection of adenovirus (Ad) producing murine (m) IL-18BP-IgG1 (which cross-reacts with rat IL-18) was explored in the rat AIA model, in which arthritis is maximal at days 14-18 post-adjuvant injection.

Methods: After induction of rat AIA, 3 rats were sacrificed at various time points (Day 0, 7, 11, 14, 18, 25, and 45). Ankle joints were homogenized and used for mRNA isolation. Rat IL-18 and IL-18BP expression at the mRNA level was assessed using qRT-PCR. In a preventative study, rats were divided into an AdmIL-18BP-IgG1 group (n=8) and an Ad green fluorescent protein (AdGFP) group (n=7). On day 8 after AIA induction, 1×10^8 plaque-forming units of the adenovirus (AdmIL-18BP-IgG1 or AdGFP) were injected into each ankle in a 10 µL volume. Clinical parameters (body weight, circumference, volume of both ankles, and articular score) were assessed on days 0, 2, 4, 7, 9, 11, 14, 16, 17, and 18 after adjuvant injection.

Results: IL-18 and IL-18BP were both expressed in joints during development of rat AIA. We found a time-dependent increase of both IL-18 and IL-18BP. Furthermore, we observed a decrease in the [IL-18BP/IL-18] expression (roughly 40%) from day 7 to day 45. Administration of AdmIL-18BP-IgG1 decreased articular index scores at days 15 and 17 compared to AdGFP therapy (mean ± SEM; 2.9 ± 0.3 vs. 3.7 ± 0.2; $p < 0.05$ at day 15 and 3.1 ± 0.3 vs. 3.9 ± 0.1; $p < 0.05$, respectively); and paw volume at day 18 (2.1 ml ± 0.1 vs. 2.6 ml ± 0.1; $p < 0.05$). We found a decrease in the change in ankle circumference (minus day 0) values at day 18 compared to day 0 in the AdmIL-18BP-IgG1 group versus the AdGFP group (19.4 mm ± 2.3 vs. 25.2 mm ± 1.8; $p < 0.05$).

Conclusion: In rat AIA, we observed a decrease in the [IL-18BP/IL-18] expression before and during arthritis development. Preventatively, AdmIL-18BP-IgG1 restored IL-18BP expression and reduced joint inflammation in rat AIA, suggesting a potential benefit of similar therapy in RA.

Disclosure: H. Marotte, None; **J. H. Ruth**, None; **S. Ahmed**, None; **M. A. Amin**, None; **P. L. Campbell**, None; **J. Dudler**, None; **A. E. Koch**, None.

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Active Immunization Against IL-23 p19 Improves Collagen-Induced-Arthritis. Emilie Duvallet[1], Rojo Ratsimandresey[2], Eric Assier[1], Laure Delavallée[1], N. Bessis[1], Jean-François Zagury[2] and Marie-Christophe Boissier[3], [1]EA 4222 Paris 13 University, Bobigny, France, [2]Paris, France, [3]AP-HP, Avicenne hospital, Bobigny, France

Purpose: IL-23 is a pro-inflammatory cytokine known to be essential for the differentiation of the Th17 lymphocytes, a subtype of T lymphocytes implied in autoimmunity. Its subunit, IL-23 p19, is specific of this cytokine. We had previously demonstrated for IL-1beta and TNF-alpha, that active immunization against these cytokines could be protective in animal models of arthritis. The aim of this study was to evaluate the effect of two vaccines targeting the IL-23 p19 subunit, IL23-K1 and IL23-K2, on collagen-induced-arthritis (CIA).

Method: Using bioinformatics, we defined two peptides in IL-23 p19. Each peptide was coupled with keyhole limpet hemocyanin (KLH). Anti-murine IL-23 immunization was performed by injecting intra-muscularly IL23-K1 or IL23-K2 formulated in incomplete Freund adjuvant (IFA), four times (D0, 7, 28, 49) in DBA/1 mice. Control groups received KLH or PBS at the same dates. CIA was induced by two subcutaneous injections of bovine type II collagen, the first at Day 40 in Complete Freund Adjuvant, the second at Day 61 in IFA. Anti-IL-23 and anti-KLH antibody levels were assessed by ELISA. Pro and anti-inflammatory cytokines were quantified by qRT-PCR on the spleen and the synovium.

Results: The clinical scores show that mice treated with either IL23-K1 or IL23-K2 develop less arthritis than the negative controls ($p<0.05$). Mice vaccinated by IL23-K1 produced more anti-IL23 antibodies than the one vaccinated by KLH ($p<0.001$). mRNA quantification showed that the IL23-K1 vaccination led to an increase of IL-10 in the spleen ($p<0.05$ vs KLH), without any effect on IL-17 level. Histology examination showed that IL23-K1 permitted a strong decrease of the joint destruction and inflammation ($p<0.01$ vs KLH and $p<0.001$ vs PBS).

Conclusion: These data show that targeting IL-23 p19 using a vaccination strategy may be efficient in CIA.

Disclosure: E. Duvallet, None; **R. Ratsimandresey**, None; **E. Assier**, None; **L. Delavallée**, None; **N. Bessis**, None; **J. F. Zagury**, None; **M. C. Boissier**, None.

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IL-17 Upregulates Neutrophil Chemokines in Macrophages and RA Synovial Tissue Fibroblasts as Well as in Experimental Arthritis. Shiva Shahrara, Sarah R. Pickens, Chiang-Ching Huang and Richard M. Pope, Northwestern University Feinberg School of Medicine, Chicago, IL

Introduction: Previous studies have shown that IL-17 plays an important role in experimental arthritis, yet the mechanism by which it may contribute to the pathogenesis of rheumatoid arthritis (RA) is undefined.

Purpose: These studies were performed to identify downstream targets of IL-17 in cells present in RA synovium, namely macrophages and RA synovial tissue (ST) fibroblasts, as well as in an IL-17 experimental arthritis model.

Methods: RA ST fibroblast from 6 patients were treated with IL-17 (50 ng/ml) for 5h or left untreated. Thereafter, cells were harvested and microarray was performed using Illumina BeadArrays. The data were normalized by a quantile normalization procedure, the chip to chip variation was adjusted by the ComBat algorithm and IL-17 differentially expressed genes were identified by Student's t test. The biological function was then identified employing the PANTHER gene ontology analysis. Genes identified by microarray were confirmed by real-time RT-PCR. Macrophages In vitro differentiated from normal monocytes were also examined for IL-17-induced target genes that were identified in RA fibroblasts. Next, we examined whether local expression of IL-17 in the ankle joints modulated the expression of IL-17 downstream target genes identified in RA fibroblasts and macrophages using ELISA. Finally, ankles harvested from adenovirally expressed IL-17 (Ad-IL-17) or the control group (Ad-CMV) were stained with GR1.

Results: Employing microarray, we found that genes upregulated by IL-17 in RA ST fibroblasts included neutrophil chemokines which consisted of CXCL1, 2, 5 and 8 as well as leukemia inhibitory factor (LIF). Expression of CXCL1, 2 and 5 was confirmed in IL-17 activated RA fibroblasts employing real-time RT-PCR. Results from these studies demonstrated that while CXCL2 was activated as early as 2h ($p<0.05$), CXCL1 and 5 were significantly upregulated within 6-8h ($p<0.05$). Interestingly, RA ST fibroblasts activated with IL-17 and TNF-a demonstrated significantly greater levels ($p<0.01$) of CXCL1, 2 and 5, compared to cells activated with IL-17 or TNF-a alone. CXCL1 and CXCL5 were also upregulated ($p<0.05$) following IL-17 stimulation employing in vitro differentiated macrophages starting at 4 to 6h, respectively. Examination of murine ankles injected with Ad-IL-17 demonstrated increased levels of CXCL1 and CXCL5 on days 4 and 10 post injection, compared to the Ad-CMV control group. In contrast CXCL2 was not different between the two groups. Consistently, anti-GR1 staining was 5 to 10 fold higher in the Ad-IL-17 group on days 4 and 10, respectively, compared to that of controls.

Conclusion: Collectively, our results obtained from control macrophages and RA ST fibroblasts, as well as the data generated from IL-17 experimental arthritis model, suggest that IL-17 can induce the expression of neutrophil chemokines and thereby modulate migration of neutrophils into the arthritic joint. IL-17 and its activated downstream factors may be a therapeutic target in patients with RA.

Disclosure: S. Shahrara, None; **S. R. Pickens**, None; **C. C. Huang**, None; **R. M. Pope**, None.

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IL-18 Receptor Null Mice Are Resistant to K/BxN Serum Transfer Arthritis Due in Part to Impaired Angiogenesis. Mohammad Amin[1], Jeffrey H. Ruth[1], Yong Hou[1], Phillip L. Campbell[1], Amrita Seehra[1] and Alisa E. Koch[2], [1]University of Michigan, Ann Arbor, MI, [2]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Interleukin-18 (IL-18) is a pleiotropic cytokine which plays a key role in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis (RA). We have previously shown that IL-18 is a novel mediator of angiogenesis, a process essential for the development of the RA synovial tissue pannus and consequent ingress of inflammatory leukocytes. This study investigated the mechanisms of decreased arthritis and angiogenesis in IL-18 receptor null mice.

Methods: We performed the K/BxN serum transfer arthritis model in IL-18 receptor null and wild type (wt) mice to determine the role of the IL-18 receptor in arthritis and angiogenesis. In this model, mice develop arthritis starting from day 2-3, and arthritis lasts for 2-3 weeks. We scored front paws and measured ankle circumference. We measured hemoglobin (Hb%), which correlates with vascularity, in arthritic ankle homogenates. We performed immunohistochemistry using rabbit anti-human von Willebrand factor (vWF) to examine blood vessels in mouse joint sections. We used Matrigel plug angiogenesis assays with IL-18 receptor null and wt mice. We performed enzyme linked immunosorbent assays (ELISAs) using ankle homogenates of arthritic mice for cytokine determination.

Results: IL-18 receptor null mice were resistant to K/BxN arthritis, showing a significant decrease in articular index and ankle circumference compared to wt mice ($p<0.05$). Mouse ankles were harvested on day 7 and homogenized to determine Hb%. We found >4 fold significant decrease in Hb% levels in IL-18 receptor null mouse ankle homogenates compared to wt mouse ankle homogenates ($p<0.05$). There was a significant ~2 fold decrease in blood vessels in IL-18 receptor null mouse joint sections compared to wt mice, as determined by vWF, an endothelial cell marker. In the Matrigel plug angiogenesis assay, acidic fibroblast growth factor induced singnificantly more angiogenesis in wt than IL-18 receptor null mice. To determine the mechanism of impaired angiogenesis and defective arthritis in IL-18 receptor null mice, we performed ELISAs for angiogenic mouse basic fibroblast growth factor (bFGF) and KC/CXCL1, a functional homologue of human IL-8, using mouse ankle homogenates. We found more than a 3 fold significant decrease in bFGF and 5 fold significant decrease in KC/CXCL1 in IL-18 receptor null mouse ankle homogenates compared to wt mouse homogenates, suggesting that the IL-18 receptor is critical in the production of potent angiogenic factors, such as bFGF and KC/CXCL1. This also suggests that the IL-18 receptor plays an important role in both angiogenesis as well as in arthritis development.

Conclusion: These studies suggest that IL-18 receptor null mice have impaired angiogenesis and arthritis in part due to decreased bFGF and KC/CXCL1. These results provide strong evidence that the IL-18 receptor plays an essential role in angiogenesis and arthritis in rodent models of RA, and suggest a novel therapeutic avenue for RA.

Disclosure: M. Amin, None; **J. H. Ruth**, None; **Y. Hou**, None; **P. L. Campbell**, None; **A. Seehra**, None; **A. E. Koch**, None.

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Blockade of the IL-7 Receptor Inhibits Collagen-Induced Arthritis and Is Associated with Reduction of T-Cell Activity and Proinflammatory Mediators. Sarita A.Y. Hartgring[1], Cynthia R. Willis[2], Dina Alcorn[2], Laurel J. Nelson[2], Johannes W. J. Bijlsma[1], Floris P.J.G. Lafeber[1] and Joel A.G. van Roon[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Amgen Inc., Seattle, WA

Purpose: High levels of IL-7 are found in several arthritic conditions including rheumatoid arthritis (RA). IL-7 induces T cell-dependent activation of monocytes, B cells, and osteoclasts. IL-7 activity is critically dependent on signaling through the IL-7receptor α (IL-7Rα). Increased intraarticular IL-7Rα expression is present in the synovium of RA patients, and this receptor is expressed on highly proliferating synovial T cells but not on regulatory FoxP3+ T cells. Inhibition of IL-7/IL-7Rα signaling *in vitro* decreased IL-7-induced Th1 activity of

mononuclear cells from RA patients. Our purpose was to evaluate the effects of prophylactic and therapeutic IL-7Rα blockade in the collagen-induced arthritis (CIA) model. Additionally, we assessed the mechanisms by which IL-7Rα blockade regulates CIA.

Method: CIA was initiated by immunizing male DBA/1 mice with chicken type II collagen. Mice were treated with 100mg anti-IL-7Rα (on day 21, 24, 27, and 30). Clinical arthritis was determined by visual examination of swelling and redness of the paws. Radiographs of the ankles were taken on day 33, and joint destruction was scored. Cellularity of thymus and spleen and numbers of T-cell subsets, B cells, macrophages, and dendritic cells were assessed. T-cell cytokines, indicative of Th1, Th2, and Th17 activity and several proinflammatory mediators were assessed by multi-analyte profiling in paw protein lysates. In addition, T-cell associated cytokines were measured by intracellular cytokine staining and by ELISA in supernatants of collagen-restimulated lymph node cell cultures.

Results: Anti-IL-7Rα treatment significantly reduced arthritis severity, associated with reduced radiological joint damage (both $p<0.05$). Both thymic and splenic cellularity were reduced by 30% upon IL-7Ra treatment. IL-7Rα blockade reduced splenic numbers of total, naïve, and memory CD4 and CD8 T cells (all $p<0.05$). Significant reductions in T-cell associated cytokines (IFNγ, IL-5, and IL-17) were measured. In addition, IL-7Rα blockade significantly decreased (at least $p<0.05$) local levels of proinflammatory cytokines, chemokines, acute phase reactants, and factors associated with tissue destruction (incl. TNFα, IL-1β, CRP, RANKL). IL-7Rα blockade did not affect numbers of B cells, macrophages, DC subsets, or B-cell activity (indicated by serum anti-collagen IgG antibodies).

Conclusion: Blockade of the IL-7Rα potently inhibited joint inflammation and destruction, associated with reductions of T-cell numbers, T-cell cytokines and numerous mediators that induce inflammation and tissue destruction. This study demonstrates an important role of IL-7R-driven immunity in experimental arthritis and indicates the therapeutic potential of IL-7Rα blockade in human arthritic conditions.

Disclosure: S. A. Y. Hartgring, None; **C. R. Willis**, Amgen Inc., 3, Amgen Inc., 1 ; **D. Alcorn**, Amgen Inc., 3, Amgen Inc., 1 ; **L. J. Nelson**, Amgen Inc., 3, Amgen Inc., 1 ; **J. W. J. Bijlsma**, None; **F. P. J. G. Lafeber**, None; **J. A. G. van Roon**, None.

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In Vitro and In Vivo Properties of MEDI-571, a Human Anti IL-17A Antibody in Development for the Treatment of Patients with Rheumatoid Arthritis. Caroline Langham[1], Caroline Russell[2], Wendy Barker[1], Mark Abbott[1], Sarah Almond[1], Elizabeth Kelly[1], Sarah Dawson[1], Maurice Needham[1], Ian Anderson[2], Fraser Welsh[2] and Matthew A. Sleeman[2], [1]Astrazeneca, Loughboruough, United Kingdom, [2]MedImmune LLC, Cambridge, United Kingdom

Purpose: IL-17A has been proposed as a key cytokine involved in the pathogenesis of a number of inflammatory diseases such as rheumatoid arthritis (RA). Recently clinical trials have been initiated with antibodies to this cytokine to investigate the IL-17 axis in RA. Using a panel of *in vitro* assays and *in vivo* models of IL-17A activity we describe the activity of a novel anti-human IL-17A IgG1 (MEDI571) for the treatment of RA.

Method: The ability of MEDI571 to neutralise IL-17A activity was assessed in multiple *in-vitro* assays. HT1080 cells, RA synovial fibroblasts and chondrocytes were stimulated with IL-17A alone or in combination with TNFa and the levels of IL-6 and/or IL-8 quantified by ELISA. The *in vivo* activity of MEDI571 was investigated using a rodent airpouch model (Willoughby et al., 1986). A dose range of MEDI571 was delivered i.p. 24hrs prior to direct challenge of the airpouch with 0.3mg of IL-17A. Total white cell influx and IL-6 levels within the pouch were calculated. The role of native IL-17A in arthritis was investigated in a rat SCW induced arthritis model using an anti-mouse IL-17A antibody (MAB421).

Results: IL-17A dose dependently induced IL-6 and IL-8 production from HT-1080 cells and OA chondrocytes, and IL-8 from RA synovial fibroblasts. MEDI-571 inhibited the production of IL-6 by IL-17A induced HT1080 cells with an IC50 of 830pM. The IC50s of MEDI571 in the human chondrocyte assay were 1.44 and 1.3nM for IL-6 and IL-8 respectively. MEDI571 inhibited IL-17A and IL-17A/TNF synergised IL-8 induction from RA synovial fibroblasts with IC50s of 2.85 and 4.97 nM respectively. *In vivo* systemic administration of MEDI571 (i.p.) prior to the administration of human IL-17A (0.3 μg) directly to the airpouch completely inhibited the white blood cell and IL-6 responses with IC50s of 0.68 mg/kg and < 0.1mg/kg respectively. To strengthen rationale we also evaluated an anti mouse IL-17 antibody in a rat SCW arthritis model. In this system blocking IL-17A had a protective effect against arthritis at 1mg/kg as determined by ankle width and radiographic score.

Conclusion: Pre-clinical research has shown that IL-17A plays a significant role in RA. Our data supports this observation, demonstrating that IL-17A is instrumental in the induction of key mediators such as IL-6 and IL-8 from synovial fibroblasts and chondrocytes. In all cases,

MEDI-571 was able to inhibit these activities. Furthermore, in vivo we demonstrated that MEDI-571 could inhibit IL-17A induced inflammation. Moreover IL-17 blockade in the SCW arthritis model could protect against joint damage. These observations support the hypothesis that in RA, inhibiting the IL-17A network within key compartments of the inflamed joint may suppress proinflammatory cytokines and inflammatory cell trafficking, thus potentially provide clinical benefit.

Disclosure: C. Langham, AstraZeneca, 3 ; **C. Russell**, MedImmune LLC, 3 ; **W. Barker**, AstraZeneca, 3 ; **M. Abbott**, AstraZeneca, 3 ; **S. Almond**, AstraZeneca, 3 ; **E. Kelly**, AstraZeneca, 3 ; **S. Dawson**, AstraZeneca, 3 ; **M. Needham**, AstraZeneca, 3 ; **I. Anderson**, MedImmune LLC, 3 ; **F. Welsh**, MedImmune LLC, 3 ; **M. A. Sleeman**, MedImmune LLC, 3 .

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ASC Deleted Mice Are Resistant to Collagen-Induced Arthritis. Hideshi Yamazaki[1], Michiko Takeoka[1], Takashi Ehara[2], Naoki Itano[1], Hiroyuki Kato[3] and Shun'ichiro Taniguchi[1], [1]Shinshu University Graduate School of Medicine, Matsumoto, Japan, [2]Shinshu Unversity School of Medicine, Matsumoto, Japan, [3]Shinshu University School of Medicine, Matsumoto, Japan

Purpose: Although the major pro-inflammatory cytokines tumor necrosis factor α (TNFα), IL-1β, and IL-6 are all considered to be key mediators in joint inflammation and cartilage and bone destruction in rheumatoid arthritis (RA), increased attention is also being given to the involvement of IL-18 in RA pathogenesis. IL-18 and IL-1β are generated via cleavage of their pro-forms in the presence of the apoptosis-associated speck-like protein containing a caspase recruit domain (ASC), a known adapter protein that activates upstream procaspase-1. As such, we investigated the involvement of ASC in the development and progression of autoimmune arthritis.

Method: In experiment 1, collagen-induced arthritis (CIA) was developed in highly susceptible DBA/1J mice and alterations in the expression of ASC, pro-inflammatory cytokines, and proteins were evaluated by immunohistochemistry and Western blot analysis. In experiment 2, CIA was developed in ASC-deleted ($ASC^{-/-}$) mice and wild-type ($ASC^{+/+}$: C57BL/6J) mice following four back-crosses to the DBA/1J background. Histological findings and expression of pro-inflammatory cytokines in knee joints were then compared between the two groups, and disease severity in joint sections was graded using a scoring system.

Results: Experiment 1 revealed that ASC, caspase-1, IL-1β, and IL-18 were expressed in the joints of CIA mice, whereas no such expression was observed in controls. In experiment 2, histological analysis and disease scores revealed significant suppression of joint destruction in the CIA-$ASC^{-/-}$ mice (n=5) compared with CIA-$ASC^{+/+}$ mice (n=6). Expression of IL-1β and IL-18 was also suppressed in the joints of CIA-$ASC^{-/-}$ mice compared with wild-type mice.

Conclusion: This study showed increased expression of ASC, caspase-1, IL-1β, and IL-18 in CIA mice and suppressed histological scores associated with diminished levels of IL-1β and IL-18 in the joints of CIA-$ASC^{-/-}$ mice. These data suggest that ASC signaling pathways that include caspase-1 activation might be involved in the exacerbation of RA. However, the expression of IL-1βand IL-18 witnessed in CIA-$ASC^{-/-}$ mice indicates that pathways other than ASC may be involved as well.

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Overexpression of T-Bet in T Cells Attenuates the Development of Collagen Induced Arthritis. Yuya Kondo, Isao Matsumoto, Yao Zhaojin, Makoto Sugihara, Taichi Hayashi, Daisuke Goto, Satoshi Ito, Satoru Takahashi and Takayuki Sumida, University of Tsukuba, Tsukuba, Japan

Purpose: CD4+ T cells play an important role in the generation of rheumatoid arthritis, however it is unclear whether Th-1 or Th-17 cells are the pathogenic mediator of arthritis. To clarify the influence of overexpression of Th-1 specific master regulator T-bet on the pathogenesis of collagen induced arthritis (CIA).

Method: 1) Arthritis was induced with chicken type II collagen (CII) emulsified with complete Freud's adjuvant (CFA) in C57BL/6 mice (B6) and T-bet transgenic (T-bet Tg) mice under CD2 promoter, the incidence and severity of arthritis was assessed. 2) Cells in draining lymph nodes harvested 10 days after immunization of CII were analyzed for the proportion and number of T cell subsets by flow cytometry. 3) After these cells were cultured *in vitro* with CII for 72 h, the expression of T-bet in CD4+ cells was analyzed by intracellular staining. 4)

Cytokine production by CD4+ T cells was analyzed by intracellular cytokine staining, and cytokine levels in supernatants were measured by enzyme-linked immunosorbent assay (ELISA). 5) CII specific IgG in sera collected 56 days after immunization was measured by ELISA.

Results: 1) The incidence and severity of arthritis was significantly suppressed in T-bet Tg mice. 2) The number of total T cells, CD4+ T cells and CD8+ T cells were decreased in the draining lymph nodes harvested from T-bet Tg mice compared with B6 mice. 3) The proportion of T-bet expression in CD4+ T cells was elevated. 4) Flow cytometry analyses in CD4+ T cells restimulated with CII in vitro revealed that the proportion of IFNγ+ cell was not increased in T-bet Tg mice. Furthermore, not only IL-17 level but also IFNγ level in supernatants were significantly reduced in T-bet Tg mice. 5) CII specific IgG production was suppressed in T bet Tg mice.

Conclusion: In T-bet Tg mice, overexpression of T-bet in T cells attenuates CIA. The mechanism might be due to decreased number of T cells and low immunity response to CII, not the predominant Th-1 differentiation.

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TGF-β-Induced CD4+Foxp3+ Cells but Not Natural CD4+CD25+ Cells Suppress Established Collagen-Induced Arthritis. Ning Kong[1], Xiao H. Zhou[2], Julie Wang[2], Huimin Fan[3], Zhongmin Liu[3], David Brand[4], Hejian Zou[5] and Song Guo Zheng[2], [1]University of Southern California, Los Angeles, CA ; Huashan Hospital, Fudan University, Shanghai, China, [2]University of Southern California, Los Angeles, CA, [3]East Hospital, Tongji University, Shanghai, China, [4]VA Medical Center, Memphis, Memphis, TN, [5]Huashan Hospital, Fudan University, Shanghai, China

Purpose: Diminished frequency and functional activity of $CD4^+CD25^+Foxp3^+$ regulatory T cells (nTregs) contribute to the development of rheumatoid arthritis (RA). Nonetheless, adoptive transfer of nTregs to established collagen-induced arthritis (CIA) failed to improve the manifestations of arthritis. Inability of nTregs in suppressing established CIA could be explained by the resistance of T effector to nTregs, abolishing effect of inflammatory cytokines on nTregs and the plasticity of nTregs in CIA. Our group recently reported that, unlike nTregs, TGF-β-induced $CD4^+CD25^+$ cells (iTregs) are more stable when stimulated with IL-6. This finding suggests that iTregs may be stable and functional following adoptive transfer of the established CIA.

Method: Naïve $CD4^+$ cells isolated from CII transgenic DBA/1 mice were stimulated with their cognate CII peptide and IL-2 with (iTregs) or without TGF-β(CD4con). nTregs were sorted from the thymus in similar mice. $5x10^6$ of these cells were i.v. injected into DBA/1J mice on the day 0 or day 28 after immunization with CII and CFA. The incidence and clinical severity of disease were measured. Arthritis severity was further evaluated by measuring specific anti-CII IgG subsets in serum and also by histological examination. To determine the fate of both nTregs and iTregs following adoptive transfer to established CIA, these cells were labeled with CFSE and intracellular IL-17, IFN-γ, IL-4 productions in donor and recipient cells were determined by flow cytometry.

Results: Adoptive transfer of iTregs and expanded nTregs but not CD4con cells to DBA/1 mice at day 0 when immunized with CII/CFA prevented the incidence and severity of arthritis. Interestingly, adoptive transfer of iTregs but not nTregs significantly ameliorated the manifestations of arthritis when these cells were adoptively transferred into DBA/1 mice at day 28 after immunization. Using CFSE-labeled donor cells, we were able to observe that relative to iTregs, nTregs were prone to apoptosis, and Th17 and Th2 conversion, and lost Foxp3 in draining lymph nodes at one week after transfer in CIA. Conversely, iTregs maintained Foxp3 expression and did not convert to T help cells in a similar inflammatory milieu. Numbers of Th17 cells in lymph nodes in CIA mice receiving nTregs were 10-fold greater than those seen in mice receiving iTregs. Conversely, the numbers of $CD4^+Foxp3^+$ cells and of $CD4^+IL\text{-}10^+$ cells in the lymph nodes were 8-fold less in mice receiving nTregs than in mice receiving iTregs.

Conclusion: iTregs, unlike nTregs, are stable and functional when adoptively transferred into established collagen-induced arthritis. They suppress Th17 cell differentiation and promote the development of $Foxp3^+$ regulatory T cells and $CD4^+IL\text{-}10^+$ cells. This study may provide a novel therapeutic approach for the treatment of Rheumatoid Arthritis.

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The Effect of Synthetic Retinoid, Am80, On T Helper Cell Development and Antibody Production in Murine Collagen-Induced Arthritis. Toshihiro Nanki, Aya Sato, Kaori Watanabe, Kayoko Kaneko, Yousuke Murakami, Miwako Ishido and Nobuyuki Miyasaka, Tokyo Medical and Dental University, Tokyo, Japan

Purpose: Retinoids are the compounds that bind to the retinoic acid binding site of retinoic acid receptors and have biological activities of vitamin A. Recent studies indicate that retinoids promote differentiation into Th2 cells and regulatory T cells (Treg), and suppress Th1 and Th17 cell differentiation in vitro. Previously it was reported that synthetic retinoid, Am80, ameliorated murine collagen-induced arthritis (CIA). In this study, we examined the effects of Am80 on CIA more precisely, and also on T helper (Th) phenotype development and antibody production in vivo.

Method: We induced CIA in DBA1/J mice by immunization with bovine type II collagen (CII) at days 1 and 22. Am80 was orally administrated once a day from day 1 for 5 weeks or from day 15 for 3 weeks. Effects of Am80 were evaluated by clinical arthritis score, paw thickness, histologically inflammatory changes, and bone destruction by radiograph. IFN-γ and IL-17 production by CII-stimulated splenic T cells and serum anti-CII Ab levels were analyzed by ELISA. Foxp3 expression in splenic CD4 T cells was examined by FACS.

Results: Treatment with Am80 from day 1 significantly lowered clinical arthritis score and paw thickness. Cellular infiltration in the ankle joint and bone destruction of MTP joint were also suppressed by the Am80 treatment. Moreover, Am80 decreased IL-17 and increased IFN-γ production by CII-stimulated splenic T cells of the CIA mice. Proportion of Foxp3+ CD4 T cells in the spleen was decreased by the treatment. It is thus indicated that Am80 inhibited Th17 and Treg, and enhanced Th1 differentiation in vivo. Serum anti-CII Ab levels were also decreased. In contrast, treatment with Am80 from day 15 did not alter clinical arthritis score. IL-17 and IFN-γ production by CII-stimulated splenic T cells was not also significantly changed by the treatment from day 15. However, proportion of Foxp3+ CD4 T cells in the spleen and serum anti-CII Ab levels were decreased.

Conclusion: Am80 has an inhibitory effect on CIA and might regulate both Th development and antibody production in vivo. Decreased Th17 by the treatment with Am80 might be responsible for the attenuation of arthritis.

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13

CTLA4-Ig Modifies Dendritic Cells From Mice with Collagen-Induced Arthritis to Increase the CD4+CD25+Foxp3+ Regulatory T Cell Population. Kyung-Su Park[1], Mi-La Cho[2], Chang-Hoon Lee[1], Ji-Min Kim[1], Ho-Sung Yoon[1], Kwi-Young Kang[1], Seung-Ki Kwok[1], Ji-Hyeon Ju[1], Hyeok-Jae Ko[3], Chong-Hyeon Yoon[4], Jun-Ki Min[5], Yeon-Sik Hong[6], Sang-Heon Lee[7], Sung-Hwan Park[8] and Ho-Youn Kim[1], [1]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Catholic Institute of Medical Sciences, The Catholic University of Korea, Seoul, South Korea, [3]Daejeon St. Mary's Hospital, Daejeon, South Korea, [4]Uijeongbu St. Mary's Hospital, Uijeongnbu, South Korea, [5]Holy Family Hospital, Bucheon, South Korea, [6]Incheon St. Mary's Hospital, Incheon, South Korea, [7]Konkuk University Hospital, Seoul, South Korea, [8]Kangnam St Mary's Hosp, Seoul, South Korea

Purpose: CTLA4-Ig is a therapeutic agent used in the treatment of rheumatoid arthritis. It binds to B7 molecule and induces dendritic cells (DCs) to express indoleamine 2,3-dioxygenase (IDO), which is known to be involved in the generation of $CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs). In this study, we investigated whether CTLA4-Ig increased $CD4^+CD25^+Foxp3^+$ Treg population in collagen-induced arthritis (CIA) mouse model.

Method: CTLA4-Ig or PBS was administered into CIA-induced mice and then arthritis index was measured and $CD4^+CD25^+Foxp3^+$ Treg and CD4+IL-17+T cell population were examined in the joint and the spleen. DCs and CD4+T cells from CIA mice were cultured with anti-CD3 in the presence of CTLA4-Ig or control-Ig and then $CD4^+CD25^+Foxp3^+$ Treg population were examined. Spleen DCs from CIA mice were pretreated with CTLA4-Ig and then adoptively transferred into CIA-induced mice. Arthritis index was measured and $CD4^+CD25^+Foxp3^+$ Treg and CD4+IL-17+T cell population were examined in the spleen of DC-transferred mice.

Results: CTLA4-Ig suppressed CIA and increased the $CD4^+CD25^+Foxp3^+$ Treg population, but decreased the $CD4^+IL\text{-}17^+$ T cell population. When DCs and $CD4^+$T cells from CIA mice were cultured with anti-CD3, CTLA4-Ig increased the $CD4^+CD25^+Foxp3^+$ Treg population in a

TGF-beta-dependent, IDO-independent manner, but control-Ig did not. When adoptively transferred, CTLA4-Ig-treated DCs suppressed CIA and increased the $CD4^+CD25^+Foxp3^+$ Treg population but untreated DCs did not.

Conclusion: CTLA4-Ig suppressed CIA by modifying DCs from CIA mice to increase CD4+CD25+Foxp3+Treg population.

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Naive CD4+ T Cells From Arthritis Susceptible DBA/1 Mice Demonstrate a Dichotomous Response to TCR Activation in the Presence of TGF-β Enhanced RORγt and Increased Th17 Expression Yet Reduced Foxp3. Yoshiaki Morita[1], Cong-Qiu Chu[2], Doaa Ismail[1] and Keith B. Elkon[3], [1]University of Washington, Seattle, WA, [2]University of Washington; Oregon Health and Science Univ, Portland, OR, [3]Division of Rheumatology, University of Washington, Seattle, WA

Purpose: DBA/1 mice are unusual in their susceptibility to collagen-induced arthritis (CIA). We previously showed that one mechanism responsible for DBA/1 susceptibility is a relatively high Th17/Th1 cytokine response following immunization with type II collagen in complete Freund's adjuvant . The goal of this study was to identify the mechanisms responsible for the differential cytokine production by $CD4^+$ T cells in DBA/1 mice.

Method: Naïve $CD4^+$ T cells were purified using magnetic beads (CD4/CD62L) separation and stimulated with anti-CD3/CD28 under Th1, Th2, Th17 and Treg conditions *in vitro*. Cytokines were quantified by intracellular staining and flow cytometry or by ELISA. Transcription factor expression was determined by RT-PCR, immunoblotting or flow cytometry.

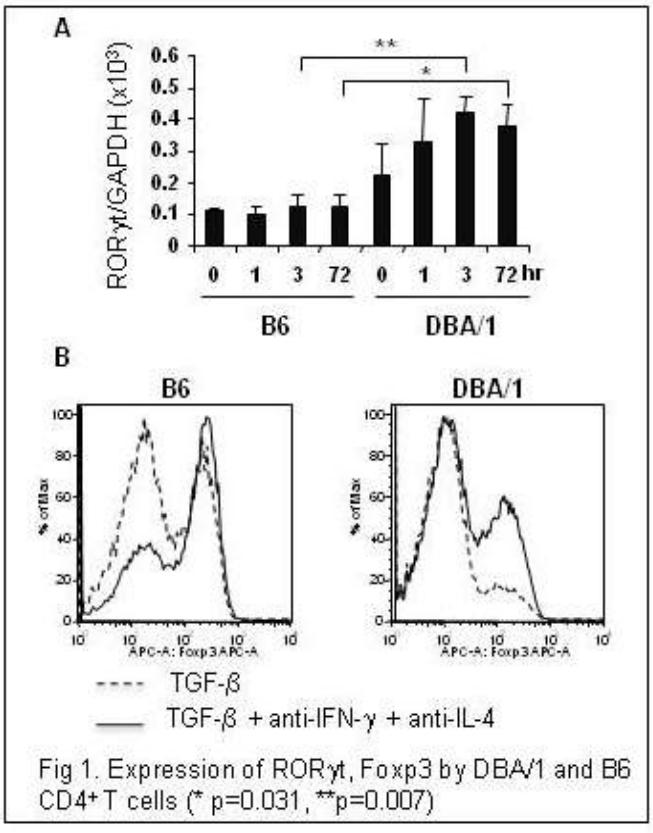

Fig 1. Expression of RORγt, Foxp3 by DBA/1 and B6 $CD4^+$ T cells (* p=0.031, **p=0.007)

Results: Purified naïve $CD4^+$ T cells from DBA/1 mice produced more IL-17 under Th17 conditions compared to B6, Balb/c or C3H mice. Consistent with this finding, naïve DBA/1 $CD4^+$ T cells also expressed increased levels of RORgt mRNA (Fig 1a). This abnormality was not, however, confined to Th17 as DBA/1 derived $CD4^+$ T cells polarized under the appropriate conditions also produced significantly higher levels of IFN-g and IL-4 compared to those from other strains. Detailed investigation revealed no differences in $CD4^+$ T cell survival, upstream TCR signaling or intracellular CD69 expression amongst strains. Since IL-17 is induced by exposure of $CD4^+$ T cells to IL-6 and TGF-b, we next examined expression of STAT3 and SOCS3. However, expression of these phosphoproteins was equivalent between strains thereby indicating a normal IL-6 pathway. DBA/1 $CD4^+$ T cell responses to TGF-b were examined under Th17 and Treg polarizing conditions (TGF-b, IL-2 and anti-IL-6). DBA/1 $CD4^+$ T showed a striking impairment of Foxp3 expression compared to controls. Although the magnitude of this difference was reduced in the presence of neutralizing IFN-g and IL-4 antibodies, Foxp3 expression remained lower in DBA/1 compared to B6 $CD4^+$ T cells following exposure to TGF-b (Fig 1b).

Conclusion: These results indicate that naïve DBA/1 $CD4^+$ T cells have a dichotomous response to TGF-b in that TGF-b promotes Th17 skewing yet fails to upregulate Foxp3, even when IFN-g and IL-4 are neutralized. This observation may help elucidate the branch point of TGF-b signal transduction and the enhanced RORgt and Th17 expression that likely contribute to greater susceptibility of DBA/1 mice to CIA.

Disclosure: Y. Morita, None; **C. Q. Chu**, None; **D. Ismail**, None; **K. B. Elkon**, None.

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GILZ Is a Novel Regulatory Protein in Collagen-Induced Arthritis. Devi Ngo[1], Elaine Beaulieu[1], Florence Apparailly[2], Gabriel Courties[2], Virginie Escriou[3], Daniel Scherman[4], Christian Jorgensen[2], Yuan Yang[1], Leilani Santos[1] and Eric F. Morand[1], [1]Monash University, Clayton, Australia, [2]Inserm U844, Montpellier, France, [3]Inserm U640, Paris, France, [4]Inserm U640, CNRS, UMR8151, University Paris Descartes, ENSCP, Paris, France

Purpose: Glucocorticoid-induced leucine zipper (GILZ) is a glucocorticoid (GC)-induced transcription factor that is reported to bind to NFκB and AP-1, inhibiting T cell and macrophage function. Its expression and function in animal models of RA have not previously been reported. We herein report GILZ expression in murine collagen-induced arthritis (CIA), and describe the function of endogenous GILZ for the first time in vivo.

Methods: GILZ was detected in mouse paw, synovium, spleen, and macrophages using immunohistochemistry, qPCR and immunoblotting. CIA was induced in DBA/1 mice and GILZ expression was silenced in vivo using cationic liposome-encapsulated (lipoplexed) GILZ siRNA.

Results: In murine CIA synovium, GILZ was detected in synovial lining and endothelial cells. The GC dexamethasone (0.25 mg/kg) significantly inhibited clinical expression of CIA, accompanied by significantly increased GILZ expression in synovium, peritoneal macrophages and spleen cells. Intravenous (IV) injection of red fluorescent siRNA lipoplexes resulted in lipofection of 20% of circulating monocytes within 4hrs. Compared to control (non-targeting) siRNA, IV administration of GILZ siRNA lipoplexes significantly inhibited GILZ protein expression in vivo. To determine the function of constitutive GILZ expression in the regulation of arthritis, GILZ was silenced in vivo in mice developing CIA. GILZ silencing resulted in marked and significant exacerbation of CIA clinical score compared to control (non-targeting) siRNA, associated with increased synovial expression of IL-1 and TNF but without affecting anti-type II collagen autoantibodies.

Conclusion: These findings demonstrate that GILZ acts as an endogenous inhibitor of inflammation and cytokine production in CIA. GILZ induction during GC inhibition of murine CIA suggests that GILZ may contribute to the therapeutic effects of GC in this model and in RA. This suggests that modulation of GILZ in human RA could be a promising therapeutic approach.

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Comprehensive Insight of the Immunosuppressive Effect of Mesenchymal Stem Cells in Arthritis. Carine Bouffi[1], Claire Bony[1], Gabriel Courties[1], Christian Jorgensen[2] and Danièle Noël[1], [1]Inserm U844, Montpellier, France, [2]Inserm u844, Unite ImmunoRhumatologie Therapeutique, Montpellier, France

Purpose: Multipotent mesenchymal stromal cells (MSC) are adult stem cells characterized by their differentiation potential and their immunosuppressive properties. Among the proposed mediators of this immunomodulatory effect, IDO, iNOS, IL-6 and PGE2 were consistently reported to play a major role, at least *in vitro*. The aim of our study was to better understand the molecular mechanisms involved in the immunosuppressive effect of MSCs *in vivo* and relied on the murine experimental model of collagen-induced arthritis (CIA).

Method: MSCs were isolated from DBA1 mice and wild type (wt), inducible nitric oxid synthase $(iNOS)^{-/-}$ or IL-$6^{-/-}$ C57Bl6 mice. Cells were immunophenotyped by flow cytometry. Their capacity to differentiate into 3 lineages was induced by culture in specific conditions and immunosuppression was evaluated in concanavalin A-induced proliferative assay. In vivo, 10^6 MSC were intravenously injected at various times after collagen II (bCII) immunization of DBA1 mice. Arthritis was evaluated by the measure of paw swelling and immunological parameters (collagen II-specific immunoglobulins, inflammatory cytokines and proliferation of T lymphocytes).

Results: All primary MSC populations were characterized by their common phenotype, trilineage differentiation potential and immunosuppressive potential. Using a proliferative assay, $iNOS^{-/-}$ or IL-$6^{-/-}$ MSCs exhibited a highly reduced immunosuppressive effect compared to wt MSCs while IDO activity was totally absent in murine MSCs. These results were confirmed *in vivo* in the CIA model. When injected on day 18 and 24, syngeneic MSCs were able to significantly decrease the incidence and the clinical signs of arthritis. A similar beneficial effect was also observed when allogeneic wt C57Bl6 MSCs were injected. The immunological parameters (proliferative assay, bCII-specific IgG1/IgG2A, cytokine profile) confirmed a decreased inflammatory response when MSCs were administered. However, when $iNOS^{-/-}$ or IL-$6^{-/-}$ MSCs were injected, the therapeutic effects of MSCs were partially reversed. This suggests that NO, IL-6-induced PGE2 secretion or IL-6-dependent dendritic cell maturation play only minor roles as well as $CD4^+CD25^+Foxp3^+$ T reg cells that were only slightly increased.

Conclusion: Our study shows the efficacy of systemic injection of syngeneic or allogeneic MSCs in the treatment of experimental arthritis in a restricted window of application. The mechanism of immunosuppression is complex and relies on more than one molecular pathway.

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A20 Gene Transfer Suppresses Inflammation and Bone Destruction through Inhibition of NF-Kappab Activation in Vitro and Vivo. Sang-IL Lee[1], Hyun-Ok Kim[2], Wan Hee Yoo[3], Eun-Gyeong Lee[3], Yun-Kyung Hong[3] and Sang-Hyon Kim[4], [1]College of Medicine, Gyeongsang National University, Jinju, South Korea, [2]Gyongsang University, Jinju, South Korea, [3]Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [4]Dongsan Medical Center, Keimyung University, Daegu, South Korea

Purpose: The nuclear factor-kappaB (NF-kB) activation plays a pivotal role to develop inflammation and bone destruction in rheumatoid arthritis (RA), and A20 downregulates NF-kB activation through the cooperative activity of its two de-ubiquitination and ubiquitin ligase domains. However, there has been no study addressing whether A20 show the therapeutic efficacy in RA. Thus, the current study was performed to determine whether A20 can block the action of fibroblast-like synoviocytes (FLS) and also suppress disease activity and joint destruction in mouse model of collagen-induced arthritis (CIA).

Method: The recombinant adenovirus carrying the gene that encodes A20 (Ad-A20) or beta-galactosidase (Ad-Bgal) were used. The inhibition of NF-kB activation and inflammatory chemokines/MMPs expression were assessed by EMSA and ELISA, respectively, after infection of Ad-A20 into FLS. The therapeutic effect was determined by clinical, histologic and immunostaining analyses after periarticular injection of Ad-A20 into the ankle joints of CIA mice. The inhibition of NF-kB activation was determined by EMSA and the levels of various cytokines in the joints and serum were measured by ELISA.

Results: Infection of FLS with Ad-A20 inhibited TNFα-induced nuclear translocation and DNA binding of NF-kB. Ad-A20 suppressed production of chemokines, such as ENA-78 and RANTES, and activation of MMP-1 and MMP-3 in FLS. Periarticular injection of Ad-A20 significantly reduced the intensity of clinical manifestations and effectively prevented joint destruction in CIA. These inhibitory effects were paralleled by diminished DNA binding of NF-kB. Furthermore, A20 treatment suppressed levels of RANKL, TNFα, and IL-6.

Conclusion: This study demonstrates that Ad-A20, most likely acts through inhibition of NF-kB activation, show therapeutic effects on inflammation and bone erosion in vitro and vivo. These results suggest that A20 can be used as a promising candidate in the field of treatment for RA.

Disclosure: S. I. Lee, None; **H. O. Kim**, None; **W. H. Yoo**, None; **E. G. Lee**, None; **Y. K. Hong**, None; **S. H. Kim**, None.

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Local Gene Therapy in Experiment Arthritis with Plasmid Encoding Soluble TNF Receptor Type I (sTNFRI). A. Denys, EA4222, Bobigny, France

Purpose: Gene therapy is an alternative for the continuous delivery of anti-inflammatory molecules such as TNF-alpha in rheumatoid arthritis (RA). We already demonstrated the interest of a non viral gene transfer strategy, namely electrotransfer (ET), to administrate sTNFRI by a systemic (im) way and to cure collagen-induced arthritis in mice (CIA). However, intra-articular (i.a) non viral gene therapy using electrotranfer is also of interest in joint-targeted diseases such as rheumatoid arthritis (RA). Our objectives were 1) to evaluate the therapeutic effect of mTNFR-Is gene intra-articular ET in CIA and 2) to investigate the mode of action by evaluating the effect on cytokine mRNA expression in the joints during arthritis development.

Methods: CIA was induced in DBA/1 mice with native collagen type II (CII) emulsified in complete Freund's adjuvant. A plasmid pVax1 mTNFR-Is/mIgG1 (encoding the fusion protein formed with murine sTNFRI and the heavy chain of IgG1) was synthetised. The plasmid was injected into both knees at time of clinical symptoms onset. After plasmid injection, an electric field was applied with electrodes placed apart on either side of the joint. mTNFR-Is joint secretion was evaluated in knee-conditioned media by ELISA. IL-10, IL-17 and TNF-α mRNA expression in the joints were measured by real time quantitative RT-PCR.

Results: After i.a. ET of various plasmid doses (10, 20 and 40 µg), a dose dependent expression of mTNFR-Is was observed in knee-conditioned media, and maximal secretion was observed after injection of 20 µg plasmid. Treatment of CIA with pVax mTNFR/mIgG1 electrotransfer have no systemic effect on clinical arthritis development. More interestingly the histological analysis revealed that 1) inflammation in ankles ($p<0.05$ versus NaCl and $p<0.001$ versus empty pVAX1) and in knees ($p<0.001$ versus NaCl and empty pVAX1) was lower in pVax1mTNFR-Is injected joints compared to controls, 2) destruction in ankles ($p<0.05$ versus NaCl and $p<0.001$ versus empty pVAX1) and in knees ($p<0.001$ versus empty pVAX1) was lower in pVax1mTNFR-Is injected joints compared to controls. In addition, increased IL-10, IL-17, TNF-*f*Ñ*f*nexpression were shown 15 days after ET in pVax1 mTNFR-Is/mIgG1 ET mice, as compared to NaCl ($p<0.01$).

Conclusion: These data demonstrate the feasibility and the effectiveness of local non viral gene therapy in arthritis and show that local mTNFR-Is gene delivery modulates some pro-and anti-inflammatory gene cytokine expression within the joints.

Disclosure: A. Denys, None.

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Targeted Adoptive Cellular Combination Gene Therapy of Inflammatory Arthritis Using Lentivirally Transduced Dendritic Cells. Ingo H. Tarner[1], Ulrich Purath[1], Remi J. Creusot[2], C. Garrison Fathman[2], Ulf Müller-Ladner[1] and Elena Neumann[3], [1]Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Stanford Univ Med Ctr, Stanford, CA, [3]Justus-Liebig-University of Giessen and Kerckhoff-Clinic, 61231 Bad Nauheim, Germany

Purpose: Systemic immunosuppressive treatment, e.g. by biologic cytokine inhibitors, of rheumatoid arthritis is limited by systemic adverse effects. Local delivery of cytokine inhibitors or anti-inflammatory molecules would therefore be advantageous. Immune cells such as lymphocytes have been shown to migrate into inflamed tissues, such as the joints in arthritis, and to deliver anti-inflammatory agents *in vivo*. Dendritic cells (DC) were chosen in this study for gene delivery because they are potent antigen-presenting cells that have been shown to modulate inflammatory responses when expressing anti-inflammatory molecules. In previous studies we have shown that gene transfer of single anti-inflammatory molecules prevents onset of arthritis in the model of collagen-induced arthritis but does not ameliorate established disease. Therefore, we hypothesized that the combined transfer of different anti-inflammatory molecules would be more effective.

Method: DC were isolated from murine bone marrow by magnetic bead-separation of T-cells, B-cells and granulocytes, cultured in presence of IL-4 and GM-CSF and transduced using three different lentiviral bicistronic constructs encoding the marker GFP and IL-12p40 (DCp40), an anti-TNF single chain variable fragment (DCTNF) or human galectin-1 (DCGal-1), respectively. Different dual (DCp40+DCGal-1, DCp40+DCTNF, DCGal-1+DCTNF) and triple (DCp40+DCGal-1+DCTNF) combinations of transduced cells were adoptively transferred into DBA/1 mice after the onset of clinical arthritis. Clinical disease severity, histological severity (pannus formation, cartilage degradation and bone erosion), systemic anti-collagen antibody levels and local cytokine gene expression were analyzed and DC migration was examined histologically.

Results: Transduced DC were found to migrate into the inflamed paws and to be localized near sites of bone erosion. The combination of DCp40 + DCGal-1 resulted in a significant reduction of pannus formation and bone erosion, whereas the other combinations did not. Clinically, there was a trend towards less disease severity in this treatment group which did not reach significance. Local expression of IL-10 in the paws was increased in the DCp40 + DCGal1 group whereas IFNg was reduced and TNF unaltered. Splenic expression of all three cytokines was reduced in this treatment group. Of note, triple gene therapy was not superior to the combination of DCp40 and DCGal-1.

Conclusion: Lentivirally transduced DC are able to migrate into inflamed joints in inflammatory arthritis. The combined transfer of the inhibitory IL-12p40 subunit and galectin-1 has anti-destructive effects and shifts the local cytokine expression towards a Th2 pattern, while clinical efficacy is limited. Routine application is impeded by the inherent complexity of the technique and the variability of gene transduction and expression.

Disclosure: I. H. Tarner, Abbott Immunology Pharmaceuticals, 5 ; **U. Purath**, None; **R. J. Creusot**, None; **C. G. Fathman**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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RNAi-Mediated Gene Therapy of PBEF Reduces the Severity of Collagen-Induced Arthritis in Mice. Gabriel Courties[1], Diego Kyburz[2], Virginie Escriou[3], Daniel Scherman[4], Christian Jorgensen[5], Steffen Gay[6] and Florence Apparailly[7], [1]Inserm U844, Montpellier, France, [2]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [3]Inserm U640,CNRS, UMR8151, University Paris Descartes, ENSCP, Paris, France, [4]Inserm U640, CNRS, UMR8151, University Paris Descartes, ENSCP, Paris, France, [5]Inserm u844, Unite ImmunoRhumatologie Therapeutique, Montpellier, France, [6]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [7]Inserm u844, Montpellier, France

Purpose: PBEF (Pre-B cell colony-enhancing factor/visfatin) is a hormone released by adipose tissue described as a new marker of inflammation in rheumatoid arthritis (RA) with pro-inflammatory and matrix-degrading activities. We previously showed that in vitro PBEF lead to the expression of pro-inflammatory mediators (IL-6, TNF) and matrix degrading enzymes (MMPs) in synovial fibroblasts and/or monocytes. The purpose of this study was to examine the therapeutic effects of systemic delivery of anti-PBEF siRNA lipoplexes in mouse arthritis pre-clinical model.

Method: Collagen-induced arthritis (CIA) was induced in male DBA/1 mice, and 0,5 mg/Kg small interfering (si)RNA against mouse PBEF (siPBEF) or non targeting siRNA (siCT) sequences formulated with the cationic liposome RPR209120/DOPE were injected intravenously weekly during arthritis progression. Clinical and biological features of the disease were investigated.

Results: Systemic siPBEF delivery significantly decreased clinical disease activity scores of CIA as evidenced by paw swelling measures. Importantly, RNAi-mediated PBEF silencing significantly decreased IL-6 secretion in both sera and spleen, without altering serum anti-collagen (bCII) antibodies levels and bCII-specific T cell proliferation. Importantly, frequencies of the IFN-γ- and IL-17A-producing CD4+ cells were decreased within spleen and liver, while frequency of the IL-10-producing CD4+/CD25+/Foxp3 cells was increased. Histological scores of inflammation and cartilage damage, bone erosion, and mRNA levels of pro-inflammatory cytokines and MMPs in the joints will be investigated, as well as immunohistochemical staining of PBEF in the joints.

Conclusion: These results provide novel evidence that systemic PBEF inhibition efficiently reduces experimental arthritis and might be proposed as novel therapeutic target for RA.

Disclosure: G. Courties, None; **D. Kyburz**, None; **V. Escriou**, None; **D. Scherman**, None; **C. Jorgensen**, None; **S. Gay**, None; **F. Apparailly**, None.

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RNA Interference Targeting the Cytosolic Phospholipase A2 ALPHA (CPLA2A) for Efficient ANTI-Inflammatory Therapy in Arthritis. Gabriel Courties[1], Michel Baron[2], Peter van Lent[3], Virginie Escriou[4], Daniel Scherman[5], Wim van den Berg[3], Alain Cantagrel[6], Christian Jorgensen[7], jean Luc Davignon[8] and Florence Apparailly[9], [1]Inserm U844, Montpellier, France, [2]Toulouse, France, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [4]Inserm U640,CNRS, UMR8151, University Paris Descartes, ENSCP, Paris, France, [5]Inserm U640, CNRS, UMR8151, University Paris Descartes, ENSCP, Paris, France, [6]JE 2510, Purpan University Hospital, Toulouse, France, [7]Inserm u844, Unite ImmunoRhumatologie Therapeutique, Montpellier, France, [8]JE2510, Toulouse, France, [9]Inserm u844, Montpellier, France

Purpose: The cytosolic phospholipase $A_2\alpha$ (cPLA2a) plays a critical role in the development and duration of inflammatory disorders. We aimed at better assessing the molecular mechanisms of the in vivo cPLA2a silencing using specific siRNA sequences and evaluating the therapeutic potential of RNAi-based anti-cPLA2a strategy.

Method: A cPLA2a siRNA sequence was validated in vitro on the NIH3T3 cell line, assessing the protein levels by western blotting and the mRNA by RT-qPCR after nucleofection. For in vivo administration, 10µg of siRNA were formulated as lipoplexes with the RPR209120/DOPE liposome and a carrier DNA, and weekly injected intravenously in DBA/1 mice before collagen-induced arthritis (CIA) onset. Clinical course of the disease was assessed by paw thickness over time, radiological and histological scores were obtained at euthanasia on day 56. The immunological balance was assessed using anti-type II collagen (bCII) assays, measuring the bCII-specific T cell proliferation, and quantifying cytokine levels in sera and knee-conditioned media by ELISA. The specific silencing of cPLA2a was assessed by RT-qPCR and functional assay using the fluorogenic phospholipase A2 substrate PED6 in organs targeted by siRNA lipoplexes.

Results: First, siRNA sequences targeting cPLA2a were shown in vitro to strongly reduce the expression of cPLA2a at both mRNA (70%) and protein (60-90%) levels. Weekly intravenous injections of anti-cPLA2a siRNA-lipoplexes significantly reduced incidence (38% versus 88%) and severity (1.97 ± 0.02 versus 2.19 ± 0.05 mm) of CIA, as compared with the irrelevant siRNA lipoplex-injected group. Histological scores of inflammation and cartilage damage or bone erosion were also lowered, as well as proteoglycan degradation and MMPs activity. The clinical effect was associated with decreased joint inflammation markers as assessed by a lower cPLA2a activity and local inhibition of IL-1β and TNF-α secretion in knee-conditioned media. Serum levels of anti-bCII IgG2a antibodies were also decreased in the cPLA2a siRNA-treated group compared with control animals, as was reduced the IFN-γ production by draining lymph nodes cells, reflecting altogether a decrease of the Th1-mediated autoimmune response.

Conclusion: Our data show that cPLA2a is a suitable target in CIA and that specific siRNAs may be used to control arthritis. Our observation opens new avenues for alternative treatment of RA.

Disclosure: G. Courties, None; **M. Baron**, None; **P. van Lent**, None; **V. Escriou**, None; **D. Scherman**, None; **W. van den Berg**, None; **A. Cantagrel**, Roche Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 8 ; **C. Jorgensen**, None; **J. L. Davignon**, None; **F. Apparailly**, Transgene SA (France), 5 .

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Arthritic Joint-Targeting siRNA/Wrapsome® as a Treatment Strategy for Rheumatoid Arthritis. Yukiko Komano[1], Nobuhiro Yagi[2], Ikumi Onoue[1], Kayoko Kaneko[1], Nobuyuki Miyasaka[1] and Toshihiro Nanki[1], [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Kyowa Hakko Kirin Co., Ltd.

Purpose: To explore the therapeutic potential of systemically administered small interfering RNAs encapsulated with Wrapsome® (siRNA/WS) for rheumatoid arthritis (RA), which contains siRNA in a core that is fully enveloped by a neutral lipid bilayer.

Method: Tissue distributions of fluorescence (Cy5)-labeled siRNA/WS or naked Cy5-labeled siRNA injected intravenously into collagen-induced arthritis (CIA) mice were assessed by fluorescence stereoscopic microscope and flow cytometry. Efficacy of siRNA targeting TNF-α/WS for CIA was evaluated with arthritis scoring system, and levels of TNF-α mRNA in joints were measured using real-time RT-PCR assay.

Results: Observation with stereoscopic microscope showed that levels of Cy5 was more intense in arthritic joints than in non-arthritic sites in mice treated with Cy5-siRNA/WS, and remained highly intense up to 48 hrs post-injection. On the contrary, the levels of Cy5 in arthritic joints in mice treated with naked Cy5-siRNA rapidly diminished. Cells in the synovium showed the highest intensity of Cy5 in those tested

including spleen, peripheral blood, lung, and bone marrow. Most of the Cy5-positive cells in the synovium were monocytes/macrophages ($CD11b^+$ or $F4/80^+$), whereas, there were a few Cy5-positive lymphocytes. Mice treated with TNF-α siRNA/WS showed decreased severity of arthritis compared with control siRNA/WS. The Levels of TNF-α mRNA in the joints of mice treated with TNF-α siRNA/WS were significantly lower than those in controls.

Conclusion: Using the Wrapsome®, efficient and targeted delivery of siRNAs to arthritic joints was achieved. The siRNA/WS were incorporated into monocytes/macrophages in the inflamed synovium, indicating that it could be a therapeutic tool to silence expressions of inflammatory cytokines produced by those cells *in situ*.

Disclosure: Y. Komano, None; **N. Yagi**, Kyowa Hakko Kirin Co., Ltd., 3 ; **I. Onoue**, None; **K. Kaneko**, None; **N. Miyasaka**, None; **T. Nanki**, None.

ACR Poster Session A

Cell-cell Adhesion, Cell Trafficking, and Angiogenesis
Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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IL-17 Is An Angiogenic Mediator in Rheumatoid Arthritis. Shiva Shahrara, Sarah R. Pickens and Richard M. Pope, Northwestern University Feinberg School of Medicine, Chicago, IL

Introduction: IL-17 has a profound effect in experimental arthritis, however its role in rheumatoid arthritis (RA) is less clear. We recently demonstrated that IL-17 and the percentage of TH-17 cells is increased in RA synovial fluids. Although IL-17 is capable in inducing selected chemokines from RA synovial fiblasts, its potential role in mediating angiogenesis of RA is undefined.

Purpose: Studies were performed to identify a novel role for IL-17 in mediating angiogenesis.

Methods: Various concentrations of IL-17 were employed to examine human microvascular endothelial (HMVEC) chemotaxis using a Boyden chamber. HMVEC chemotaxis was examined with heat inactivated IL-17, as well as neutralization of IL-17 by an anti-IL-17 antibody or IgG control. A series of checkerboard experiments were performed by placing increasing doses of IL-17 together with HMVECs in the lower chamber, in addition to placing different concentrations of IL-17 in upper chamber. Next we determined the role of IL-17 receptors in IL-17-mediated HMVEC chemotaxis. We also examined the signaling pathways associated with IL-17-induced HMVEC chemotaxis and tube formation.

Results: IL-17 was chemotactic for HMVECs at concentrations ranging from 0.01 ng/ml ($p<0.05$) to 100 ng/ml ($p<0.05$) ($n=5$). The mean concentration of IL-17 in the 30 RA synovial fluid analyzed was 233 ± 64 pg/ml, a concentration that was highly chemotactic for HMVECs. Consistently, heat inactivation of IL-17 or incubation of IL-17 (50 ng/ml) with IL-17-neutralizing antibody suppressed HMVEC migration. Checkerboard experiments demonstrated that IL-17 was chemotactic not chemokinetic. Next experiments were performed to determine which IL-17 receptor is involved in HMVEC chemotaxis. Although some reduction of HMVEC chemotaxis was noted with each antibody, a significant ($p<0.05$) reduction was noted only when both IL-17RA and IL-17RC were neutralized. Our results also demonstrate that IL-17 stimulates phosphorylation of ERK, JNK and AKT1 in HMVECs, while it had no effect on p38. To determine which signaling pathways mediate HMVEC migration, cells were pre-incubated with chemical inhibitors to ERK, JNK and PI3K prior to performing chemotaxis. Results from these studies demonstrate that while the inhibition of ERK and JNK was ineffective inhibition of PI3K markedly reduced ($p<0.05$) IL-17-mediated HMVEC chemotaxis. Consistently, inhibition of PI3K also reduced IL-17-mediated tube formation by 60% ($p<0.05$), whereas inhibitors to ERK and JNK were ineffective.

Conclusion: These results suggest that IL-17 may be a key initiator of angiogenesis in the RA joint, supporting IL-17 as a potential therapeutic target in RA.

Disclosure: S. Shahrara, None; **S. R. Pickens**, None; **R. M. Pope**, None.

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Variant Angiopoietin-1 with 269Gly Insertion Contributes to the Pathogenesis of Pulmonary Hypertension: A Novel Mechanism for Stimulating Pulmonary Smooth Muscle Cell Growth. Aya Mashida[1], Akira Hashiramoto[2], Takako Kawazoe[2], Koichiro Komai[1] and Shunichi Shiozawa[3], [1]Department of Biophysics, Graduate School of Health Sciences, Kobe University, Kobe, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, [3]Department of Biophysics Graduate School of Health Sciences, Kobe University/ The Center for Rheumatic Disease, Kobe University Hospital, Kobe, Japan

Purpose: Pulmonary hypertension (PH) is often a major fatal cause in rheumatic diseases such as Mixed Connective Tissue Disease (MCTD) and Systemic sclerosis (SSc). We previously identified two variants of *Ang-1* mRNA with or without having 3-bp GGT that encodes ^{269}Gly; we call them as Ang-1/ins and Ang-1/del, respectively. Notably, Ang-1/ins is genetically associated with the PH of patients with MCTD and SSc (Shiozawa K *et al*, Arthritis Rheum. 52: suppl (9). S283, 2005). We also reported that Tie2, a specific receptor for Ang-1, was highly expressed in Human Pulmonary Artery Endothelial Cells (HPAEC) as compared with Human Pulmonary Artery Smooth Muscle Cells (HPASMC), and Ang-1/ins strongly induced phosphorylation of ERK in HPAEC and in a co-culture of HPAEC and HPASMC (Kawazoe T *et al*, Arthritis Rheum. 58: suppl (9). S1321, 2008). The present study clarifies the mechanism that HPASMC is stimulated by HPAEC, where Ang-1/ins plays a role in over stimulating pulmonary smooth muscle growth.

Method: HPAEC was stimulated with Ang-1 variants, and phosphorylation of Tie2 was evaluated by immunofluorescent staining. HPAEC or HPASMC were cultured to 70, 100 and 120% confluence state, and the phosphorylated ERK (pERK) upon stimulation of Ang-1 variants was examined by westernblot. After stimulated with Ang-1 variants, culture supernatant of HPAEC was collected and further incubated with HPASMC to determine pERK by westernblot. Finally, the release of endothelin-1 (ET-1) from HPAEC was measured by ELISA upon stimulation with Ang-1 variants.

Results: In a culture of HPAEC, Ang-1/ins phosphorylated Tie2 to the levels far stronger than those with Ang-1/del under immunofluorescent staining. Under confluency, while the extent of phosphorylation of ERK by Ang-1/ins was comparable to the levels by Ang-1/del in HPASMC, the phosphorylation of ERK by Ang-1/ins was significantly higher than those by Ang-1/del in HPAEC. The culture supernatant of HPAEC stimulated with Ang-1/ins phosphorylated ERK of HPASMC more strongly than the supernatant stimulated by Ang-1/del. Similarly, the release of ET-1 from HPAEC was significantly higher when stimulated with Ang-1/ins as compared with those with Ang-1/del ($p<0.05$).

Conclusion: Ang-1/ins increases the phosphorylation of ERK directly in HPAEC and indirectly in HPASMC *via* mediators released from HPAEC. Enhanced production of ET-1 in HPAEC could be one of such mediators. Ang-1/ins, therefore, could contribute to the progression of vasoconstriction and smooth muscle cell hyperplasia in the pathogenesis of PH.

Disclosure: A. Mashida, None; **A. Hashiramoto**, None; **T. Kawazoe**, None; **K. Komai**, None; **S. Shiozawa**, None.

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Engagement of Tie2 Signaling Is Enhanced in the Synovial Tissue of Patients with Rheumatoid Arthritis Compared to Psoriatic Arthritis and Is a Consequence of Angiopoietin 1 Activation of Macrophages. Sarah Krausz[1], Daphne de Launay[1], Paul P. Tak[2] and Kris A. Reedquist[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Angiogenesis makes critical contributions to inflammation and joint destruction in rheumatoid arthritis (RA)and psoriatic arthritis (PsA). Angiopoietins (Ang) 1 and 2, which mediate blood vessel remodeling, as well as their receptor Tie2, are expressed in RA and PsA synovial tissue. Although Tie2 expression has been reported on synovial endothelial cells, fibroblast-like synoviocytes (FLS) and macrophages, little is known about how Tie2 signaling contributes to pathology in RA. Here, we examined the expression of Ang1 and Ang2, and the cellular distribution of total and active, phosphorylated active Tie2 in RA and PsA synovial tissue.

Method: Quantitative analysis of Ang1, Ang2, Tie2 and active phospho (p)-Tie2 expression in the synovial tissue of patients with active RA (n=17) and PsA (n=14) was performed by immunohistochemical staining and quantitative digital analysis. Immunofluorescent double staining was performed on synovial tissue biopsy sections using anti- Tie2 and p-Tie2 antibodies in combination with antibodies recognizing cellular markers (CD3, CD22, CD31, CD55, C68, CD163, and vWF). Tie2 expression on human peripheral blood (PB) monocytes and PB-derived macrophages were examined for Tie2 expression by FACs analysis.

Results: Ang1 expression was significantly higher in RA synovial tissue compared to PsA ($p<0.005$). In contrast, Ang2 expression was higher in PsA synovial tissue than in RA ($p<0.01$). Comparing the relative expression of Ang1 and Ang2 in each patient, we found that the ratio of Ang1 expression to Ang2 was approximately 10-fold higher in RA synovial sublining tissue (4.04+/-0.80, mean+/-SEM, arbitrary units) than in PsA (0.48+/-0.09) ($p<0.001$). This was associated with increased relative activation of Tie2 in RA synovial tissue compared to PsA ($p<0.05$). Within the RA patient cohort, a signficant positive correlation was observed between Ang1 expression and Tie2 phosphorylation ($R = 0.412$, $p<0.05$) which was not observed in PsA. Instead, a strong negative correlation was observed between Ang2 expression and Tie2 phosphorylation in PsA ($R = -0.782$, $p<0.001$). Immunofluorescent staining of RA synovial tissue detected active Tie2 predominantly in synovial macrophages, and only infrequently in endothelial cells and FLS. FACS analysis confirmed that Tie2 was expressed on the surface of not only PB monocytes, but also PB-derived macrophages.

Conclusion: Ang1 expression relative to Ang2 is significantly increased in RA synovial tissue compared to PsA, associated with increased activation of Tie2. Macrophages are the primary targets of Ang/Tie2 signaling in RA and PsA synovial tissue, identifying a novel functional interaction between angiogenic factors and macrophages in RA and PsA.

Disclosure: S. Krausz, None; **D. de Launay**, None; **P. P. Tak**, None; **K. A. Reedquist**, None.

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Macrophage Polarization Conditions and Relative Availability of Ang-1 and Ang-2 Determine the Contributions of Tie2-Bearing Macrophages to Inflammation and Tissue Remodeling. Sarah Krausz[1], Carmen A. Ambarus[1], Dominique L. Baeten[2], Paul P. Tak[3] and Kris A. Reedquist[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: We have recently identified Tie2-expressing macrophages as the primary targets of angiopoietin (Ang) signaling in rheumatoid arthritis (RA) synovial tissue. Although Ang-1 and Ang-2 are thought to contribute to blood vessel generation and remodeling needed for the maintenance of inflammation and tissue remodeling in RA, the (patho)physiological consequences of macrophage Tie2 engagement are unknown. Here, we examined how polarizing stimuli might regulate Tie2 expression on human macrophages and the effect of Ang-1 and Ang-2 stimulation on macrophage production of cytokines, chemokines and factors regulating tissue remodeling.

Method: Tie2 expression on human peripheral blood (PB) monocytes and PB-derived macrophages differentiated in the absence or presence of GM-CSF, IFN-gamma, LPS, TNF-alpha, M-CSF, IL-4, IL-10, or IL-6 were examined for expression of Tie2 and other macrophage markers by FACs analysis. Effects of Ang-1 and Ang-2 stimulation, alone or in combination with TNF-alpha or LPS, on macrophage IL-6 and IL-8 production were assessed by ELISA. Proteomic approaches were used to identify soluble factors involved in angiogenesis and tissue remodeling in culture supernatants of macrophages stimulated with Ang-1 and Ang-2, and candidate secreted products were validated by ELISA.

Results: Tie2 was expressed monocytes, and most polarizing stimuli had no effect on Tie2 expression. Exceptions included IFN-gamma and IL-10, which upregulated Tie2 expression, and IL-4, which suppressed Tie2 expression. Compared to macrophages differentiated in medium alone, Tie2 expression was significantly enhanced in macrophages exposed to IL-10 ($p<0.05$). Tie2 expression was associated with expression of CD163, a marker of alternatively-activated macrophages. Ang-1 induced IL-6 production in GM-CSF-differentiated macrophages ($p<0.01$) and enhanced TNF and LPS-induced IL-6 production ($p<0.05$), while effects of Ang-2 were limited to suppression of LPS-induced IL-6 production. In IL-10-differentiated macrophages, Ang-2 enhanced LPS-dependent IL-6 production. No effects of Ang-1 or Ang-2 on IL-8 production were observed. Proteomic analyses identified CCL2, CCL3, MMP-9, TIMP-1, and uPA as secreted gene products regulated by macrophage Tie2 signaling.

Conclusion: Macrophage Tie2 expression is tightly regulated by the polarizing conditions macrophages are exposed to during differentiation at sites of inflammation. Macrophage Tie2 is functional and differentially contribute macrophage expression of inflammatory cytokines, chemokines, and tissue remodeling factors dependent upon polarization conditions, relative levels of Ang1 and Ang2, and presence of other inflammatory stimuli, such as TNF-alpha and LPS. Tie2-bearing macrophages may be important in coordinating angiogenic and inflammatory stimuli to determine the balance of tissue destruction and remodeling in the synovium of patients with inflammatory arthritis.

Disclosure: S. Krausz, None; **C. A. Ambarus**, None; **D. L. Baeten**, None; **P. P. Tak**, None; **K. A. Reedquist**, None.

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Aggressiveness of Rheumatoid Arthritis Synovial Fibroblasts Is Characterized by Fast Transendothelial Migratory, Invasive and Neoangiogenic Potential. Birgit Zimmermann[1], Stephanie Lefèvre[1], Silvia Fischer[2], Julia Gansler[2], Angela Lehr[3], Stefan Rehart[3], Henning Stürz[2], Jürgen Steinmeyer[2], Ulf Müller-Ladner[1] and Elena Neumann[1], [1]Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Justus-Liebig-University of Giessen, Giessen, Germany, [3]Markus-Hospital, Frankfurt, Germany

Purpose: In rheumatoid arthritis (RA), synovial fibroblasts (SF) are activated cells that participate in cartilage degradation and joint destruction. Recently, we demonstrated the long-distance migratory behavior of RASF and examined the early events in this process that may contribute to the spreading of the disease between joints.

Method: In vitro transmigration assays through human umbilical vein endothelial cells (HUVECs) cultured in monolayers on rat tail collagen in transwell-chambers were performed. RASF were placed on the endothelial monolayer and the number of migrating RASFs was counted at different time points (4-16 h). RASF migration in vivo was investigated using the SCID mouse model of RA: $1.5x10^5$ RASF were implanted together with healthy human cartilage in a carrier matrix at the ipsilateral site (I). Cartilage without RASF was implanted at the contralateral site (IL) of the SCID mice. Neoangiogenesis adjacent to the implated cartilage was determined (35 hours, 6, 12, 18, 24, 30 days). Implants and spleens were removed and cartilage invasion of RASF was analyzed histologically using an established scoring system. Implants and spleens were analyzed immunohistochemically with species-specific antibodies.

Results: RASF transmigration through endothelial monolayers and collagen coating was already detectable after 4 hours (21.8%±0.2%). In all settings, the number of migrating cells increased over time. At the ipsilateral implant, invasion started at day 18 (mean invasion score: 0.86), at the contralateral site after 24 days of implantation (mean invasion score: 0.43). The invasion increased continously over time. Interestingly, RASF could be detected in all spleens of the SCID mice at every timepoint. Neoangiogenesis and vessel formation into both implants could be observed already after 35 h, which was more prominent at the ispilateral site.

Conclusion: Neoangiogenesis appears to be a very early event in RASF migration in the SCID mouse model for RA, which facilitates not only the rapid transmigration of RASF into the circulation and the migration to the contralateral implant but adds also to the knowledge of the pathophysiologic puzzle of spreading of human RA.

Disclosure: B. Zimmermann, None; **S. Lefèvre**, None; **S. Fischer**, None; **J. Gansler**, None; **A. Lehr**, None; **S. Rehart**, None; **H. Stürz**, None; **J. Steinmeyer**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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Regulation of the Fusion of Mononuclear Osteoclasts Into Bone-Resorbing Osteoclasts by GM-CSF Via RAS/ERK Pathway. Eun Gyeong Lee[1], Hee Jin Yun[1], Yun Kyung Hong[1], Myung Soo Lee[2], Sang-IL Lee[3], Hyun-Ok Kim[4], Min Ho Hwang[5], Sung Il Kim[6] and Wan-Hee Yoo[1], [1]Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Wonkwang university hospital, Iksan, South Korea, [3]College of Medicine, Gyeongsang National University, Jinju, South Korea, [4]Gyongsang University, Jinju, South Korea, [5]Presbyterian medical center, Jeonju, South Korea, [6]Pusan National University Mediacal School, Busan, South Korea

Purpose: GM-CSF has been shown to suppress RANKL-mediated osteoclast differentiation by inhibiting c-Fos. However, GM-CSF plays a critical role in osteoclast-mediated bone destruction under certain pathologic conditions including rheumatoid arthritis. Thus, this study was performed to define the role of GM-CSF in fusion of mononuclear osteoclasts for osteoclast differentiation and bone resorption.

Methods: Prefusion osteoclasts (pOCs) were generated from bone marrow macrophages treated with M-CSF and RANKL. pOCs were cultured to investigate the effect of GM-CSF on multinuclear cell formation. Expression of c-Fos, NFATc1, and DC-STAMP were determined by RT-PCR and Immunoblotting. We used constitutively active (CA)-MEK adenovirus to examine the phosphorylation of ERK induced by GM-CSF.

Results: GM-CSF enhanced the fusion of pOCs for osteoclastogenesis. GM-CSF-stimulated pOCs had intact actin ring and could resorb bone. GM-CSF induced the expression of DC-STAMP, which was mediated by inducing NFATc1 via induction of c-Fos. The expression of c-Fos and NFATc1 was regulated by ERK pathway. In addition, pOCs infected with constitutively active (CA)-MEK adenovirus expressed

c-Fos and NFATc1. The ectopic expression of CA-MEK induced NFATc1 binding to the DC-STAMP promoter and promoted the expression of DC-STAMP. CA-MEK-infected pOCs undergo cell-cell fusion and resorb bone.

Conclusion: GM-CSF can induce the fusion of pOCs into multinucleated osteoclasts by inducing the expression of DC-STAMP and thus involve in osteoclast differentiation. GM-CSF-stimulated pOCs have a typical actin ring structure and can induce bone resorption.

Disclosure: E. G. Lee, None; **H. J. Yun**, None; **Y. K. Hong**, None; **M. S. Lee**, None; **S. I. Lee**, None; **H. O. Kim**, None; **M. H. Hwang**, None; **S. I. Kim**, None; **W. H. Yoo**, None.

ACR Poster Session A

Cytokines, Mediators, and Gene Regulation I

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Role of Endogenous Tachykinins in Methotrexate-Induced Hepatotoxicity. Jaroslaw Biernat, Ryszard Sendur, Rafal Obuchowicz, Tomasz Brzozowski and Wieslaw W. Pawlik, Jagiellonian University, Cracow, Poland

Purpose: Methotrexate (MTX), a folic acid antagonist, is widely used as a chemotherapeutic agent and as immunomodulator substance in rheumatoid and psoriatic arthtritis as well. However, the efficacy of this agent often is limited by severe side effects especially in in the liver, including progressive hepatic fibrosis and cirrhosis.

MTX is tranformed in the liver to its major extracellular metabolite, 7-hydroxymethotrexate whilst inside the cells, MTX is stored in a polyglutamated form. Long-term administration leads to MTX polyglutamates accumulation and thus decreases folate levels by inhibition of dihydrofolate reductase,

In our previous experiments upon hepatoprotective mechanisms of the liver we showed that vanilloid-sensitive neurons play an important role in the dilation of hepatic artery branches and that microcirculatory hepatic blood flow is crucial for maintaining antioxidative function of hepatocytes. Basing on these observations we decided to compare and contrast the effects of sensory denervation and CGRP receptor antagonist in the protective circulatory mechanisms of the liver subjected to single and repeteated doses of MTX. In addition, we used NK-1, NK-2 and NK-3 receptor antagonists to find the role of endogenous tachykinins in this model of liver injury.

Method: Experiments were performed on Wistar rats weighing 200-220g. under pentobarbital anesthesia. Mean arterial blood pressures (AP), portal blood flow (PBF) and microcirculatory hepatic blood flow (HBF) using laser-Doppler flowmetry were measured. At the end of each experiment, the venous blood samples were taken to establish the levels of hepatic tissue injury markers (ALT, AST). Experimental groups: control group (placebo pre-treated), MTX – single dose 10 mg/kg i.p., MTX – 5 consecutive doses 10mg/kg i.p. for 5 days, single dose of MTX + sensory denervation (capsaicin), 5 doses of MTX + sensory denervation (capsaicin), single dose of MTX + CGRP receptor antagonist (CGRP 8-37), 5 doses of MTX + CGRP receptor antagonist (CGRP 8-37), MTX + NK-1, NK-2 or NK-3 receptor antangonists..

Results: Single dose of MTX (10 mg/kg i.p.) failed to increase both hepatic tissue injury markers (ALT, AST) and hemodynamic parameters however when given repeatedly for 5 days in 30% of rats ALT and AST increased 2-3 times. In this group non-sigificant reduction of HBF and HABF was recorded.

Both sensory denervation and blockade of CGRP receptors (but not NK-2 or NK-3) significantly excerbated hepatic tissue injury induced by dosing of MTX (80 and 90% of animals resepectively). In both groups HBF was reduced by 25 and 31 % respectively.

Interestingly blockade of NK-1 receptors protected the liver against MTX without interfering with circulatory parameters.

Conclusion: Above results indicate that blockade of NK-1 receptors protects the liver against repeteated doses of MTX and this mechanism is independent of vasodilatatory mechanisms of hepatic artery branches. However both sensory denervation and the blockade of CGRP receptors exacerbate the course of liver injury subjected to repeteated doses of MTX .

Disclosure: J. Biernat, None; **R. Sendur**, None; **R. Obuchowicz**, None; **T. Brzozowski**, None; **W. W. Pawlik**, None.

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Blocking ERK1/2 Reduces TNF-α-Induced-IL-18 Bioactivity in Rheumatoid Arthritis Synovial Fibroblasts by Induction of IL-18BP. Hubert Marotte[1], Salahuddin Ahmed[2], Jeffrey H. Ruth[1] and Alisa E. Koch[3], [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Toledo, Toledo, OH, [3]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Rheumatoid arthritis (RA) and osteoarthritis (OA) are two common chronic joint disorders whose etiology remains unknown. Interleukin-1 (IL-1) family members play a key part in the pathogenesis of both RA and OA. Among the IL-1 cytokine family members, IL-18 is a proinflammatory cytokine which modulates Th1 development. A defect of the natural inhibitor of IL-1 was previously described in RA and blockade of IL-18 bioactivity by the use of its natural inhibitor IL-18 binding protein (IL-18BP) appears to be a promising novel therapeutic strategy. We previously observed that TNF-α induced IL-18 and IL-18BP in a time dependent manner.

Methods: Levels of IL-18 and IL-18BP expression were determined by enzyme-linked immunosorbent assays (ELISA) in OA and RA synovial fluids, followed by free IL-18 calculation. IL-18 and IL-18BP synthesis in RA synovial fibroblasts treated with TNF-α were assessed by qRT-PCR and ELISA, respectively, followed by IL-18 bioactivity determination using human myelomonocytic KG-1 cells. Since caspase-1 is needed to cleave pro-IL-18 to bioactive IL-18, its expression and its activity were determined by a qRT-PCR and colorimetric assay, respectively. Chemical signaling inhibitors and antisense oligonucleotides were used for validation of the signal transduction pathways involved in IL-18BP/IL-18 regulation.

Results: IL-18BP was lower in RA synovial fluid than in OA synovial fluid ($p < 0.05$; n=8 donors) and free IL-18 was higher in RA synovial fluid than in OA synovial fluid. TNF-α induced RA synovial fibroblast IL-18, caspase-1, and IL-18BP at the mRNA level ($p < 0.05$; n=3); caspase-1 activity ($p < 0.05$; n=4); and IL-18 bioactivity. Evaluation of signaling pathways suggested that TNF-α-induced-IL-18 production through extracellular signal-regulated kinases (ERK)1/2, protein kinase C (PKC)δ, and Src pathways, whereas IL-18BP synthesis was mediated through nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), PKC, Src, and c-Jun N-terminal kinases (JNK) pathways. Furthermore, addition of exogenous IL-18BP-Fc reduced the RA synovial fibroblast phosphorylation of ERK1/2 induced by TNF-α.

Conclusion: These results suggest that IL-18BP reduces IL-18 bioactivity induced by TNF-α, by regulating the ERK1/2 pathway in RA synovial fibroblasts. Targeting IL-18 by induction or addition of exogenous IL-18BP may provide another therapeutic option in the management of RA.

Disclosure: H. Marotte, None; **S. Ahmed**, None; **J. H. Ruth**, None; **A. E. Koch**, None.

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TANK Binding Kinase (TBK1)-Dependent Gene Expression in Synoviocytes. Deepa Hammaker, David L. Boyle and Gary S. Firestein, UCSD School of Medicine, La Jolla, CA

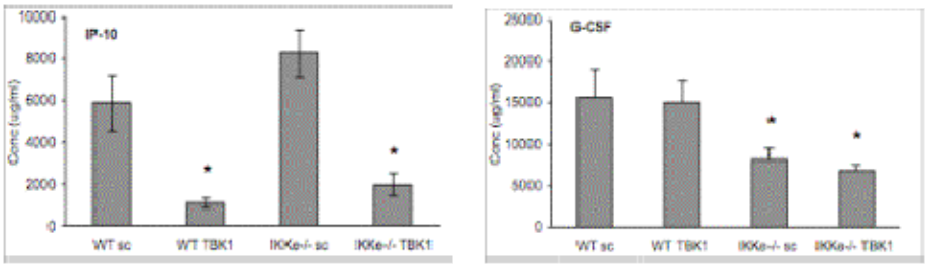
Purpose: Innate immune responses in rheumatoid synovium are activated by toll-like receptors (TLRs) in response to endogenous and exogenous antigens. TLR3 is activated by viral RNA as well as dsRNA from necrotic cells in the rheumatoid synovium, leading to increased proinflammatory mediator production. TLR3 is a potent activator of two I kappa B kinase (IKK)-related kinases, IKKe and TANK-binding kinase 1 (TBK1). Recent studies demonstrate that K/BxN serum-induced arthritis is less severe in IKKe-/- mice and that IKKe regulates chemokine, protease and IFN gene expression. However, it is not clear whether the two IKK-related kinases are redundant or whether targeting one of them might have a more prominent effect on IFN signatures. Therefore, we determined which genes are regulated by IKKe or TBK1 in cultured synoviocytes.

Method: Mouse fibroblast-like synoviocytes (FLS) from wild type (WT) and IKKe-/- mice were cultured and transfected with either scrambled (sc) or TBK1 siRNA by nucleofection. The cells were then stimulated with 20ug/ml polyI:C (PIC) for 1, 2, 3, 6, and 24h. Gene expression was assayed by qPCR. Cytokine production in culture supernatants was assayed by ELISA or multiplex analysis after 24h. IP-10 and IFNb luciferase reporter constructs were used to assay promoter activity.

Results: To determine the effect of TBK1 deficiency in the presence or absence of IKKe, WT and IKKe-/- FLS were transfected with TBK1 siRNA and then stimulated with PIC. Four patterns of IKKe/TBK1-mediated gene regulation emerged. 1) Genes regulated by TBK1 but not IKKe: IFNb, IP-10 gene, and IRF7 expression were decreased significantly by TBK1 but not IKKe deficiency after PIC stimulation (see

Figure; 94±10%, 76±10%, and 67±5% inhibition, respectively; n=3/group, $p<0.05$). Combined deficiency was not additive indicating that TBK1 is the primary regulator. Luciferase promoter constructs for IFNb and IP-10 promoters showed that TBK1 deficiency decreased gene transcription. 2) Genes regulated by IKKe but not TBK1: G-CSF had the opposite profile because it required IKKe but not TBK1 (see Figure, n=3, *$p<0.02$). Combined deficiency was not additive, indicating that TBK1 does not participate. 3) Genes regulated by both IKKe and TBK1: RANTES, IL-6, and KC expression were decreased by either IKKe or TBK1 deficiency. 4) Genes not regulated by IKKe or TBK1: MIP-1a and MCP1 were unaffected by either TBK1 or IKKe deficiency.

Conclusion: IKKe and TBK1 independently regulate cytokine and IFN responses after TLR3 ligation, indicating that the two signaling pathways are not redundant. Of the two kinases, TBK1 is the critical regulator of PIC-induced IFNb, IP-10, and IRF7 expression in FLS. Because IRF7 can serve as a master control of type I IFN responses in autoimmunity, TBK1 might be a better therapeutic target than IKKe.



Disclosure: D. Hammaker, None; **D. L. Boyle**, None; **G. S. Firestein**, None.

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GILZ Is a Novel Regulatory Protein in RA. Elaine Beaulieu[1], Devi Ngo[1], Qiang Cheng[1], Leilani Santos[1], Malcolm Smith[2], Michelle Leech[1] and Eric F. Morand[1], [1]Monash University, Clayton, Australia, [2]Repatriation General Hospital, Adelaide, Australia

Purpose: Glucocorticoid-induced leucine zipper (GILZ) is a glucocorticoid (GC)-induced transcription factor with recently described inhibitory effects on T cell and macrophage function via binding to NFκB and AP-1. Its expression and function have not previously been reported in RA. We herein report GILZ expression in human RA, and novel regulatory functions in FLS and human endothelial cells.

Methods: GILZ was detected in synovial sections from normal and RA subjects, and in cultured RA FLS and umbilical vein endothelial cells (HUVEC), using immunohistochemistry, qPCR and immunoblotting. The effects of GILZ overexpression on RA FLS and HUVEC cytokines and chemokines were examined, and GILZ effects on whole blood leukocyte adhesion and rolling interactions with HUVEC were examined in a flow chamber.

Results: GILZ was detected in normal synovium in lining and sublining layers. Compared to normal synovium, synovial sublining and endothelial GILZ were significantly increased in active RA. In RA FLS, the GC dexamethasone (Dex) potently and highly significantly upregulated GILZ mRNA and protein, with up to a 150-fold increase in mRNA within 4 hours which was GC receptor-dependent. In contrast, TNF and LPS significantly inhibited both endogenous and Dex-induced RA FLS GILZ expression. RA FLS release of the pro-inflammatory cytokines IL-6 and IL-8 was inhibited by GILZ without affecting proliferation. Unexpectedly, GILZ was also expressed in synovial endothelial cells and cultured HUVEC. HUVEC GILZ was significantly increased by Dex and inhibited by TNF. TNF also induced leukocyte rolling and adhesion interactions with HUVEC, which were in turn inhibited by restoration of GILZ. This was not due to an effect of GILZ on HUVEC release of the chemokines IL-8, RANTES, IP-10 and MCP-1.

Conclusion: We report the first expression and functional data regarding GILZ in human RA and human endothelial cells. GILZ expression in RA FLS is exquisitely sensitive to induction by GC, and its expression inhibits FLS cytokines. GILZ is expressed in vascular endothelial cells, where it inhibits leukocyte–endothelial interactions. These findings identify GILZ as a novel regulatory protein in RA.

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IL-6 Reduces Blood Lipid Levels Via up-Regulation of VLDL Receptor. Misato Hashizume, Hiroto Yoshida, Nobuo Koike, Miho Suzuki and Masahiko Mihara, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

Purpose: It is reported that the treatment of rheumatoid arthritis (RA) patients by IL-6 or TNF-α blocker increased blood levels of total cholesterol (T-Chol), and triglyceride (TG), which were inversely related to the disease activity of RA. But it remains to be clear why blockades of IL-6 and TNF-α change lipid level. On the other hand, there are reports describing that T-Chol and TG levels are low in RA patients. Serum lipid level is controlled by the lipid synthesis in liver and the lipid uptake into tissues mediated by lipoprotein receptor. In the present study, we investigated the influence of IL-6 and TNF-α on lipid metabolisms.

Method: Vascular skeletal muscle cells (VSMC) were cultured in the presence of IL-6, IL-6 + soluble IL-6 receptor (sIL-6R) or TNF-α for 24 h. After culture, mRNA expression of very-low-density lipoprotein receptor (VLDL receptor), low-density lipoprotein receptor (LDL receptor) and low-density lipoprotein-related protein-1 (LRP-1) were measured by real-time PCR. Human IL-6 was injected into mice twice a day for 2 weeks and then VLDL receptor protein expression in liver, adipose tissue and heart and blood T-Chol and TG levels were investigated. Anti-IL-6R antibody was injected once at 2 weeks after first IL-6 injection. Two weeks after anti-IL-6R antibody injection blood was collected and then lipid levels and SAA level were measured.

Results: At first, we examined if IL-6 induced the expression of mRNA for VLDL receptor, LDL receptor and LRP-1 in VSMC. IL-6 + sIL-6R significantly induced expression of VLDL receptor mRNA in VSMC, but IL-6 or sIL-6R alone and TNF-α did not do so. None of these cytokines induced LDL receptor and LRP-1 mRNA expression. Therefore, we examined if IL-6 actually induced VLDL receptor expression and reduced blood lipid levels in vivo. Continuous injection of IL-6 into mice significantly increased the expression of VLDL receptor in heart, adipose tissue and liver and simultaneously decreased blood T-Chol and TG levels. Furthermore, the injection of anti-IL-6R antibody normalized the reduced levels of T-Chol and TG caused by IL-6 injection, whereas it never influenced blood levels of T-Chol and TG in normal mice.

Conclusion: We demonstrated here that IL-6 increased VLDL receptor expression in several tissues and decreased blood lipid levels. Taken together with the fact that IL-6 is overproduced in RA patients, we conclude that the elevation of lipid levels in anti-IL-6 therapy is due to the inhibition of IL-6 signaling which caused reduction in lipid levels. And the elevation of lipid levels in anti-TNF therapy is mediated the suppression of IL-6 production. The study to investigate the influence of IL-6 on lipid synthesis is now underway.

Disclosure: M. Hashizume, Chugai Pharmaceutical. Co., Ltd, 3 ; **H. Yoshida**, Chugai Pharmaceutical Co., Ltd, 3 ; **N. Koike**, Chugai Pharmaceutical, 3 ; **M. Suzuki**, Chugai Pharmaceutical Co., Ltd, 3 ; **M. Mihara**, Chugai Pharmaceutical Co. Ltd., 3 .

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Ltα_1ß$_2$-Ltßr Signaling Is Crucial for the Tolerance Against Extractable Nuclear Antigens. Jens T. Van Praet[1], Inge Vanassche[1], Sigurd Delanghe[1], Michael Drennan[1], Nele Degryse[1], Julie Coudenys[1], Tine Decruy[1], Amélie Dendooven[2], Filip De Keyser[1], Carl F. Ware[3] and Dirk Elewaut[1], [1]Ghent University Hospital, Ghent, Belgium, [2]Utrecht University Medical Center, Utrecht, Netherlands, [3]La Jolla Institute for Allergy and Immunology, La Jolla, CA

Purpose: The lymphotoxin-β receptor (LTβR), a member of the immediate TNF family, controls the development of lymph nodes and Peyers' patches. In the adult, LTβR signaling is required for the maturation and maintenance of the microarchitecture of lymphoid tissue. The membrane-bound $LT\alpha_1\beta_2$ and LIGHT are its currently identified ligands. A soluble lymphotoxin-β receptor-immunoglobulin (LTβR-Ig) fusion protein antagonizes LTβR signaling and is currently being tested for treatment of autoimmune diseases. As the induction of antinucleair antibodies and anti-dsDNA antibodies during TNFα blockade is a well known phenomenon, we examined whether LTβR signaling is involved in tolerance against nuclear antigens.

Methods: Sera were collected from $LT\alpha^{-/-}$, $LT\beta^{-/-}$, $LT\beta R^{-/-}$, $LIGHT^{-/-}$, and wild-type controls, as well as from C57BL/6 mice treated with different regimens of LTβR-Ig or control IgG. $LT\beta R^{-/-}$ mice and wild-type controls were sacrificed at 24 weeks of age and kidneys were removed for pathological analysis. Sera from cell specific knockouts of LTβ by Cre mediated recombinase in CD4 T cells (CD4-$LT\beta^{-/-}$), B cells (MB1-$LT\beta^{-/-}$), or epithelial cells (K5-$LT\beta^{-/-}$) were analyzed. Anti-extractable nuclear antigen (anti-ENA) antibodies were detected by line immune assay (INNO-LIA ANA update), anti-dsDNA antibodies by ELISA (Alpha Diagnostic International).

Results: We observed at least one anti-ENA in 24 % of 3 months old and 27% of 6 months old $LT\beta R^{-/-}$ mice, in contrast to none of age-matched wild-type controls ($p<0.05$). At the age of 6 months, the most prevalent anti-ENA were anti-RNP (20%), anti-CENPB (20%) and

anti-Topo-I/Scl70 (20%). No anti-dsDNA antibodies could be detected. Similar patterns were found in $LT\alpha^{-/-}$ and $LT\beta^{-/-}$, but not $LIGHT^{-/-}$ mice. Intriguingly, preliminary data suggested T nor B cell specific deletion of LTβ results in anti-ENA at the age of 3 months, whereas epithelium specific deletion resulted in the occurrence of at least one anti-ENA in 1 out of 4 mice. When LTβR-Ig was administered during fetal ontogeny only, no anti-ENA induction in 3 months old offspring was observed. In contrast, prolonged postnatal administration until the age of six weeks induced anti-ENA at the age of 3 months (39% vs. 0% control Ig, $p<0.05$). Histopathological analysis did not reveal signs of lupus nefritis in $LT\beta R^{-/-}$ mice nor controls.

Conclusion: These studies provide a novel role for the $LT\alpha_1\beta_2$-LTβR pathway in maintaining tolerance against extractable nuclear antigens. The presence of anti-ENA was not dependent on the structural lymphoid defects caused by the embryological absence of LTβR signaling. Surprisingly, epithelial deletion of LTβ seems to be sufficient for developing anti-ENA. The uncoupling of detection of antinuclear antibodies and pathological damage parallels the observations seen in patients under TNFα blocking therapy.

Disclosure: J. T. Van Praet, None; **I. Vanassche**, None; **S. Delanghe**, None; **M. Drennan**, None; **N. Degryse**, None; **J. Coudenys**, None; **T. Decruy**, None; **A. Dendooven**, None; **F. De Keyser**, Schering-plough , 5, gsk , 5, Roche Pharmaceuticals, 5, Abbott Laboratories, 5 ; **C. F. Ware**, None; **D. Elewaut**, None.

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IL-18 as An In Vivo Mediator of Monocyte Recruitment in Animal Models of Rheumatoid Arthritis. Jeffrey H. Ruth[1], Christy C. Park[2], M. Asif Amin[1], Charles A. Lesch[1], Shiva Shahrara[3] and Alisa E. Koch[4], [1]University of Michigan, Ann Arbor, MI, [2]Univ of Tennessee, Knoxville, TN, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Interleukin-18 (IL-18) is a type-1 cytokine associated with proinflammatory properties. IL-18 is present at increased levels in serum and the rheumatoid synovium, as well as in the bone marrow in many human rheumatologic conditions including rheumatoid arthritis (RA), juvenile RA, adult-onset Still's disease, and psoriatic arthritis. IL-18 function was investigated in pertinent animal models of rodent RA to determine its proinflammatory and monocyte recruitment properties. We have previously shown that IL-18 acts on endothelial cells to induce angiogenesis and cell adhesion, however little is known about the monocyte chemotactic activity of IL-18. We clarified the cellular and molecular mechanisms induced by IL-18 on monocyte activation and recruitment contributing to the joint pathology observed in various rodent RA models.

Methods: We utilized a modified Boyden chemotaxis system to examine monocyte recruitment to recombinant human (rhu) IL-18 *in vitro*. Monocyte recruitment to rhuIL-18 was then tested *in vivo* using an RA synovial tissue (ST) severe combined immunodeficient (SCID) mouse chimera. We defined monocyte specific signal transduction pathways induced by rhuIL-18 by Western blotting analysis, and linked this to *in vitro* monocyte chemotactic activity. Finally, the ability of IL-18 to induce a cytokine cascade during acute joint inflammatory responses was examined by inducing wild-type (Wt) and IL-18 gene knockout mice with zymosan induced arthritis (ZIA).

Results: We engrafted SCID mice with RA ST and examined rhuIL-18 mediated monocyte migration into human ST. We found that intragraft injected rhuIL-18 was a robust monocyte recruitment factor to both human ST and regional (inguinal) murine lymph node (LN) tissue. IL-18 gene knockout mice also showed pronounced reductions in joint inflammation during ZIA compared to Wt mice. Many proinflammatory cytokines were reduced in IL-18 gene knockout mouse joint homogenates during ZIA including macrophage inflammatory protein-3α (MIP-3α/CCL20), vascular endothelial cell growth factor (VEGF) and IL-17. Signal transduction experiments revealed that IL-18 signals through p38 and ERK½ in monocytes, and that IL-18 mediated in vitro monocyte chemotaxis can be significantly inhibited by disruption of this pathway.

Conclusion: Our data shows that IL-18 is chemotactic for monocytes *in vitro* and signals in monocytes through the p38 and ERK½ pathways. Using the RA ST SCID mouse chimera, we found that IL-18 stimulates monocyte recruitment to engrafted ST and murine inguinal LNs. We also found that IL-18 initiates a proinflammatory cytokine cascade in acute articular inflammatory responses during ZIA by promoting IL-17, MIP-3α/CCL20 and VEGF production. These findings support the notion that IL-18 serves a hierarchal position for initiating joint inflammation during arthritis development.

Disclosure: J. H. Ruth, None; **C. C. Park**, None; **M. A. Amin**, None; **C. A. Lesch**, None; **S. Shahrara**, None; **A. E. Koch**, None.

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The Effects of Interleuikin-32 Alpha On Development of Inflammatory Synovitis and Cartilage Destruction in Mice. Masanori Nakayama and Yasuo Niki, Keio University, Tokyo, Japan

Purpose: Recently, interleukin-32 (IL-32) has been reported to participate in the inflammatory process of rheumatoid arthritis (RA) through production of TNF-alpha (TNFα). IL-32 expression in RA synovia correlates with serum inflammatory markers (i.e. CRP and ESR) and the levels of TNFα, IL-6 and IL-1. It is still known that IL-32 has six subtypes; alpha-sigma. In this study, arthritogenic role of IL-32 alpha (IL-32α) was investigated by genetic overexpression of IL-32α in mice and intra-articular injection of recombinant human IL-32 alpha (rhIL-32α).

Method: We generated IL-32 transgenic (Tg) mice, which overexpressed human IL-32α under a control of ubiquitous CAG promoter constructed by the first intron of the chicken beta-actin gene and a portion of the rabbit beta-globin gene. IL-32 Tg mice do not spontaneously exhibit arthritic phenotype despite high level of IL-32 expression in joints. Knees of Tg mice and normal C57BL/6 mice were injected once with LPS (100 ng) or Zymosan (100ng). Injection of PBS to the contralateral knee was served as a control. A week after injection, histopathological examination was performed, and TNFα mRNA expression was quantitatively measured using real time PCR.

Knees of two different background wild type mice (C57BL/6, Balb/C) were injected with rhIL-32α (100ng). A week after the injection, histopathological analysis and TNFαmRNA expression were measured as well.

Results: A single intra-articular injection of LPS resulted in development of severe synovitis with articular cartilage destruction in Tg mice but not in normal C57BL/6 mice. Less severe arthritic changes were observed in Tg mice receiving Zymosan injection. TNFα mRNA expression in synovia from Tg mice was prominent and significantly higher than that from normal C57BL/6 mice.

After intra-articular injection of rhIL-32, histopathological examination revealed that both C57BL/6 and Balb/c mice represented inflammatory synovitis and depletion of proteoglycan as assessed by safranin O staining. TNFα mRNA expression in synovia was equally upregulated in both Balb/c and C57BL/6 mice with statistically significance as compared to control mice injected with PBS.

Conclusion: The present study revealed that IL-32α contributes to development of inflammatory arthritis in mice. Given that single intra-articular injection of LPS induced inflammatory arthritis in IL-32α Tg mice, IL-32α may augment Toll-like receptor-4 (TLR-4) signaling pathway, which may result in production of variety of inflammatory cytokines including TNFα. Moreover, single injection of rhIL-32α was capable of inducing synovitis and cartilage degradation in wild type mice, indicating that IL-32 modulates inflammatory process in combination with natural ligand of TLR-4.

Disclosure: M. Nakayama, None; **Y. Niki**, None.

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Up-Regulation of the Histone Methyltransferase EZH2 by TNF-α in Synovial Fibroblasts Is Mediated through NF-KB/JNK-Activity and Enhances Cell Migration. Michelle Trenkmann[1], Matthias Brock[2], Renate E. Gay[1], Christoph Kolling[3], Rudolf Speich[2], Beat A. Michel[1], Steffen Gay[1] and Lars C. Huber[2], [1]Center of Experimental Rheumatology, Zurich Center of Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland, [2]Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland, [3]Schulthess Clinic, Zurich, Switzerland

Purpose: Previously we reported that the histone methyltransferase Enhancer of Zeste homologue 2 (EZH2) is up-regulated in rheumatoid arthritis (RA) compared to osteoarthritis (OA) synovial fibroblasts (SF) and is further induced by TNF-α. Beside its function in epigenetic gene silencing, EZH2 has also been shown to play a role in actin polymerization and therefore might contribute to cell migration. Here we addressed the pathways by which TNF-α regulates EZH2 and investigated the impact of EZH2 on migration of SF.

Method: RASF and OASF were pre-treated with the IKK-2 inhibitor sc-514 (50 μM), JNK Inhibitor II (20 μM), ERK Inhibitor II (10 μM) or p38 inhibitor SB203580 (10 μM) for 1h and stimulated with TNF-α (10 ng/ml) (n=4 each). After 48h, expression of EZH2 mRNA was quantified by real-time PCR. The effects of the kinase inhibitors were calculated for each individual experiment as compared to TNF-α-stimulation alone. For a reportergene assay, RASF were transfected with a luciferase vector containing the EZH2 promoter or the EZH2 promoter with a mutated binding site for the transcription factor E2F. Luciferase activity was measured upon stimulation with TNF-α for 24h

(n=7). For migration analysis, RASF and OASF (n=5 each) were transfected with a vector containing the coding sequence of EZH2 and cell migration was measured using a modified fluorescence Boyden chamber assay.

Results: Stimulation with TNF-α induced the expression of EZH2 by 4±1.4-fold in RASF and 4.4±2-fold in OASF. The inhibitors for IKK-2 and JNK had both a strong effect on the expression of EZH2 by reducing the TNF-α-mediated up-regulation by 105±14% (IKK2) and 47±17% (JNK) in RASF and 86±17% and 81±4% in OASF ($p<0.05$ for each). The ERK inhibitor decreased the induction of EZH2 by 77±18% in OASF ($p<0.05$) while the result in RASF was not significant (26±64%). Inhibition of p38 did not affect the expression of EZH2.

To detect upstream regulators of EZH2, a reportergene assay was performed employing a mutated E2F binding site. TNF-α increased the activity of the EZH2 promoter in RASF by 1.54±0.7-fold whereas mutation of the E2F binding site abolished this effect (0.98±0.3-fold, $p<0.05$). Moreover, SF transfected with EZH2 revealed an increased migratory activity as compared to the mock control (RASF: 398±191 vs. 351±156 RFU, $p<0.09$; OASF: 420±95 vs. 286±68 RFU, $p<0.04$).

Conclusion: Our data emphasize that the TNF-α induced up-regulation of EZH2 in SF is mediated through the NF-κB and JNK pathways and that the EZH2 promoter activity is directly regulated by the transcription factor E2F. Enhancing their migratory activity through the induction and overexpression of EZH2 might contribute to the aggressive phenotype of RASF.

Disclosure: M. Trenkmann, None; **M. Brock**, None; **R. E. Gay**, None; **C. Kolling**, None; **R. Speich**, None; **B. A. Michel**, None; **S. Gay**, None; **L. C. Huber**, None.

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Regulation of Pleitropic Effect of TRAIL On RAFLS by TRAIL-R1 and -R2. Rachel Audo[1], Angelique Bruyer[1], Bernard Combe[2], Michael Hahne[1] and Jacques Morel[2], [1]IGMM-CNRS UMR5535, Montpellier, France, [2]Department of Immuno-rheumatology, Montpellier, France

Purpose: A hallmark of rheumatoid arthritis (RA) is the pseudo-tumoral expansion of fibroblast-like synoviocytes (FLS), and RAFLS have been proposed as a therapeutic target. TNF-related apoptosis-inducing ligand (TRAIL) has been described as a pro-apoptotic factor on RAFLS and suggested as a potential drug. We have previously shown that exposure to TRAIL induces apoptosis only in a portion of RAFLS. In the surviving cells, TRAIL induced RAFLS proliferation. To evaluate possibilities to overcome TRAIL resistance in RAFLS, we compare FLS resistant (RAFLS-R) and RAFLS-sensible (RAFLS-S) to TRAIL-induced apoptosis including expression levels of the TRAIL receptors (TRAIL-R).

Method: Cell surface expression of the four membrane-bound TRAIL-R was measured by flow cytometry. To examine the implication of TRAIL-R in TRAIL apoptosis and proliferation, RAFLS were transfected with siRNA against TRAIL-R1 and TRAIL-R2. After 3 days, efficiency of silencing was assessed by western blot and FACS analysis. RAFLS were then cultured with TRAIL for 24 hours. Apoptosis was analyzed by flow cytometry, using annexin V-FITC binding and TOPRO-3 up-take. Proliferation was measured using incorporation of [3H] thymidine.

Results: Depending on the patient, we observed inter-individual variability in sensitivity of RAFLS to TRAIL-induced apoptosis. We therefore classified the cultures depending on their sensitivity (<10%; RAFLS-R and > at 30%, RAFLS-S). We observed that TRAIL-R4 and, surprisingly also TRAIL-R1 were significantly more expressed in RAFLS-R ($p=0.034$ and $p=0.0015$ respectivly). Silencing of TRAIL-R2 significantly reduced TRAIL induced apoptosis or proliferation (25.2±2.6 to 8.9±5.9; $p<0.01$, $n=7$). In contrast, silencing of TRAIL-R1 sensitized RAFLS for TRAIL-induced apoptosis (25.2±2.6 to 35.8±6.7; $p<0.05$; $n=7$) while it did not influence the TRAIL-induced cell death.

Conclusion: Using siRNA silencing, we confirmed the implication of TRAIL-R2 in apoptosis and proliferation induced by TRAIL. Using this approach, we also found that TRAIL-R1 may not be involved in RAFLS apoptosis or proliferation induced by TRAIL, but could be a survival factor protecting RAFLS against TRAIL-induced apoptosis. This is consistent with our observation that TRAIL-R1 is significantly more expressed in the cell surface of RAFLS-R.

Disclosure: R. Audo, None; **A. Bruyer**, None; **B. Combe**, None; **M. Hahne**, None; **J. Morel**, None.

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Critical Role for Apoptosis Signal-Regulating Kinase in the Development of Inflammatory K/BxN Serum Induced Arthritis. Stephen J. Mnich[1] and Medora M. Hardy[2], [1]Pfizer Corp, St Louis, MO, [2]Pfizer Corp, St. Louis, MO

Purpose: Apoptosis signal-regulating kinase 1 (ASK1), is a member of the MAP3K family that activates both JNK and p38 MAPK in response to stress-related stimuli. ASK1 has been implicated in the pathogenesis of a variety of apoptosis- and stress-related diseases. Notably, activation of ASK1 has been reported to occur via the TNF receptor. In this report, we show that ASK1-/- mice were resistant to inflammation and the infiltration of inflammatory cells into the ankle joints induced in the K/BxN serum transfer model of RA.

Method: Arthritis was induced in this model by injection of serum from K/BxN mice into healthy, female ASK1-/- and wild type (wt) C57BL/6 mice. The p38a MAPK inhibitor, SD-0006 was administered to wt mice as a comparator. Inflammatory repsonses were assessed at various times through 12 days. Ankle edema, histopathological and immunohistological evaluation of inflammatory cell infiltration, and transcriptional profiling were evaluated.

Results: Both ASK1 deficiency and p38 inhibition resulted in marked attenuation of edema, cartilage damage, bone absorption, and inflammatory cell infiltration. Transcriptional profiling of mRNA prepared from pulverized paw tissue demonstrated that the production of many proinflammatory genes including IL-6, IL-1b, TIMP1, MMP-3 were maintained at basal levels by either ASK1 deficiency or prophylactic p38 MAPK inhibition in K/BxN mice. To understand the role of ASK1 in human RA, *in vitro* studies using human RA synovial fibroblasts (RASF) suggest that ASK1 plays a role in the proinflammatory responses to TNF-a. Synovial fibroblasts from RA patients produced elevated levels of IL-6 following stimulation with TNF- *a.* Consistent with a role for ASK1, both p38 and JNK were activated by this stimulation. IL-6 production was only blocked partially (~30%) by either a SD-0006 or SP600125, a JNK inhibitor. In contrast, dual inhibition with both p38/JNK inhibitors almost completely abolished TNF-a-induced IL-6 production from these cells. Finally, ablation of ASK1 expression in RASF using siRNA for ASK1, but not ASK2, inhibited ASK1 mRNA and protein, and resulted in an ~60% inhibition of TNF-a-induced IL-6 production.

Conclusion: This study is the first to suggest that ASK1 is critical for the development of RA and that ASK1 may be involved in the production of proinflammatory mediators in response to TNF-a stimulation in the RA joint.

Disclosure: S. J. Mnich, Pfizer Corp., 3 ; **M. M. Hardy**, Pfizer Inc, 3 .

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Annexin-1 Regulates Inflammation and Glucocorticoid Sensitivity of Human RA Synovial Fibroblasts. Yuan Yang[1], Yuan Jia[1], Wuqi Song[1], Devi Ngo[1], Zhanguo Li[2] and Eric F. Morand[1], [1]Monash University, Clayton, Australia, [2]Peking University People's Hospital, Beijing, China

Purpose: Annexin-1 (Anxa1) is a mediator of the anti-inflammatory actions of glucocorticoids (GC). Anxa1 is expressed in RA synovium, and Anxa1-/- mice exhibit increased experimental arthritis. The mechanism of action of Anxa1 is not well understood. We explored inflammatory signal transduction events modulated by Anxa1 in rheumatiud arthritis (RA) synovial like fibroblasts (FLS) and normal human lung fibroblasts (NHLF).

Methods: Anxa1 siRNA, GC-induced leucine zipper (GILZ)- and mitogen-activated protein kinase (MAPK) phosphotase-1 (MKP-1)-luc plasmid were transfected using lipofectamine and Amaxa. Promoter activities were examined by luciferase assay. Transfected fibroblasts were treated with TNF and/or dexamethasone (DEX) or TNF and/or MAPK or NF-kB inhibitors. IL-6 was measured by ELISA and real-time PCR. MAPK activities were detected by Western Blot and ELISA kits. Proliferation was measured by H3-thymidine incorporation.

Results: Anxa1 mRNA and protein were successfully knocked down in RA FLS using Anxa1 siRNA. Anxa1 silencing in RA FLS significantly increased TNF-induced proliferation and impaired inhibitory effect of DEX on TNF-induced IL-6 production. ERK and serine-536 NF-kB –p65 phosphorylation were increased by Anxa1 silencing. Inhibition of ERK, JNK or NF-kB pathways significantly reduced TNF-induced proliferation of RA FLS. GC induction of FLS expression of the anti-inflammatory genes G ILZ and MKP-1 was significantly impaired in the absence of Anxa1, which paralleled the impaired inhibitory effect of DEX on TNF induced

IL-6. Similarly, silencing of Anxa1 in NHL fibroblasts significantly increased responsiveness to TNF, including increased IL-6, proliferation, and ERK activity, impaired inhibitory effects of DEX on TNF-induced IL-6 release, and impaired DEX-induced GILZ and MKP-1 mRNA. Cotransfection studies in NHL fibroblasts showed that Anxa1 silencing significantly reduced DEX-induced GILZ- and MKP-1 promoter activity in comparison to control siRNA transfected cells.

Conclusion: These data demonstrate that endogenous Anxa1 is a critical endogenous inhibitory regulator of cytokine expression, proliferation and MAPK activation, and mediates GC sensitivity via activation of GILZ and MKP-1.

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Elevated Serum CX3CL1 Levels in Patients with Idiopathic Inflammatory Myopathy. Nobuyuki Yajima[1], Michihito Sato[2], Ryo Takahashi[2], Kuninobu Wakabayashi[2], Takeo Isozaki[2], Tuyoshi Odai[2], Yusuke Miwa[3] and Tsuyoshi Kasama[2], [1]Tokyo, Japan, [2]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [3]Showa University, School of Medicine, Shinagawa-ku Tokyo, Japan

Purpose: Given that the chemokine CX3CL1 plays an important role in the pathogenesis of a variety of inflammatory diseases, our aim in the present study was to determine the involvement of soluble CX3CL1 in idiopathic inflammatory myopathies such as dermatomyositis (DM) and polymyositis (PM), and its relationship to disease activity and systemic complications.

Method: Twenty-three patients presenting with an idiopathic inflammatory myopathy such as DM (n=15) or PM (n=8) participated in this study between March 2004 and February 2008. Serum samples were collected from all patients during both active (newly diagnosed, untreated) and inactive disease states (after clinical remission), and were also collected from 52 healthy individuals, who served as controls. Serum levels of CX3CL1 were measured using an enzyme-linked immunosorbent assay. The relationship between serum levels of CX3CL1 and those of creatine kinase (CK) was examined. Serum CK levels were determined as an index of the myositis disease activity. In addition, the correlations between serum CX3CL1 levels and systemic complications were examined.

Results: Serum CX3CL1 levels were significantly higher in all inflammatory myositis patients than in healthy individuals (6212.4±2353.9 pg/ml vs. 92.3±83.3 pg/ml). Within the myositis group, serum CX3CL1 levels were significantly higher in patients with DM (9058.1 ±3501.8 pg/ml) than in those with PM (1232.4±539.9 pg/ml), and were significantly higher in DM patients with interstitial pneumonitis than in those without the pulmonary complication. There was a significant correlation between serum CX3CL1 and CK levels, and serum CX3CL1 levels were significantly diminished after clinical remission.

Conclusion: Our findings suggest that CX3CL1 plays a crucial role in the pathogenesis of idiopathic inflammatory myopathies, especially DM, and that CX3CL1 in serum may serve as an additional serologic marker of inflammatory disease activity in DM patients.

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Ablation of CCR2 Exaggerates Arthritis and Enhances Bone Destruction in IL-1ra-/- Mice. Fujii Hiroshi[1], Baba Tomohisa[2], Hamano Ryoko[1], Yamada Kazunori[1], Onoe Tamehito[1], Mitsuhiro Kawano[1], Yamagishi Masakazu[3] and Mukaida Naofumi[2], [1]Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [2]Cancer Research Institute, Kanazawa University, Kanazawa, Japan, [3]Kanazawa University Graduate School of Medicine, Japan

Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the infiltration of macrophages and neutrophils into the joint space. Chemokine receptors, CCR2 and CX3CR1, are expressed on macrophages infiltrating into the synovium of RA patients. However, it still remains unclear on the roles of CCR2- or CX3CR1-mediated signals in RA. Hence, we investigated the roles of CCR2- or CX3CR1-mediated signals in arthritis developed spontaneously in IL-1ra-deficient mice, by ablating CCR2 or CX3CR1 gene in IL-1ra-deficient mice.

Method: IL1ra-deficient, IL1ra-CX3CR1-double deficient and IL1ra-CCR2-double deficient mice underwent clinical assessment of arthritis, histological examination, assessment of bone mineral density, determination of cytokine and protein levels and assessment of osteoclastogenesis.

Results: Consistent with the previous report, IL-1ra-deficient mice developed multiple arthritis until 12 weeks after birth. Ablation of CCR2 gene but not CX3CR1 gene exaggerated arthritis in IL-1ra-deficient mice, as evidenced by augmented arthritis clinical scores and histopathological scores characterized by an aberrant neutrophil accumulation. Moreover, IL-1ra-CCR2-double deficient mice exhibited lower bone mineral density on computer tomography and higher serum concentration of cartilage oligomeric matrix protein, than IL-1ra-deficient mice. Furthermore, tartrate-resistant acid phosphatase-positive osteoclasts were increased in the joints of IL-1ra-CCR2-double deficient mice, compared with IL-1ra-deficient mice. Immunohistochemical analysis revealed that neutrophils in the inflamed joint expressed RANKL and ADAM 8, factors crucially involved in osteoclast formation. **Conclusion:** Ablation of CCR2 could aggravate arthritis developed spontaneously in IL-1ra-deicient mice, with enhanced accumulation of neutrophils, which express RANKL and ADAM 8, thereby inducing bone destruction.

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Correlation Between Serum Visfatin/PBEF and BAFF Levels After Rituximab Treatment in Patients with Active Rheumatoid Arthritis. Ladislav ŠEnolt[1], Hana Hulejová[1], Olga Krystufkova[1], Markéta Polanská[1], Maria Filková[1], Karel Pavelka[1] and Jiri Vencovsky[2], [1]Institute of Rheumatology, Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Institute of Rheumatology, Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Prague 2, Czech Republic

Purpose: Visfatin, also known as pre-B cell colony-enhancing factor (PBEF), is an insulin mimetic adipokine that is up-regulated in a variety of inflammatory diseases including rheumatoid arthritis (RA). Increased levels of visfatin in the systemic circulation of patients with RA were demonstrated to correlate with the clinical disease activity. Visfatin mRNA has been shown previously up-regulated in B-cells by BAFF (B-cell activation factor of the TNF family), a crucial cytokine for B-cell maturation and survival. In addition, BAFF serum levels increase during B-cell depletion. The aim of this study was to characterize the effect of B-cell depleting treatment (rituximab) on the serum levels of visfatin and study whether visfatin correlates with the changes of disease activity, B-cell depletion or serum BAFF levels.

Method: Serum levels of visfatin (BioVision, USA) and BAFF (R&D Systems Inc.) were measured in 31 patients (26 female, 5 male) with active RA before and 16 weeks after the rituximab treatment (W16). Disease activity was assessed by DAS28. CD19+ B-cells were examined in fresh peripheral blood mononuclear cells by seven-color flow cytometry (CyAn ADP).

Results: Following rituximab treatment, a majority of patients experienced significant reduction of disease activity (DAS28: 6.77±0.93 vs. 4.98±1.38; $p<0.0001$) and B-cell depletion (0.17±0.12 vs. 0.004±0.01 G/l, $p<0.0001$). Serum levels of visfatin significantly decreased (1.92±1.65 vs. 0.94±0.7 ng/ml; $p<0.01$), while BAFF levels significantly increased (1.43±1.02 vs. 4.22±2.27 ng/ml; $p<0.0001$) following the treatment. Serum BAFF, but not visfatin levels, correlated negatively with the B-cell numbers only at baseline ($r= -0.45$, $p=0.01$). Visfatin did not correlate with BAFF at baseline, however it negatively correlated with BAFF at W16 ($r= -0.46$, $p=0.01$). Visfatin levels correlated neither with C-reactive protein nor DAS28 both at baseline or W16.

Conclusion: In this study we found, that therapeutic B-cell depletion in patients with active RA has a differential effect on serum levels of the two B-cell effecting proteins - visfatin and BAFF and induces their correlation. We suggest that the lack of B–cells and improvement of disease activity can be responsible for the visfatin decrease in the circulation. The several time-point follow-up longitudinal studies could elucidate the association of visfatin with the extent of B-cell depletion and further repopulation and return of disease activity.

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The PEG Component of Certolizumab Pegol Inhibits Degranulation by Stimulated Mast Cells. Sabrina Lamour, Marguerite Bracher and Andrew Nesbitt, UCB, Slough, United Kingdom

Purpose: The administration of some conventional injectable TNF inhibitors is associated with severe injection-site pain (ISP), including stinging and burning. ISP may be linked to the inflammatory mediators released upon degranulation of mast cells, which are highly responsive skin cells that can rapidly secrete an array of inflammatory mediators. In contrast to conventional TNF inhibitors, the anti-TNF certolizumab pegol (CZP) lacks an Fc region and instead consists of a Fab' molecule site-specifically linked to a 40 kDa PEG moiety. A low incidence of ISP has been observed in patients receiving CZP in clinical trials in patients with rheumatoid arthritis.(1-3) The objective of our investigations was to determine if the PEG moiety of CZP inhibits the non-immune–stimulated degranulation of mast cells and may be responsible for the low incidence of ISP associated with CZP.

Methods: Mast cells were cultured in vitro from stem cells over an 8–12 week period using the method of Saito et al.(4) The development of stem cells into mast cells was confirmed by identification of mast cell markers, including CD117, CD203c and CD32, using flow cytometry. Mast cell degranulation, as measured by β hexosaminidase release, was stimulated by the addition of compound 48/80, a known non-immune activator of mast cells, which causes degranulation. Titrations of CZP, PEG, and a mixture of PEG and naked Fab' at a PEG concentration of 45mg/mL were incubated with the mast cells and a fixed amount of compound 48/80 to determine the effect on mast cell degranulation. Mast cell viability at the end of the experiment was assessed using the Promega Cell titer 96 Aqueous One Solution cell proliferation assay.

Results: Compound 48/80 stimulated mast cell degranulation as measured by β hexosaminidase release, although the absolute level varied between cell preparations. PEG (45 mg/mL) inhibited mast cell degranulation stimulated by 20μM and 200μM compound 48/80 by 66% (n=3) and 57.5% (n=4) respectively (P< 0.001). CZP (100 mg/mL), PEG alone (45mg/mL) and the mixture of PEG (19.8mg/mL) and naked Fab' (23.9 mg/mL) all inhibited the majority of mast cell degranulation. None of the reagents affected overall cell viability.

Conclusion: PEG inhibited compound 48/80–stimulated degranulation of mast cells. The concentrations at which an effect is observed are what might be expected at the injection site but not systemically. This beneficial effect of PEG on mast cells may explain the low level of ISP observed with CZP in clinical trials. However, the exact mechanism behind this activity is unclear and warrants further investigation.

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3. Fleischman R, et al. Ann Rheum Dis 2009;69: 805-811.
4. Saito H, et al. Nature Protocols 2006;1:2178–2183.

Disclosure: S. Lamour, UCB, 3 ; **M. Bracher**, UCB, 3 ; **A. Nesbitt**, UCB, 3 .

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Utilising Assay Systems Relevant to IL-6 Mechanisms in Rheumatoid Arthritis to Demonstrate Efficacy of a Novel Human Anti-IL-6 Antibody, CAT6001. Donna K. Finch[1], Elizabeth Rendall[2], Sylvia Salter[2], Monisha Sinha[1], Nicholas Cox[2], Caroline Grahames[2], Jamie Campbell[1], Steven Lane[1], David Lowe[1], Duncan Cochrane[1], Matthew Sleeman[1], S. Cruwys[2] and Philip R. Mallinder[2], [1]MedImmune Ltd, Cambridge, United Kingdom, [2]AstraZeneca R&D Charnwood, Loughborough, United Kingdom

Purpose: IL-6 was first identified as a B-cell differentiating factor. Recent clinical data with tocilizumab have shown IL-6 to have multiple effects in RA. Using a panel of *in vitro* and *in vivo* assays, each designed to reflect an aspect of RA pathology with IL-6 involvement, we describe the activity of a novel anti human IL-6 neutralizing antibody (CAT6001), engineered for very high affinity to IL-6.
Method: The IL-6-dependent proliferation of TF1 and B9 cells was measured using 3H-thymidine incorporation. IL-6-dependent IgM release from a B cell line (SKW6.4), was measured by ELISA. Primary fibroblast-like synoviocytes from RA patients were stimulated with IL-1β and IL-6Rα for 48hrs to produce IL-6 and VEGF, which were detected by ELISA. In a model of murine acute phase protein production, mice were treated with 12μg/kg huIL-6 i.p. daily for 7 days; CAT6001 (8 to 467 μg/kg s.c.) or isotype control was given in a single administration. Animals were sacrificed on day 7 and plasma haptaglobin levels measured.

Results: CAT6001 (<1 pM affinity for IL-6) potently blocked IL-6 driven cell proliferation of the haematopoietic cell line TF-1 (pIC50 1.61pM). IL-6-induced production of IgM from a B cell line (SKW6.4) and IL-6 induced proliferation of a B cell hybridoma cell line (B9), were potently inhibited by CAT6001 (pIC50 2.63pM and Kb 0.3pM respectively). Primary fibroblast-like synoviocytes from RA patients

dose dependently expressed IL-6 upon stimulation with IL-1β. The addition of exogenous soluble IL-6Rα resulted in the release of VEGF, a key angiogenic factor. CAT6001 blocked this IL-1β-stimulated VEGF release (IC50 340pM). Thus IL-6 plays a key role in mediating the effects of other pro-inflammatory cytokines on angiogenic factor release from activated RA synovial fibroblasts. In a murine *in vivo* model, recombinant human IL-6 induced an increase in serum levels of the acute phase protein haptoglobin. The production of this acute phase protein was inhibited in a dose dependent manner by administration of CAT6001.

Conclusion: These assay systems were used to exemplify the classical role of IL-6 in RA, such as IgM production from B cells, proliferative effects on multiple cell lineages, activation of synovial fibroblasts and production of angiogenic factors *ex vivo*, and systemic release of acute phase proteins *in vivo*. In all these models, CAT6001 potently inhibited these IL-6 driven mechanisms which supports the continued development of this molecule as a possible therapeutic agent for patients with RA.

Disclosure: D. K. Finch, MedImmune Ltd, 3 ; **E. Rendall**, AstraZeneca, 3 ; **S. Salter**, AstraZeneca, 3 ; **M. Sinha**, Medimmune, 1 ; **N. Cox**, AstraZeneca, 3 ; **C. Grahames**, AstraZeneca, 3 ; **J. Campbell**, Medimmune, 3 ; **S. Lane**, MedImmune Ltd, 1 ; **D. Lowe**, Medimmune, 3 ; **D. Cochrane**, Medimmune, 3 ; **M. Sleeman**, MedImmune, 3 ; **S. Cruwys**, AstraZeneca, 3 ; **P. R. Mallinder**, AstraZeneca, 3 .

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Progesterone Receptor Is Not Required for Progesterone Suppression of TLR-Induced Cytokine Production by Dendritic Cells in Vitro. Grant C. Hughes, Chang Li, Alan Wong, Kevin E. Draves and Edward A. Clark, University of Washington, Seattle, WA

Purpose: Progesterone (Pg) is a steroid hormone that governs reproductive functions in mammals. In reproductive tissues, Pg acts through a ligand-activated transcription factor called Pg receptor (PR) and through putative membrane Pg receptors (mPRs). Pg also can regulate inflammation and immunity. Specifically, Pg treatment can directly suppress TLR-induced interferon-alpha (IFN-α) production by plasmacytoid dendritic cells (pDCs) and suppress Th1-related autoimmunity in mice. While pharmacologic experiments suggest PR may be important in mediating Pg's immunoregulatory effects, the exact receptors involved are not known. Therefore, we used mice deficient in PR (PRKO) to assess the role of PR in TLR-induced IFN-α production and Th-related immune responses.

Method: Spleens, bone marrow and sera were obtained from mice heterozygous (PR+/-) or homozygous (PR-/-) for deletion of PR. PRKO mice were provided by Dr. Bert O'Malley of Baylor College of Medicine, Houston, TX. Freshly isolated splenocytes were assessed for production of IFN-α and Th-related cytokines after stimulation with various TLR ligands. Bone marrow-derived dendritic cells (BMDCs) were similarly analyzed. Serum IgM and IgG subclass levels from non-immunized mice were assessed. Cytokine and Ig levels were compared with paired T-tests. Pg 50% maximum inhibitory concentrations (IC50) were estimated by non-linear regression analysis.

Results: pDC-restricted, CpG-induced IFN-α induction in splenocytes from PR+/- and PR-/- mice showed similar sensitivity to Pg (est. IC50 4.6 x 10-7 M vs. 1.0 x 10-6 M, respectively) or medroxyprogesterone acetate (MPA, est. IC50 1.1 x 10-7 M vs. 7.7 x 10 -8 M, respectively) suppression. A similar result was obtained with CpG-induced IL-12p40. BMDCs from PR+/- and PR-/- mice showed similar degrees of sensitivity to Pg suppression of CpG- and LPS-induced IL-12p40. However, the absolute amount of CpG-induced IFN-α produced by pDCs in PR-/- splenocytes was significantly higher than that produced by PR+/- pDCs, a difference that could not be accounted for by pDC numbers. TLR-induced IL-12p40 production, by either splenocytes or BMDCs, showed more variability and no statistically significant differences. Given the known effects of Pg and IFN-α on Th-related immune and autoimmune responses, we measured serum Ig levels. We observed no statistically significant differences in serum IgM, IgG, IgG1, IgG2a, or IgG3, though there was a trend toward decreased IgG1/IgG2a ratios in PR-/- mice.

Conclusion: PR does not appear to be required for the in vitro suppressive effects of Pg on TLR-induced cytokines, suggesting the involvement of other molecules such as mPRs or glucocorticoid receptors. However, PR signaling appears to regulate TLR-induced IFN-α induction in vivo, perhaps indirectly, via cells other than splenic or bone marrow leukocytes. The role of PR in TLR-induced immune responses is the subject of ongoing investigation.

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Systemic Sclerosis Organ Involvement Is Associated with Increased Adipokine Expression. Elena Neumann[1], Klaus Frommer[1], Massimiliano Vasile[2], Tim Schmeiser[1], Oliver Distler[3], Steffen Gay[3], Valeria Riccieri[2], Andreas Günther[4], Elke Roeb[5] and Ulf Müller-Ladner[1], [1]Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Cattedra di Reumatologia, Dip Clinica e Terapia Medica, Sapienza Università di Roma, Roma, Italy, [3]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [4]Internal Medicine / Pneumology, University of Giessen, Gießen, Germany, [5]Internal Medicine / Gastroenterology, University of Giessen, Gießen, Germany

Purpose: Systemic sclerosis (SSc) is a connective tissue disorder characterized by progressive fibrosis of the skin and remodeling of the microvasculature. Increased extracellular matrix deposition also affects most internal organs including the gastrointestinal (GI) tract and lungs. Lung fibrosis represents the most common cause of death in SSc. We recently showed that severe fibrosis, increased expression of profibrotic cytokines and numbers of inflammatory cells are important hallmarks in the gastric wall (GW) of SSc patients. Adipokines such as adiponectin, visfatin/PBEF or resistin are immunomodulatory cytokine-like mediators. The present study analyzed whether adipokines are present in SSc-associated inflammation.

Method: Gastric biopsy samples obtained during esophagogastroscopy (corpus, esophagus, antrum) of 5 SSc patients and 2 healthy controls; lung tissues from patients with IPF, EAA/NSIP, controls as well as skin biopsy samples (2 SSc; 2 controls) were obtained. In bronchoalveolar lavages (BAL) of healthy controls (9), patients with SSc (22), IPF (6), and EAA/NSIP (4) adiopokines were measured (ELISA). Adiponectin, visfatin and resistin immunohistochemistry and double stainings with CD45 (LCA), CD3 (T cells), CD20 (mature B cells), CD68 (macrophages), vimentin (fibroblasts), CD31 (endothelial cells) were performed. Affymetrix analysis was performed using skin fibroblasts stimulated with adiponectin.

Results: Expression of adipokines in fibrotic skin, fibrotic lung tissue and the GI-tract of SSc was increased as compared to controls. In the GW, adipokines were localized at sites of inflammation in the mucosal layer without fibrosis in this area. Strongest expression showed adiponectin and visfatin. Adipokines were expressed by fibroblasts, inflammatory cells (CD45) and perivascular. In fibrotic lung tissue increased amounts of adipokines were detectable. Adipokine levels were increased in the BAL of fibrotic lungs when compared to controls (2.5fold) and to idopathic pulmonary fibrosis (1.7fold). Affymetrix array results showed a reduced expression of matrix components and an upregulation of matrix-degrading enzymes (MMPs).

Conclusion: The data show that in SSc patients adipokines are increased at sites of fibrosis in skin and lung. In contrast, adipokines are expressed in the GW at site of inflammation without fibrosis. Further analysis of the role of adipokines in fibrosis and inflammation may help to understand the pathophysiological mechanisms in SSc. Especially the role of adipokines with anti-fibrotic potential are of distinct interest for future investigations.

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ACR Poster Session A

Epidemiology and Health Services

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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New Directions for Environmental Research: Results From the Genetic and Environmental Factors in Systemic Lupus Erythematosus (GenES) Study. Glinda S. Cooper[1], Joan E. Wither[2], Sasha R. Bernatsky[3], Jaime O. Claudio[4], Ann E. Clarke[3], John D. Rioux[5], Andrew Paterson[6], CaNIOS LuNNET Investigators and P. R. Fortin[7], [1]US EPA, Washington, DC, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]McGill University Health Center, Montreal, QC, [4]Toronto Western Hospital, Toronto, [5]Montreal Heart Institute, Montreal, QC, [6]The Hospital for Sick Children Research Institute, Toronto, ON, [7]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: The aim of this study was to examine the associations between occupational and non-occupational exposures to sunlight and other potential risk factors for systemic lupus erythematosus (SLE) in the GenES study, a case-control study conducted through the Canadian Network for Improved Outcomes in SLE (CaNIOS).

Methods: SLE cases (n=258) fulfilling ACR disease classification criteria were recruited through 11 rheumatology centers across Canada. Controls (n=263) were randomly selected using lists of working phone numbers and matched to cases by area of residence, sex, and age. Participants completed a structured telephone interview with sections on work history and leisure time activities, with a focus on specific exposures including sunlight, silica, and solvents. All exposures were limited to experiences that occurred before diagnosis age (patients) or corresponding reference age (controls). We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusting for age, sex, and area.

Results: An association was seen with outdoor work in the 12 months preceding diagnosis (OR 2.0, 95% CI (1.1, 3.8)), but there was no association with total number of years of outdoor work. The frequency of responses concerning most of the specific types of leisure time sun exposure during the 5 years preceding diagnosis was similar in patients and controls. The exception was beach or other sunny vacations, which was reported more often by patients than controls (OR 2.4, 95% CI (1.5, 3.7)). There was little difference between patients and controls in smoking history, personal use of permanent hair dyes, occupational exposure to hair dyes, permanents and relaxers, gasoline, or pesticides, work involving drawing blood or giving injections, or work in a dry cleaner. Relatively strong but imprecise associations were seen with several exposures not previously reported with respect to SLE: artist working with paints, dyes or developing film (OR 3.9, 95% CI (1.2, 12.1)), work that included applying nail polish or nail applications (a source of exposure to di-*n*-butyl phthalate, OR 10.5, 95% CI (1.3, 84.3)), and work involving sterilizing dental equipment (OR 3.9, (0.8, 20.0)); these estimates are based on small numbers of exposed individuals. Patients were more likely than controls to report participation in pottery or ceramics work as a leisure time activity, with an increased risk seen among individuals with a total frequency (i.e, product of number of years times the average number of days per year) of at least 26 days (OR 2.2, 95% CI (1.2, 3.8)).

Conclusion: In addition to silica dust, these data support the role of other specific environmental exposures in the development of SLE.

These authors' views do not necessarily reflect the views or policies of the U.S. EPA.

Disclosure: G. S. Cooper, None; **J. E. Wither**, None; **S. R. Bernatsky**, None; **J. O. Claudio**, None; **A. E. Clarke**, None; **J. D. Rioux**, None; **A. Paterson**, None; **P. R. Fortin**, Canadian Institute of Health Research, 2, President, 6 .

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A Tobit Model for Predicting Health Utilities Index Mark 3 From Osteoarthritis Disease Duration: a Population-Based Study. Eric C. Sayre[1], Philippe Finès[2], William M. Flanagan[2], Jolanda Cibere[3], M. Mushfiqur Rahman[1], Jaafar Aghajanian[1], Weiqun Kang[1], Nick J. Bansback[4], Aslam H. Anis[5], Elizabeth M. Badley[6] and Jacek Kopec[3], [1]Arthritis Research Centre of Canada (ARC), Vancouver, BC, [2]Statistics Canada, Ottawa, ON, [3]University of British Columbia and ARC, Vancouver, BC, [4]University of British Columbia, Vancouver, [5]Univ of British Columbia, Vancouver, BC, [6]Toronto Western Res. Institute, Toronto, ON

Purpose: Osteoarthritis (OA) is usually a slowly progressive disease. With longer disease duration, health-related quality of life (HRQoL) declines, but this has not been well quantified. The purpose of this study is to understand the decline in HRQoL over time due to OA disease duration (OAD).

Method: We used biyearly longitudinal data (1994-2002) from the National Population Health Survey (n=10,920), weighted for the 2002 Canadian population. Self-reported arthritis/OA was extracted from each cycle to determine a discrete (interval) OAD variable, which was categorized into 4 levels: no OA; <4 years; 4-7.9 years; 8+ years. Latent HRQoL (LHRQoL; unbounded above) was measured by the observed Health Utilities Index Mark 3 (HUI3; bounded above at 1). LHRQoL in 2002 was predicted in a cross-sectional Tobit regression model from OAD as of 2002, adjusted for gender, age group (decades) and BMI (<25, 25-29.9, 30+). Interactions were tested between gender and OAD (dropped at alpha=0.05), and gender and BMI (retained). Variance estimates were bootstrap adjusted. Regression coefficients represent effects on LHRQoL; predicted LHRQoL can be truncated above at 1 to convert to HUI3 scale.

Results: Table 1 lists the regression coefficients with 95% confidence intervals (CIs). Compared to no OA, the effect (95% CI) on LHRQoL due to <4 years of OA is -0.078 (-0.101, -0.055), the effect of 4-7.9 years of OA is -0.143 (-0.198, -0.088), and the effect of 8+ years of OA is -0.162 (-0.203, -0.120). Other variables that were associated with lower HUI3 included female, older age (a nearly monotonic decline

decade to decade), and heavier BMI (in males, a reduced effect). Except on covariate combinations that predict LHRQoL above 1, coefficients may be interpreted as effects on HUI3.

Table 1. Tobit model for HUI3

Variable	Coefficient (95% CI)
OAD (reference=No OA)	*
<4 years	-0.078 (-0.101, -0.055)
4-7.9 years	-0.143 (-0.198, -0.088)
8+ years	-0.162 (-0.203, -0.120)
Gender (reference=Female)	*
Male	0.060 (0.028, 0.091)
Age group (reference=80+)	*
12-19	0.250 (0.206, 0.295)
20-29	0.246 (0.206, 0.286)
30-29	0.247 (0.206, 0.288)
40-49	0.215 (0.173, 0.257)
50-59	0.170 (0.130, 0.210)
60-69	0.167 (0.125, 0.209)
70-79	0.113 (0.070, 0.155)
BMI (reference=30+)	*
<25	0.070 (0.044, 0.097)
25-29.9	0.053 (0.024, 0.083)
Male & BMI <25	-0.065 (-0.100, -0.030)
Male & BMI 25-29.9	-0.022 (-0.060, 0.015)
[1]Scale	0.217 (0.208, 0.225)

[1]Scale estimates the standard deviation of the normal error term.

Conclusion: LHRQoL is affected in a monotonic, nonlinear way by OA disease duration. Adjusted for age, gender and BMI, the average drop in HUI3 between no OA and <4 years of OA is nearly matched by the subsequent drop between <4 years and 4-7.9 years of OA. However, the reduction from there to 8+ years of OA is only a quarter the size of the previous declines. Most of the negative effects of OA on LHRQoL appear to occur in the first 8 years. This may (in part) be due to disease adaptation, or treatments such as eventual surgery.

Disclosure: E. C. Sayre, None; **P. Finès**, None; **W. M. Flanagan**, None; **J. Cibere**, None; **M. M. Rahman**, None; **J. Aghajanian**, None; **W. Kang**, None; **N. J. Bansback**, None; **A. H. Anis**, None; **E. M. Badley**, None; **J. Kopec**, None.

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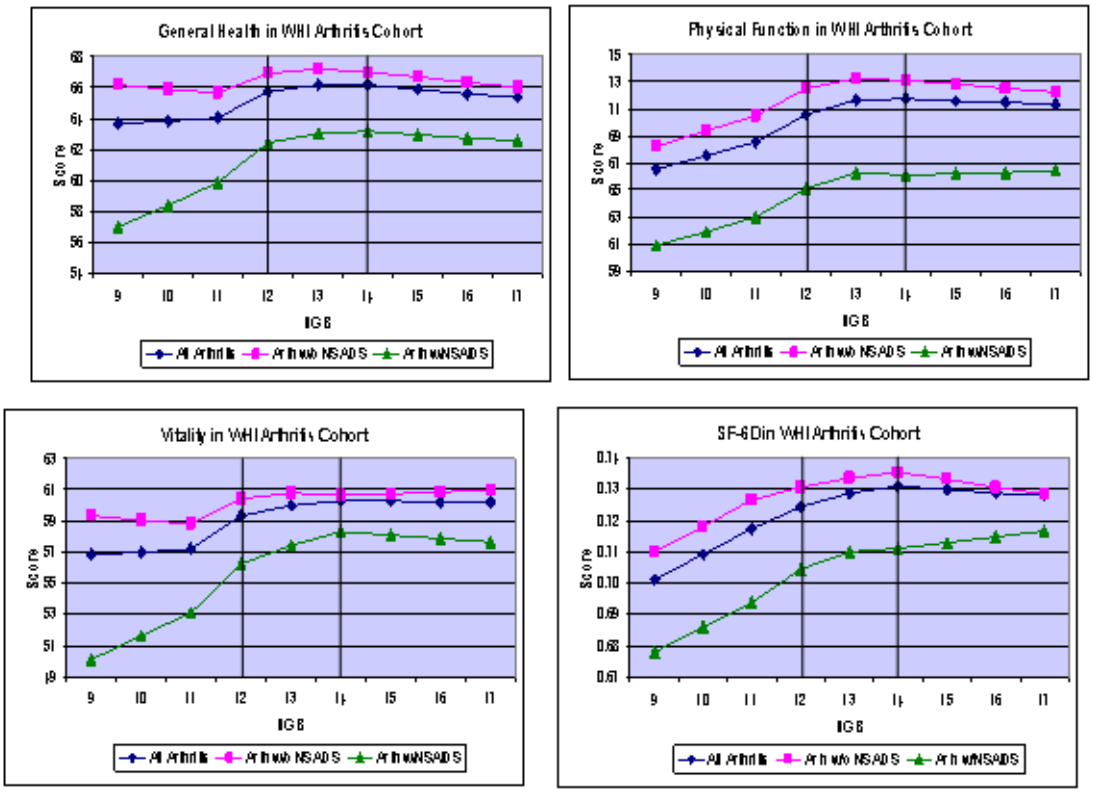
Relationship of Functional Outcomes to Hemoglobin Levels in Women with Self-Reported Arthritis: Results From the Women's Health Initiative. Charles B. Eaton[1], Marc C. Hochberg[2], Byron Cryer[3] and Annlouise R. Assaf[4], [1]Alpert Medical School of Brown University, Pawtucket, RI, [2]University of Maryland School of Medicine, Baltimore, MD, [3]University of Texas Southwestern, Dallas, TX, [4]Pfizer, Inc. and Alpert Medical School of Brown University, Providence, RI

Purpose: Gastrointestinal (GI) blood loss is a recognized complication of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with arthritis. We examined the relationship of patient reported outcomes of Overall Health, Vitality, Physical Function, and Quality of Life to hemoglobin levels in elderly women to determine whether hemoglobin levels as marker of chronic blood loss were associated with functional outcomes.

Method: Post-menopausal women (N=65,181) with self-reported arthritis at baseline in the WHI clinical trial (RCT) and observational cohorts, excluding participants with a self-reported diagnosis of sickle-cell anemia, chronic kidney disease, congestive heart failure, cancer, rheumatoid arthritis (RA), or those who reported being on erythropoietin, had hemoglobin levels measured and completed Short Form Health Survey (SF-36) subscales for patient centered outcomes of: overall health, vitality/fatigue, physical function and quality of life (SF-6D). Multiple linear regression analysis adjusted for age, race, education, RCT, Body Mass Index (BMI), depression, physical activity, disability, hospitalizations, lupus, diabetes, cardiovascular disease, and liver disease was performed. Multi-covariate adjusted least square (LS) means for each level of hemoglobin are plotted below.

Results:



Participants with arthritis had worse functional outcomes when hemoglobin levels were below 14 g/dL compared to ≥14 g/dL (P<.001). Participants with arthritis who were taking NSAIDs had worse outcomes than those not taking NSAIDs at all levels of hemoglobin (P<.05)

Conclusion: Differences in hemoglobin levels are related to differences in functional outcomes in post-menopausal women with self-reported arthritis excluding RA. This effect appears more profound in subjects taking NSAIDs.

Disclosure: C. B. Eaton, Pfizer Inc, 5 ; **M. C. Hochberg**, Osteoarthritis Research Society International, 6, Bayer Health Care LLC, 5, Bioiberica S.A., 5, Combinatorx, 8, Endo Pharmaceuticals, 8, Ferring Pharmaceuticals, 8, Genzyme Corporation, 5, Merck & Co., Inc., 8, NiCox, S.A., 5, Novartis Pharmaceutical Corporation, 5, Pozen Inc., 5, NIAMS-NIH, 2, Pfizer Inc, 5 ; **B. Cryer**, Pfizer Inc, 5 ; **A. R. Assaf**, Pfizer Inc, 3 .

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How Valuable Is a Rheumatologist: An Analysis of Downstream Revenue. Gary S. Firestein, UCSD School of Medicine, La Jolla, CA

Purpose: As a cognitive specialty, rheumatology experiences many problems faced by primary care in terms of low compensation and high overhead. In a group practice, the downstream benefits of a rheumatologist to the enterprise are rarely considered when determining the value of the services. To address the this question, the downstream revenue that accrues to a medical system was evaluated to provide a more accurate assessment of the marginal benefit of adding a clinical rheumatologist to the practice.

Method: Retrospective reviews were performed to assess professional fees and hospital services (imaging and laboratory) for patients with osteoarthritis (OA; Dx 715.20) or rheumatoid arthritis (RA; Dx 714.0) at the UCSD Medical Center Hillcrest Arthritis Clinic. Infusion center and physical therapy was not evaluated because the charges for these activities could not be captured.

Results: Two separate analyses were performed. First, 100 consecutive patients with OA seen in consultation by rheumatology in 2004 were identified and their disposition over the ensuing 3 years was determined. Of these, 28% of patients were referred to orthopedics for consultation. 42% of these had a surgical procedure, most commonly total joint replacement. Because the average OA patient is seen about 3 times/yr by our rheumatology service, a practice with 3600 visits/yr and, therefore, 1200 unique patients would be expected to contribute 141 surgeries/yr after 3 years. Based on current reimbursement, this would generate $1,075,000 in additional professional fee charges for orthopedics. In the second analysis, RA patients in the the health care system that were followed primarily by rheumatology were evaluated for downstream revenue in a single year (2006). 724 separate visits were tracked at one of our clinic sites. In addition to professional fees for the rheumatologist, $1,400,000 in professional fee charges for these patients were generated through consultation and non-rheumatology services, including Anesthesia ($200,000), Cardiology ($116,000), Orthopedics ($557,000), Radiology ($452,000), and Pathology ($48,000). Outpatient hospital charges for imaging and laboratory services during the same period were $1,011,000. Combined, each RA patient generated an average of $3000 in downstream charges, not including infusion center charges or physical therapy.

Conclusion: A clinical rheumatologist has profound effects on utilization in an integrated health care system. Every professional fee dollar charged by a rheumatologist for an RA patient generates approximately 20-30 fold additional charges for the enterprise. Clinical activity for a rheumatologist can lead to a substantial numbers of orthopedic procedures for OA patients, with additional impact on Anesthesia and Radiology. Therefore, an integrated healthcare system seeking to optimize utilization and enhance revenue should provide support to increase and incentivize rheumatology clinical services.

Disclosure: G. S. Firestein, None.

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Disappearing Act? Trends in the Extra-Articular Manifestations of Rheumatoid Arthritis (1995-2007). Elena Myasoedova[1], Cynthia S. Crowson[1], Carl Turesson[2], Sherine E. Gabriel[1] and Eric L. Matteson[1], [1]Mayo Clinic, Rochester, MN, [2]Malmö, Sweden

Purpose: To evaluate recent incidence trends in extra-articular manifestations of rheumatoid arthritis (ExRA).

Method: Information on ExRA manifestations was abstracted by medical record review of a population based incident cohort of patients with RA who first fulfilled 1987 ACR criteria for RA between 1/1/1995 and 1/1/2008. The patients were followed from 1/1/1995 until death, migration, or 1/1/2009. The date of ExRA incidence was recorded and ExRA were classified according to predefined criteria used in our previous studies (Ann Rheum Dis 62:722-727, 2003). ExRA events prior to the RA incidence date were excluded from each analysis. The cumulative incidence of ExRA adjusted for competing risk of death was estimated at 10 years follow-up. Incidence rates were compared to those reported for the previous decade (i.e. incident RA cases between 1/1 1985 and 12/31/1994 from the same population base, followed through 12/31/2000 (J Rheumatol 29:62-67, 2002).

Results: The study population included 463 RA patients with incident RA (mean (SD) age at incidence 55.6 (15.6) years). Of these, 320 (69%) were female; rheumatoid factor (RF) was present in 306 (66%) patients. The mean (median) follow-up was 6.3 (5.8) years (total of

2,956 person-years). ExRA developed in 159 patients, including 22 who developed severe disease manifestations of ExRA. The 10-year cumulative incidence for ExRA during the 1985-94 decade was similar to the 1995-2007 period (43.5% vs 46%), whereas there was a slight decrease in severe ExRA (8.4% vs. 6.5%, respectively). The most common ExRA in our cohort were subcutaneous nodules (n=110, 10-year cumulative incidence 30.9%) and keratoconjunctivitis sicca (n=39, 10-year cumulative incidence 9.9%). The 10-year cumulative incidence of vasculitis decreased significantly from the 1985-94 decade (3.6%) to 0.6% in 1995-2007 period, p=0.03).

Conclusion: During the 1995-2007 period, incident ExRA were common with a 10-year cumulative incidence of 46% of RA patients, which is similar to the previous decade. News of the demise of ExRA is premature, but there may be a decrease in the incidence of severe ExRA, in particular vasculitis.

Disclosure: E. Myasoedova, None; **C. S. Crowson**, None; **C. Turesson**, None; **S. E. Gabriel**, None; **E. L. Matteson**, None.

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Patients' Reactions to ACR Hotlines. Liana Fraenkel[1] and Ellen Peters[2], [1]Yale University, New Haven, CT, [2]Decision Research, Eugene, OR

Purpose: The ACR response to reports of extremely rare, but serious, adverse events (AEs) includes publishing a “hotline” recommending that physicians inform their patients of newly recognized risks. There are no data, however, describing how patients react to this information, and the consequences of disclosing dreaded, albeit rare AEs, on treatment planning are not known. The objective of this study was to examine how patients react to the disclosure of rare AEs associated with medications commonly used by rheumatologists.

Methods: Patients' risk perceptions are most often studied using written scenarios. In order to more closely represent how information is communicated in clinical practice, we developed a video in which a physician described the availability of a new medication associated with a rare AE (jaw osteonecrosis or progressive multifocal leukoencephalopathy). Consecutive patients attending outpatient clinics viewed the video and then rated their willingness to take the medication, as well as their worry and perceived chance of developing the rare AE on 11-point numeric rating scales. We examined the association of demographic variables with patients' reactions using logistic regression. Willingness, worry, perceived chance, and age were classified into two groups using the median. Race was classified as White vs non-White. Education was classified as college graduate or higher vs some college or less. Self-reported health status was included in the model as a covariate.

Results: 216 patients participated. The mean age (SD) was 59 (13), 39% were college graduates, 70% were White, 26% were Black, and 62% were female. The median (Q1-Q3) willingness to take the medication was 5 (0-8). The median level of worry was 8 (3-10), and the median perceived chance of developing the AE was 5 (3-10). Women were less willing to take the medication, were more worried about the AE and perceived a greater chance of developing the AE compared to men (Table 1). A similar pattern was seen for non-White vs White subjects. Lower education was also associated with increased worry and perceived chance (Table 1). Dummy variable regression demonstrated that black women were significantly less willing to take the medication [Adj OR (95%CI) = 0.37 (0.14 - 0.95)] and more worried about the risk of the AE [Adj OR (95%CI) = 3.05 (1.32 - 7.06)] than White women or men after adjusting for education, age and health status.

Conclusion: Demographic characteristics influence how patients react to risks of rare, but serious, AEs. More socially vulnerable individuals appear to be especially affected. The results are consistent with risk reactions in the environmental science literature and emphasize the need for further research to facilitate risk communication in clinical practice.

Table 1. Associations between Demographic Characteristics and Reactions to Risk Information

	Adjusted Odds Ratio (95% CI)		
Characteristic	Willingness	Worry	Perceived Chance
Female vs Male	0.47 (0.26 - 0.85)	2.46 (1.31 - 4.61)	3.62 (1.90 - 6.91)
Non-White vs White	0.47 (0.23 - 0.93)	2.30 (1.25 - 4.57)	2.09 (1.07 - 4.07)
Less vs More Education	0.84 (0.46 - 1.54)	1.92 (1.02 - 3.62)	2.79 (1.47 - 5.31)

Older vs Younger	0.54 (0.30 - 0.99)	0.91 (0.50 - 1.66)	1.62 (0.88 - 3.02)

Disclosure: L. Fraenkel, NIH, AF, 2 ; **E. Peters**, None.

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WCWL Rheumatology Priority Referral Score Reliability and Validity Testing. Avril Fitzgerald[1], Barbara Conner Spady[1], Carolyn DeCoster[1], Ray Naden[2], Gillian A. Hawker[3], Thomas Noseworthy[1] and the WCWL Investigators[4], [1]University of Calgary, Calgary, AB, [2]New Zealand Ministry of Health, Auckland, New Zealand, [3]Women's College Hospital, Toronto, ON, [4]Calgary, AB

Purpose: Rheumatology consultation demand exceeds supply of rheumatologists in many countries. Western Canada Waiting List (WCWL) has developed a diagnosis independent, priority-referral score (PRS) for rating relative urgency for referral to rheumatologists by primary care providers (PCPs). This paper reports the reliability and validity of the PRS.

Method: To develop WCWL PRS, a clinical panel of 5 rheumatologists and 5 PCPs, using anonymous case scenarios, engaged in a deliberative process leading to development of criteria and levels. Relative weights were generated using discrete choice experiment software (1000 Minds ®). Reliability and validity of PRS were tested independently with another 14 rheumatologists and 10 PCPs. These physicians clinically ranked, and then PRS scored, 16 case scenarios representative of the range of case-mix and urgency of referrals from PCPs to rheumatologists. Participants also rated relative urgency using visual analogue scale (VAS) and maximum acceptable waiting time (MAWT) for each case. Retesting was performed 6-12 weeks later, using altered case identifiers.

Results: The inter- and intra-rater reliability coefficients (ICC) for PRS and clinical ranking are shown for rheumatologists, and inter-rater reliability coefficients for PCPs (retesting in progress).

Inter-rater Correlation Coefficients (ICC) for Urgency Scores

	Rheumatologists		PCPs
Method	Time 1	Time 2	Time 1
PRS	0.80	0.80	0.81
Clinical Rank	0.81	0.78	0.60
VAS	0.70	0.75	0.69
MAWT	0.46	0.43	0.38

Intra-rater Correlation Coefficients (ICC) for Urgency Scores

Method	Rheumatologists	
	Average	Range
PRS	0.83	0.57-0.97
Rank	0.94	0.74-

		0.97
VAS	0.82	0.74-0.95
MAWT	0.85	0.65-0.96

Three emergent cases were correctly identified by 14, 12 and 10 rheumatolgists initially, and 14, 13 and 13 on retesting. These emergent cases were correctly identified by 10, 8 and 7 of the 10 PCPs.

Conclusion: Average correlation between rheumatologists' clinical rankings and PRS-derived rankings is moderately strong at 0.71. Inter-rater and intra-rater ICCs for clinical ranking and PRS for rheumatologists are strong and consistent over six weeks. PCPs demonstrate higher inter-rater reliability with PRS than clinical ranking. Using PRS, PCPs have similarly high inter-rater reliability as rheumatologists. Emergent cases are identified by rheumatologists correctly, or score high on urgency. These results show acceptable performance of the PRS, albeit further testing of specific case mix groups is required. Implementation and pilot testing is in progress.

Disclosure: A. Fitzgerald, None; **B. Conner Spady**, None; **C. DeCoster**, 3 ; **R. Naden**, None; **G. A. Hawker**, None; **T. Noseworthy**, None.

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Validation of Administrative Data to Identify Rheumatoid Arthritis. Liron Caplan[1], Jay R. McDonald[2], Janis Kuhn[2], Angelique L. Zeringue[2], Prabha Ranganathan[3], Lisa A. Davis[1], Fran Cunningham[4] and Seth A. Eisen[5], [1]Univ of CO Denver School of Med, Aurora, CO, [2]St. Louis Veterans Affairs Medical Center, St. Louis, MO, [3]Washington University, St Louis, MO, [4]Hines, IL, [5]St. Louis Veterans Affairs Medical Center, Washington, DC

Purpose: Observational studies frequently rely on International Classification of Diseases (ICD)-9 codes and pharmacy data to identify subjects with rheumatoid arthritis (RA). Prior studies have examined the diagnostic parameters for ICD-9 codes and/or pharmacy data, however, these studies have drawn subjects only from rheumatology clinics (Arthritis Rheum 2004;51(6):952-957; Arthritis Rheum 2000;40(9):1594-1600) or limited the eligible population to total knee replacement recipients (J Clin Epi 2003;56:515-519), introducing the possibility of bias. The purpose of our study was to determine the diagnostic metrics of ICD-9 codes for RA from inpatient and outpatient administrative data.

Methods: This retrospective study utilized administrative data from inpatient and outpatient national VA databases based on clinical encounters from 10/1998 until 9/2006. We defined RA by the presence of an ICD-9 code compatible with RA and a disease modifying antirheumatic drug (DMARD), and matched these cases to controls (subjects without an RA ICD-9). The sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy of the administrative data was then determined by applying two different gold standards, based upon the electronic medical record: 1) clinician documentation of RA; or 2) presence of at least 4 of 7 American College of Rheumatology Classification Criteria for RA.

Results: Diagnostic parameters listed in Table 1 were determined from a sample of 150 cases and 530 controls. Sensitivity was very high and specificity was modest, regardless of the chosen gold standard.

Conclusion: The combination of an ICD-9 compatible with RA and a DMARD is a highly sensitive method of identifying cases of rheumatoid arthritis from administrative data.

		Gold standard = Clinician documentation of RA			**Gold standard = At least 4 of 7 ACR criteria for RA**		
Parameter	**Definition**	Proportion	Confidence Interval		Proportion	Confidence Interval	
		Estimate	Lower	Upper	Estimate	Lower	Upper
Sensitivity	a/(a+c)	0.9933	0.9803	1.0064	1.0000	1.0000	1.0000

Specificity	d/(b+d)	0.7075	0.6688	0.7463	0.6104	0.5719	0.6489
Likelihood Ratio +	a/(a+c)/(b/b+d))	3.3966	2.9734	3.8800	2.5667	2.3251	2.8333
Likelihood Ratio -	c/(a+c)/(d/b+d))	0.0094	0.0013	0.0665	0.0000	#DIV/0!	#DIV/0!
Pos Pred value	a/(a+b)	0.4901	0.4339	0.5463	0.2105	0.1647	0.2564
Neg Pred value	d/(c+d)	0.9973	0.9921	1.0025	1.0000	1.0000	1.0000
Accuracy	(a+d)/(a+b+c+d)	0.7706	0.7390	0.8022	0.6471	0.6111	0.6830

Disclosure: L. Caplan, None; **J. R. McDonald**, None; **J. Kuhn**, None; **A. L. Zeringue**, None; **P. Ranganathan**, None; **L. A. Davis**, None; **F. Cunningham**, None; **S. A. Eisen**, None.

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Increased Risk of Lower Gastrointestinal Events (GI) in Rheumatoid Arthritis (RA). Elena Myasoedova, Nicholas J. Talley, Cynthia S. Crowson and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: There is strong evidence of increased risk of upper GI disorders in RA as compared to non-RA subjects. Lower GI complications in RA are much less studied. The purpose of this study was to estimate the risk of incident lower GI events in RA patients compared to non-RA subjects.

Method: We collected data on incident lower GI events from the medical records of a retrospectively identified population-based inception cohort of RA patients first diagnosed with RA (1987 ACR criteria) between 1/1/1980 and 1/1/1998. Data on incident lower GI events were obtained similarly for a comparison cohort of non-RA subjects from the same population matched for age, sex and calendar year to RA patients. Person-years methods were used to estimate the incidence of lower GI events within the RA and non-RA cohorts. Subjects with a history of upper and/or lower GI events prior to RA incidence date or the corresponding index date for non-RA subjects were excluded from the analysis of each individual GI event. Relative risks (RR) were estimated by dividing the rates of lower GI events in RA patients by the rates of those in non-RA subjects.

Results: The study population included 423 RA patients (mean age [SD] 56.5 [16.1], 68% female) and 422 non-RA subjects (56.3 [16.4], 68% female). Non-RA subjects had more diagnoses of lower GI events prior to the index date (p=0.03). Other baseline characteristics (number of upper GI diagnoses, number of surgeries and hospitalizations due to GI disorders prior to incidence/index date) were similar in both cohorts. RA patients were more likely than non-RA subjects to experience lower GI bleeding/perforation (RR 1.5; 95% confidence interval [CI] 1.01,2.1), diverticulitis (RR 2.6; 95% CI 1.3, 5.5), lower GI ulcers (RR 2.9; 95% CI 1.2, 9.1) and appendicitis (RR 4.7; 95% CI 1.1, 66.5). RA patients were more likely than non-RA subjects to undergo any lower GI surgery (RR 1.8; 95% CI 1.1, 3.0), particularly surgery due to bowel obstruction (RR 2.5; 95% CI 1.01, 8.0). RA patients had higher risk of hospitalization for any GI-related reason (RR 1.7; 95% CI 1.2, 2.3). In particular, RA patients were more likely to be hospitalized for diverticular disease (RR 3.5; 95% CI 1.7, 8.2), GI bleeding/perforation (RR 1.8; 95% CI 1.2, 2.7) and infectious colitis (RR 2.5; 95% CI 1.01, 8.0). No differences were found between RA and non-RA subjects regarding the risk of other lower GI events such as erosions and vasculitis.

Conclusion: RA patients are at increased risk of incident lower GI events as compared to non-RA subjects. RA patients have increased risk for surgical interventions and hospitalizations for lower GI events than subjects without RA. Further studies are underway to determine the reasons for the increased risk of lower GI events in RA.

Disclosure: E. Myasoedova, Roche Pharmaceuticals, 2 ; **N. J. Talley**, Roche Pharmaceuticals, 2 ; **C. S. Crowson**, Roche Pharmaceuticals, 2 ; **S. E. Gabriel**, None.

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Are Rheumatoid Arthritis Patients Experiencing Less Coronary Heart Disease in Recent Years? Cynthia S. Crowson, Elena Myasoedova, Veronique Roger, Eric L. Matteson, Hilal Maradit Kremers, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of coronary heart disease (CHD) and heart failure (HF). The purpose of our study was to examine whether the risk of CHD and HF in RA patients has changed in recent years.

Method: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA between 1-1-1980 and 1-1-2008 was assembled and followed until death, migration, or 7-1-2008. The presence of CHD (physician diagnosis of coronary artery disease, hospitalized or silent myocardial infarction [MI], revascularization, angina) and HF (Framingham diagnostic criteria) was ascertained by review of the medical record. Cox proportional hazards models with age as the time scale and adjusted for sex were used to assess the risk of CHD and HF according to calendar year of RA incidence (1980-84 vs. 1995-2007). Patients with CHD or HF prior to RA incidence were excluded from the analyses.

Results: The study included 741 RA patients (mean age [SD] 56 [15.8] years, 69% women). The patients were followed up for a mean of 9.6 years during which 89 patients developed CHD (excluding 83 patients with CHD prior to RA incidence] and 82 patients developed HF (excluding 20 patients with HF prior to RA incidence). The 5 year risk of CHD was 7.0% and 4.9% for patients with incident RA in 1980-94 and 1995-2007, respectively. The age and sex adjusted risk of CHD was significantly lower in 1995-2007 compared to 1980-94 (hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.35, 0.95; p=0.03). The 5 year risk of HF was 6.0% and 5.5% for patients with incident RA in 1980-94 and 1995-2007, respectively). The age and sex adjusted risk of HF was similar in 1995-07 compared to 1980-94 (HR: 0.87; 95% CI: 0.54, 1.40; p=0.57).

Conclusion: The risk of CHD for patients with incident RA declined over time, but the risk of HF was unchanged. This suggests that efforts to reduce CHD risk in RA patients may have been effective in reducing the excess burden. However, the mechanism underlying HF in RA patients may differ from that of CHD. More research is needed to understand the reasons for these trends in the risk of CHD and HF in RA along with intensification of the efforts to prevent HF.

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The Effect of Hydroxychloroquine and Methotrexate On Glycated Hemoglobin. Laura R. Rekedal, Elena Massarotti, Rajesh K. Garg, Radhika Bhatia, Bing Lu and Daniel H. Solomon, Brigham & Women's Hospital, Boston, MA

Purpose: Cardiovascular disease is a common comorbidity of many rheumatic diseases and inflammation appears to promote insulin resistance. Data suggest that hydroxychloroquine (HCQ) may improve insulin metabolism and lower glycated hemoglobin (HbA1c) in non-rheumatic patients. Additionally, epidemiologically it may reduce the risk of diabetes among those with RA. However, there is little information on HCQ's effect on rheumatic disease patients with diabetes mellitus (DM) or the effect of methotrexate (MTX) on HbA1c. We examined medical records of patients with DM to measure changes in HbA1c from before to after starting HCQ or MTX.

Method: We utilized a longitudinal medical record system to search for patients who meet all of the following criteria: a) initiated either HCQ or MTX, b) have a diagnosis of DM or HbA1c $\geq$ 7%, and c) have 2+ HbA1c measurements. The individuals meeting these criteria, with HbA1c readings both before and within 12 months after initiation of the drugs of interest, were reviewed using a structured data abstraction form examining rheumatologic diagnosis (RA, SLE, or other rheumatologic condition), use of oral corticosteroids in the twelve months post-HCQ or MTX initiation, body mass index (BMI), age, and gender. Adjusted linear regression models were examined to determine change in HbA1c from pre-drug values to lowest post-drug values within twelve months. **Results:** We identified 82 patients who met inclusion criteria: 45 HCQ users and 37 MTX users. The patients were similar in age (mean 61), gender (79% female) and mean pre-drug HbA1c levels (HCQ 7.71% and MTX 7.38%, p = 0.35). Mean BMI for HCQ users (35.4 kg/m^2) was slightly higher than MTX users (32.2 kg/m^2). Steroid use in the 12 months after DMARD initiation was more common in MTX (44%) than HCQ (33%). The mean reduction in HbA1c between pre and post HCQ was 0.66% (95% CI 0.26 – 1.05) versus 0.11% (95% CI -0.18- 0.40) for MTX. In fully adjusted analyses the drop in HbA1c among HCQ users was 0.54% greater than the drop among MTX users (p = 0.041).

Conclusion: HCQ initiation was associated with a significant reduction in HbA1c among rheumatic disease patients with DM or pre-treatment HbA1c ≥ 7%. MTX may be associated with a reduction in HbA1c but our sample size was small and there were several possible confounders. This work is an extension of previous randomized controlled trials of anti-malarials in non-rheumatic diabetic populations, in whom HCQ was associated with a significant reduction in HbA1c. Further prospective studies are warranted to determine the clinical relevance of HCQ's potential benefits on insulin resistance in rheumatic disease.

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Different Utility Measurement Instruments May Not Discriminate Across Disease Severity: Results From a Cohort of Rheumatoid Arthritis Patients in Portugal. Elizabeth Benito-Garcia[1], Sofia Pedro[1], Joana Vasconcelos[1], Rita A. Marques[1], Andreia Rodrigues[1], Irina Chaves[1] and Pieter Drost[2], [1]Bioepi, Oeiras, Portugal, [2]Bristol-Myers Squibb International Corporation, Braine-l'Alleud, Belgium

Purpose: Decision-making in Rheumatoid arthritis (RA) is often based on non-specific disease outcome measures as improvement in Health-Related Quality of Life (HRQoL). It is therefore crucial that HRQoL discriminate across RA severity. Several utility measures have been validated, either direct (i.e. standard gamble) or indirect (i.e. EuroQol (EQ-5D), Brazier's Short Form-6D (SF-6D), VAS-QoL). These utility values are commonly mapped to the Health Assessment Questionnaire (HAQ) to discriminate HRQoL across different RA disease states. We evaluated whether the EQ-5D, SF-6D and the VAS would lead to similar utility values and if they would discriminate across disease severity among a cohort of RA patients in Portugal.

Method: A total of 713 patients from an ongoing biannual cohort of Portuguese RA patients since 2003 (NDB-Portugal), were included in this study. Utility measures were assigned to each level of HAQ defined from previously determined cut off points, using 0.50 intervals. Mean and standard deviation utility measures were calculated using the last observation per patient.

Results: Table 1 shows the results of the utility measures per level of HAQ (by 0.50 intervals).Overall, utilities decreased as HAQ scores worsened. However, the mean utility values of patients varied significantly depending on the utility measurement method. Mean utility measured using the EuroQOL-5D was 0.48 and mean HAQ was 1.4 (0-3, 3 corresponding to the worst disability). Utilities per HAQ intervals using SF-6D did not differentiate across the different levels of disease severity (HAQ 0-0.5 = 0.67 ; HAQ 2.5-3 = 0.55). The EQ-5D differentiated more across the severity groups (HAQ 0-0.5 = 0.83 ; HAQ 2.5-3 = 0.08). VAS-Qol only discriminated marginally (HAQ 0-0.5 = 0.74 ; HAQ 2.5-3 = 0.45).

Conclusion: In a cohort of Portuguese RA patients, different utility measurement instruments resulted in different utility scores. Furthermore, not all utility measures discriminated across disease severity. The results of this analysis show that the use of different HRQoL measurement instruments may lead to different utility values, and therefore, to different resource allocation decisions.

Table 1. Euro-Qol, SF-6D and VAS-QoL utility measures for RA patients stratified by level of HAQ using 0.50 intervals.

	EQ-5D (n=672)			**SF-6D (n=471)**			**VAS-QoL (n=516)**		
HAQ Score	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
0.0≤0.5	0,83	0,18	110	0,67	0,10	70	0,74	0,19	91
0.5<&≤1.00	0,69	0,23	106	0,59	0,07	68	0,60	0,19	85
1.00<&≤1.5	0,55	0,28	165	0,60	0,08	117	0,59	0,21	127
1.50<&≤2	0,37	0,30	138	0,56	0,07	104	0,54	0,20	98
2.00<&≤2.5	0,31	0,28	119	0,55	0,06	86	0,51	0,21	89
2.5<&≤3.00	0,08	0,18	34	0,55	0,06	26	0,45	0,28	26
Total	0,51	0,33	672	0,59	0,08	471	0,59	0,22	516

Disclosure: E. Benito-Garcia, Bristol-Myers Squibb, 5 ; **S. Pedro**, Bristol-Myers Squibb, 5 ; **J. Vasconcelos**, Bristol-Myers Squibb, 5 ; **R. A. Marques**, Bristol-Myers Squibb, 5 ; **A. Rodrigues**, Bristol-Myers Squibb, 5 ; **I. Chaves**, Bristol-Myers Squibb, 5 ; **P. Drost**, Bristol-Myers Squibb, 3 .

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Mortality Trends Related to Dermatomyositis and Polymyositis, State of Sao Paulo, Brazil, 1985-2007: A Study Using Multiple-Cause-of-Death. Deborah C.C. Souza[1], Augusto H. Santo[2], José M.P. Souza[2], Celso Escobar Pinheiro[3] and Emilia I. Sato[1], [1]Escola Paulista de Medicina, Sao Paulo, Brazil, [2]Faculdade de Saude Publica/USP, Sao Paulo, Brazil, [3]Datasus, Ministério da Saúde, Rio de Janeiro, Brazil

Background: Dermatomyositis (DM) and polymyositis (PM) are rare systemic autoimmune rheumatic diseases with high fatality rates. Population-based mortality studies in DM/PM are few around the world and absent in Brazil.

Purpose: To study the mortality related to DM/PM in the State of Sao Paulo, Brazil, from 1985 to 2007.

Methods: The mortality data came from the annual multiple-cause-of-death files of the State Data Analysis System Foundation, the institution in charge of vital statistics in Sao Paulo. All deaths which listed DM or PM on any line of the medical form of the death certificate were selected. The variables sex, age and underlying, associated or total mentions of causes of death were studied. Statistical analyses were performed by chi-square and H Kruskal-Wallis tests, variance analysis and linear regression. A p value less than 0.05 was regarded as significant.

Results: In this period 318 deaths related to DM and 316 related to PM occurred. Among them 55.2% were selected as an underlying cause and 44.8% as an associated cause of death. Seventy-one percent of deaths occurred among women. The DM age-and sex-standardized mortality rates did not present significant trend variation, however a decrease of PM underlying and total mentions death rates was observed ($p<0,05$). Considering all DM and PM deaths for the entire period, the mean ages at death were 47.76±20.81 and 54.24± 17.94, respectively ($p=0.0003$) and the mean standardized mortality rates were 0.39 deaths per million inhabitants in both DM and PM. Among PM deaths in women an increasing mean age at death was observed over the 23 years period ($p=0.004$). For DM and PM as an underlying cause, the main associated causes of death were, respectively: pneumonias (43.8%; 33.5%), respiratory failure (34.4%; 32.3%), interstitial pulmonary diseases and others pulmonary conditions (28.9%; 17.6%) and septicemias (22.8%; 15.9%). Among DM and PM deaths as an associated cause, the main underlying causes of death were, respectively, respiratory disorders (28.3%; 26.0%), circulatory disorders (17.4%; 20.5%), neoplasms (16.7%; 13.7%), infectious and parasitic diseases (11.6%; 9.6%) and gastrointestinal disorders (8.0%; 4.8%). Among 318 deaths related to DM, 36 neoplasms, and among 316 related to PM, 20 neoplasms occurred concurrently ($p=0.03$).

Conclusion: The mortality related to DM occurs at an earlier age in relation to PM deaths. The increase of the mean age of female deaths observed in deaths related to PM might reflect an increase in life expectancy of the state population. The association between neoplasms and DM and in lower degree with PM deaths is consistent with latest researches. Practically half of deaths related to DM and PM have been underestimated in primary mortality statistics, where DM reaches 28,4% and PM 26,8% as an underlying cause of death. The comprehension of the natural history of DM/PM has been extended due to the consideration of all mentions of causes of death.

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Race Is Associated with the Risk of Developing Hyperuricemia in Men: Findings From the Coronary Artery Risk Development in Young Adults (CARDIA) Cohort. Angelo L. Gaffo[1], David R. Jacobs Jr.[2], Cora E. Lewis[3], T. R. Mikuls[4] and Kenneth G. Saag[3], [1]Birmingham VA Medical Center, Birmingham, AL, [2]University of Minnesota, Minneapolis, MN, [3]University of Alabama at Birmingham, Birmingham, AL, [4]U Nebraska, Omaha, NE

Purpose: The association between race and serum urate (SU) concentrations has not been well defined. Some but not all studies suggest that being African-American has an independent association with higher concentrations of serum urate. We sought to determine if this was true in a bi-racial cohort of young African-Americans and Whites.

Methods: Data from 5115 participants at cohort baseline and follow-up of up to 20 years was utilized, with balanced proportions of Caucasians and African Americans. SU was measured at baseline and at years 10, 15, and 20 of follow-up. The relationships between SU, hyperuricemia (defined as a SU of 6.8 mg/dL or more), and race/ethnicity were determined in sex-specific multivariable adjusted cross-sectional and Cox-proportional hazard analyses. The latter analysis was performed only among those who did not have

hyperuricemia at baseline. Covariates included age at inception, body mass index, development of hypertension, serum creatinine, medication use, diet and alcohol intake, and menopausal symptoms in women.

Results: Referent to Whites, African-American men and women had significantly lower concentrations of SU at the beginning of follow-up. For African-American men the risk of developing hyperuricemia compared with Whites was significantly decreased by approximately 30% at year 20, after multivariable adjustment. African-American women had an approximate 43% greater risk of developing hyperuricemia when compared to Whites, but this increase was not significant after multivariable adjustment (Table). Renal function, presence of hypertension, and use of diuretics had stronger associations with higher concentrations of SU in women than in men.

Conclusion: Contrary to what has been previously reported and hypothesized given the association between race and hypertension, we found that African-American men had lower risks of developing hyperuricemia than Whites and African-American women had a non-significant increased risk. Differences in renal handling of SU, like higher rates of filtration with lower rates of excretion or reabsorption in African-American men could help explaining these findings.

Table. Sex-specific, multivariable-adjusted risk of developing hyperuricemia* by race (HR=Hazard ratio, CI=Confidence interval, AA= African-Americans, NA=not applicable).

	Men HR	**95% CI**	**Women HR**	**95% CI**
	AA vs. Whites (ref)		**AA vs. Whites (ref)**	
Age-adjusted	0.88	0.74-1.04	2.78	2.02-3.85
Model 1	0.77	0.64-0.93	1.51	1.07-2.14
Model 2	0.67	0.55-0.82	1.26	0.87-1.84
Model 3	NA		1.43	0.90-2.28
Hyperuricemia**	32%		7%	

Model 1: adjusted for age at inception, average BMI, average serum creatinine, use of diuretics, use of antihypertensive medication
Model 2: Model 1 + average intake of beer, wine, liquor, meat, seafood, dairy, total protein
Model 3: Model 2 + self report of menopause (women only)
*Defined as a SU of 6.8 mg/dL or more
**At the end of 20 years of follow-up, only among those without hyperuricemia at baseline

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Obesity, Weight Gain, and Risk of Prevalent Gout in Women in the Atherosclerosis Risk in Communities (ARIC) Study. Janet W. Maynard[1], Mara A. McAdams[2], Alan N. Baer[1], Anna Kottgen[2], Josef Coresh[2] and Allan C. Gelber[1], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins School of Public Health, Baltimore, MD

Purpose: Gout is a major form of inflammatory arthritis in women; yet, few studies have focused on the epidemiology of gout in women. In the Atherosclerosis Risk in Communities (ARIC) Study, we evaluated the relationship of obesity, and of weight change, with gout in women.

Methods: ARIC is a population-based cohort study of 15,792 individuals (55% women) recruited in 1987-1989. Our study population consisted of African-American and Caucasian women who were followed for up to 12 years. A woman was considered to have gout if one or more of the following criteria were met: [a] gout was self-reported, [b] surveillance of hospital discharge summaries revealed an ICD-9 code for gout (274.0, 274.1, 274.8, or 274.9), or [c] use of a medication taken exclusively to treat gout at any study visit. Anthropometric variables were obtained at cohort entry. We grouped body mass index (BMI) into 5 categories: <25, 25-30, 30-35, 35-40, and >40. Obesity was defined as BMI >30. High waist-to-hip ratio (WHR) was defined as >0.8. Weight change was calculated by subtracting the participant's weight at cohort entry from her self-reported weight at age 25. Weight change was categorized as: no weight change (weight loss or gain

<10 lbs), low weight gain (weight gain of >10 to <30lbs), and high weight gain (>30 lbs). Baseline characteristics included dietary habits, comorbidities, and medication use. Prevalence ratios rather than odds ratios were used as gout was not a rare outcome.

Results: 399 women (4.8%) have gout in the ARIC cohort. Higher BMI, weight gain, and weight at age 25 are strong risk factors for gout in women.

	Unadjusted		Adjusted^	
	PR	CI	PR	CI
BMI				
<25 (reference)	1.0		1.0	
25-30	2.22	1.61-3.04**	1.66	1.19-2.32**
30-35	3.56	2.59-4.91**	2.47	1.76-3.47**
35-40	6.10	4.37-8.51**	3.72	2.57-5.37**
>40	8.55	6.02-12.13**	5.39	3.64-7.99**
Obesity	3.18	2.62-3.86**	2.30	1.86-2.83**
High WHR	2.64	1.73-4.04**	1.78	1.14-2.78*
Weight change				
No change (reference)	1.0		1.0	
Low weight gain	1.65	1.12-2.42*	1.50	1.02-2.22*
High weight gain	2.99	2.11-4.24**	1.99	1.38-2.85**

^ Adjusted for baseline age, race, organ meat, protein, alcohol, and shellfish intake, diuretic and oral contraceptive pill use, menopausal status, hypertension, diabetes, and chronic renal insufficiency.

Key: PR=Prevalence ratio; CI=confidence interval; BMI=body mass index; WHR=waist-to-hip ratio

*=p<0.05 **=p<0.001

Conclusion: Obesity, elevated waist-to-hip ratio, and weight gain are strongly related to risk of prevalent gout in women. The magnitude of the association between both BMI and weight gain with gout became greater with increasing categories, indicative of dose-response relationships. To our knowledge, our study is the first to demonstrate an association between anthropometric measures and gout in women. The mechanisms by which obesity predisposes to gout are important to elucidate and may offer complementary management strategies.

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Factors Associated with Prolonged Follow-up of Osteoarthritis in a Tertiary Level Rheumatology Service. Carol M. Sinnott, John Stack and Sinead Harney, Cork University Hospital, Cork, Ireland

Purpose: Osteoarthritis (OA) is the commonest cause of disability in the elderly and the second most common diagnosis made in older patients attending their general practitioner. 25% of people over 55 years have OA associated pain. The mainstay of healthcare provision in this group occurs in a primary care setting, with referral to tertiary rheumatological outpatients (ROP) only made in severe, complex or unclear cases. Given the high prevalence of the disease, ongoing follow-up of these patients at ROP has a considerable impact on services, where long waiting lists already exist. The aim of this study was to examine factors associated with prolonged follow-up of patients with OA at a tertiary level rheumatology department, in an effort to optimize the outpatient service provided.

Method: A retrospective review of eighty consecutive patients with a diagnosis of OA attending ROP was performed. All patients were referred by their general practitioner. OA was clinically and radiologically diagnosed. Exclusion criteria included a history of inflammatory arthritis, connective tissue disease, gout or other active medical conditions. Prolonged follow-up was defined as greater than the median number of consultations. Data was collected on sociodemiographic variables, disease characteristics, use of diagnostic tools and attendance at ROP. Statistical analysis was conducted using Minitab 15.

Results: 80 patients were included in the analysis. 81.25% (n=65) were female. The mean age was 62years (SD 11, IQ range 56 to 72). The median number of consultations per patient was 3 (IQ range, 2 to 5). 42.5% (n=34) patients had greater than 3 consultations. Table 1 demonstrates diagnostic tools and management options used.

Table 1. Investigations and Management Options Used

Investigations requested	**No of patients (%)**
Plain radiographs	78 (97.5%)
Magnetic resonance imaging	16 (20%)
Auto-antibodies	53 (66.25%)
Inflammatory markers	63 (78.75%)
Management options used	
Paracetamol	43 (53.75%)
Nonsteroidal anti-inflammatories	29 (36.25%)
Opiates	42 (52.5%)
Glucosamine	9 (11.25%)
Physiotherapy referral	56 (70%)
Orthopaedic referral	24 (30%)
Weight loss advice	7 (8.75%)

On univariate analysis, prolonged follow- up was associated with age greater than 70years ($p<0.05$), referral for magnetic resonance imaging ($p<0.05$), prescription of opiate analgesia ($p<0.05$) and referral to orthopaedic ($p<0.05$) or physiotherapy services ($p<0.05$). On multivariate regression analysis for number of consultations versus significant factors on univariate analysis, referral to orthopaedic services and older age were significantly associated with longer follow-up.

Conclusion: Patients who require prolonged follow up for OA in ROP are older and require orthopaedic referral. A potential explanation for this is the long wait list that exists for orthopaedic outpatient consultation, necessitating interval review at ROP. Strategies that increase the capacity of orthopaedic services or enhance appropriate referral from the primary care sector direct to orthopaedic services may help reduce the necessary number of patient visits to ROP, thereby optimizing use of and access to tertiary rheumatological services.

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Work Productivity Measures as Treatment Goals Beyond Signs and Symptoms. V. Strand[1], O. Purcaru[2] and Arthur Kavanaugh[3], [1]Stanford University, Palo Alto, CA, [2]UCB, Brussels, Belgium, [3]UCSD, San Diego, CA

Purpose: Rheumatoid arthritis (RA) significantly impairs patients' ability to work outside the home and to perform household duties and participate in leisure, social and family activities. However, data from randomized, controlled trials (RCTs) on treatment impact on work and home productivity are limited. This analysis reviews the available productivity data from RCTs of anti-TNF agents in early- and late-stage RA.

Method: Published studies of anti-TNFs for the treatment of both early- and late-stage RA were examined for productivity measures. 6 studies were identified: 4 in early RA (ASPIRE, COMET, DE032 [PREMIER companion study], and PROWD), and 2 in late-stage RA (RAPID 1 and 2) (Table). ASPIRE, COMET, and PROWD assessed changes in employment or working time lost; DE032 and RAPID 1 and 2 assessed absenteeism (work days missed due to RA) and presenteeism (decreased productivity at work). DE032 and RAPID 1 and 2 also assessed home productivity.

Results: All 6 trials showed that anti-TNFs significantly decrease productivity losses at paid work, although all used different measures (Table). DE032 and RAPID 1 and 2 also demonstrated that anti-TNFs significantly decrease productivity losses at home. Results from RAPID 1 and 2 using the novel Work Productivity Survey demonstrated that certolizumab pegol significantly reduces household days lost, household days with productivity reduced ≥50%, and days of lost participation in family, social and leisure activities relative to PBO + MTX.

RCT	**Work Productivity**		**Home Productivity**	
ASPIRE (Change from BL to Wk 54)	PBO + MTX	INF + MTX		
Became unemployable	14%	8%*		
Became employable	36%	40%		
COMET (Wk 52)	PBO + MTX	ETN + MTX		
Stopped work since prior visit	24%	9%*		
PROWD (Wk 56)	PBO + MTX	ADA + MTX		
Working time lost	18.4%	8.6%*		
All cause or impending job loss	39.7%	18.7%*		
DE032 (Wk 52)‡	PBO + MTX	ADA + MTX	PBO + MTX	ADA + MTX
Days missed due to RA	24	11*	12	6*
Degree of work performance affected (0-100 VAS; change from BL)	-28.2	-35.8*	-26.8	-36.6*
RAPID 1 (Wk 52)	PBO + MTX	CZP† + MTX	PBO + MTX	CZP† + MTX
Days missed due to RA per month	4.5	1.0*	7.2	2.4*
Days with productivity reduced by ≥50% per month	4.4	2.1*	7.3	4.2*
Days missed social/family/leisure activities per month			3.7	1.6*
RAPID 2 (Wk 24)	PBO + MTX	CZP† + MTX	PBO + MTX	CZP† + MTX
Days missed due to RA per month	2.5	1.3	6.5	2.7*
Days with productivity reduced by ≥50% per month	9.3	3.1*	9.2	5.2*

Days missed social/family/leisure activities per month			3.8	1.4*

*P≤0.05 vs control group. †CZP 200 mg group. ‡Home productivity results based on homemakers only.

ADA=adalimumab; CZP=certolizumab pegol; ETN=etanercept; INF=infliximab; PBO=placebo.

Conclusion: Reductions in productivity loss may substantially improve the overall quality of life for patients with RA. Productivity measures, which assess both work and home productivity should be considered for inclusion into RCTs as well as registries for patients with RA.

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Factors Associated with Fatigue in Early Arthritis: Results From the ESPOIR Cohort. AC Rat[1], J. Pouchot[2], B. Fautrel[3], P. Boumier[4], P. Goupille[5] and F. Guillemin[6], [1]Nancy-University CIC-EC CIE6, Nancy, France, [2]Paris University, Internal medicine, France, [3]Rheumatology, Paris VI University, France, [4]CHU Amiens, France, [5]Tours university, France, [6]Nancy-University EA 4003, France

Purpose: Fatigue has a major impact on patients in early arthritis (EA) and its measure is highly recommended. However, to interpret such a measure, factors associated with fatigue and its change should be known not only in established rheumatoid arthritis (RA) but also in EA. The aims of this study based on the data of the ESPOIR cohort, were: 1) to study determinant factors of fatigue in patients with early arthritis at baseline, 2) to analyse factors associated with fatigue changes during the first year following inclusion.

Method: The ESPOIR cohort is a multicenter national cohort of 813 patients followed for arthritis of less than 6 months duration. At baseline and at each visit (every 6 months) a set of clinical and biological variables are recorded: sociodemographic, disease characteristics, and patient reported outcome measures (fatigue visual analogue scale (f-VAS), SF36, AIMS2-SF). Determinant factors of fatigue were studied with various regression models using the f-VAS and the vitality dimension of the SF36 as dependant variables for fatigue assessment.

Results: A total of 813 patients with early arthritis (48 ± 13 years, 77% women, DAS28 11 ± 1, ACR criteria for RA 71%) were included. At baseline, only 22% of the patients reported having no fatigue (f-VAS ≤ 20 mm).The level of fatigue decreased at 6 months and then remained stable at 1 year. Results of the multivariate analysis of determinant factors of fatigue at baseline are reported in the table. Over time, factors independently associated with a higher fatigue level decrease were a larger improvement of physical function (p=0.03) and mental health (p<.0001) dimensions of the AIMS2-SF for the model with the vitality dimension of the SF36,and a larger improvement of the DAS28 (p=0.003), and of the mental health (p<.0001) dimension of the AIMS2-SF and the absence of a Sjogren syndrome (p=0.001), for the model with f-VAS.

Conclusion: Factors associated with fatigue are slightly different for the 2 studied measures of fatigue. Demographic, patient, and disease characteristics and QoL are independently associated with fatigue at baseline. The evolution of fatigue is mainly associated with the evolution of the different dimensions of QoL.

Table: determinant factors of fatigue at baseline: multivariate analysis

	Vitality (SF36) (R^2=0.44)		Fatigue (VAS) (R^2=0.24)	
	ß	p	ß	p
Age	0.1(0.0)	0.009	-0.2(0.1)	0.003
Sex (male/female)		NS	5.8(2.2)	0.007
Socio-economic level (low/interm/high)	1.8(0.6)	0.005	-4.0(1.1)	0.0003

Smoker (yes/no)		NS	-5.9(2.2)	0.008
Comorbidity (yes/no)	2.2(1.1)	0.05	4.1(1.9)	0.03
Wake up at night (yes/no)	-2.0(1.2)	0.09	4.6(2.1)	0.03
DAS28	-1.1(0.5)	0.03	2.3(0.8)	0.007
Sjrogren syndrom (yes/no)		NS	7.5(2.1)	0.0003
AIMS2-SF physical function	-2.1(0.4)	<.0001	1.7(0.7)	0.01
AIMS2-SF symptoms	-2.1(0.5)	<.0001	0.8(0.5)	NS
AIMS2-SF mental health	-6.3 (0.7)	<.0001	2.4(0.5)	<.0001

SF36 and AIMS2-SF scores range from 0 (worst QoL) to 100 (best QoL). Fatigue VAS range from 0 (no fatigue) to 100 (worse fatigue)

Disclosure: A. Rat, None; **J. Pouchot**, None; **B. Fautrel**, None; **P. Boumier**, None; **P. Goupille**, None; **F. Guillemin**, None.

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Relationship Between Radiographic Damage and Employment Over Time in Patients with Early Rheumatoid Arthritis (RA): Results From the PREMIER Health Economic Companion Study DE032. Ronald van Vollenhoven[1], Mary Cifaldi[2], Sanjoy Roy[2], Naijun Chen[2] and Martin J. Bergman[3], [1]Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden, [2]Abbott Laboratories, Abbott Park, IL, [3]Taylor Hospital, Ridley Park, PA

Purpose: The relationship between joint damage and outcomes in early RA is poorly characterized. We evaluated the relationship between radiographic progression and employment status in the PREMIER health-economic companion study DE032.

Methods: PREMIER was a 2-year, multi-center, randomized, double-blind trial of adalimumab (ADA), methotrexate (MTX), and ADA+MTX in patients with early RA (<3 years). The DE032 companion study collected pharmacoeconomic data on a large subset of participating patients. A multivariate logistic regression model was used to evaluate the association between baseline radiographic scores (modified total Sharp score [mTSS]) and baseline self-reported employment status, with adjustments for age, sex, and baseline Health Assessment Questionnaire (HAQ). A receiver-operating characteristic (ROC) analysis determined the baseline mTSS cut-off value to differentiate between employed vs. unemployed patients with an optimum balance between sensitivity and specificity. Generalized estimating equation (GEE) models were used to estimate the relationship between mTSS and employment status over time, controlling for age, sex and HAQ. At the end of the study, whether patients gained or retained their employment was compared for patients who were radiographic progressors (ΔmTSS>0) vs. those who were non-progressors (ΔmTSS≤0) within treatment groups.

Results: At baseline, 55% of patients were employed, and patients with lesser mTSS scores were more likely to be employed. For each unit increase of the mTSS, patients had 1.2% decreased odds of being employed ($p< 0.05$) compared with those with a 1-point lesser score. An absolute mTSS of 14 was the cut-off value for being employed with the greatest sum of sensitivity (60%) and specificity (58%). Over 2 years, patients with greater mTSS progression were more likely to stay or become unemployed; a 1-point increase in mTSS was associated with 1.1% decreased odds of being employed ($p<0.01$). Further, patients with mTSS>14 were 40% more likely to be unemployed than patients with mTSS≤14. The ADA+MTX group was more likely to have unchanged or decreased mTSS (non-progressors) and retained or gained employment than the MTX group (29% vs. 11%, $p<0.0001$). Patients who were progressors and lost employment or stayed unemployed were less likely to be in the ADA+MTX group than the MTX group (19% vs. 29%; $p<0.001$).

Conclusion: Patients with early RA with lesser baseline mTSS were more likely to be employed than patients with greater mTSS. Over 2 years, the beneficial radiographic effect of combination therapy with ADA+MTX was associated with more favorable employment status.

Disclosure: R. van Vollenhoven, Bristol Meyers Squibb, 5, Schering-Plough, 2, Abbott Laboratories, 5, Wyeth Pharmaceuticals, 2, Roche, 2, Centocor, Inc., 2, Bristol Meyers Squibb, 2, Abbott Laboratories, 2, Centocor, Inc., 5, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Schering Plough, 5 ; **M. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **S. Roy**, Abbott Laboratories, 3 ; **N. Chen**, Abbott Laboratories, 3 ; **M. J. Bergman**, Abbott Laboratories, 5,

Abbott Laboratories, 2, Abbott Laboratories, 8, Amgen, 5, Amgen, 2, Bristol Meyers Squibb, 8, Bristol Meyers Squibb, 5, Bristol Meyers Squibb, 2, UCB, 8, UCB, 5, Roche/Genentech, 5 .

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Care for RA Has Not Improved Overtime: A Population Based Study. Diane V. Lacaille[1], M. Mushfiqur Rahman[2] and John Esdaile[3], [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada / University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Purpose: Treatment guidelines for rheumatoid arthritis (RA) have shifted to early, aggressive, and persistent use of disease-modifying anti-rheumatic drugs (DMARDs) and referral to a rheumatologist when possible. Previous quality of care studies in RA have consistently shown suboptimal care. The purpose of this study was to evaluate whether compliance with guidelines, and quality of care for RA, have improved over time.

Method: Using administrative billing data from the Ministry of Health, we have assembled a population-based cohort of all RA cases who received care by a physician for RA between 01/1996 and 03/2006. Previously published RA criteria included: at least 2 MD visits, at least 2 mos apart, where ICD-9 code for RA was used for reimbursement of MD visits. Cases were excluded if they had at least 2 subsequent visits for another type of inflammatory arthritis, if assessment by a rheumatologist did not confirm the diagnosis of RA made by another physician, or if no subsequent RA visits occurred over > 5 years. Administrative data on all health care services used were obtained, including all meds, MD visits, hospitalizations and procedures. To evaluate quality of care over time, we compared the cumulative incidence of first DMARD use and rheumatologist referral in 3 incident cohorts with first RA visits in 1997-99; 1999-01 and 2001-03, using Kaplan Meier analysis. We also compared prevalence of DMARD use and other quality of care indicators, over a 3 year period, in 3 prevalent cohorts followed over the years: 1997-99; 2000-02; 2003-05.

Results: Our population-based cohort includes 37,151 RA cases with 192,735 person-yr of follow-up, yielding an RA prevalence of 0.96%. The cumulative incidence of first DMARD use over 3 years of follow-up after diagnosis, was 25% after 1 yr, 28% after 2 yrs and 30% after 3 yrs, in the incident cohort diagnosed in 1997-99. DMARD use did not improve in incident cohorts diagnosed later, with incidence of DMARD use of 25% and 26% at 1 yr, and of 29% and 30% at 3 yrs, in the 1999-2001 and 2001-2003 incident cohorts, respectively. Cumulative incidence of rheumatologist referral at 3 yrs was 38%, 38% and 40% for the 1997-99, 1999-01, and 2001-03 incident cohorts, resp. Prevalence of DMARD use, rheumatologist referral and other quality of care indicators did not increase over time either, when assessed over 3 year periods in prevalent cohorts (Table 1).

	1997-1999 cohort N = 16,989	2000-2003 cohort N = 23,572	2003-2005 cohort N = 26,748
DMARD use	48.7%	45.2%	49.6%
Referral to rheumatologist	45.2%	42.5%	46.8%
Proportion of time on DMARDs once started	78%	79%	80%
Glucocorticosteroid use	38.8%	35.3%	36.9%
Traditional NSAID use	66.3%	56.3%	55.5%
Coxib use	17.9%	37.3%	30.2%
Orthopedic procedure	3%	1.9%	1.4%

Conclusion: Care for RA remains suboptimal despite current treatment guidelines and does not appear to have improved over time. Efforts to educate family physicians and consumers about the shift in RA treatment paradigms and to improve access to rheumatologists are needed.

Disclosure: D. V. Lacaille, None; **M. M. Rahman**, None; **J. Esdaile**, None.

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Impact of Maintaining Physical Function On Employment Status Over Time. Chris Bojke[1], Mary Cifaldi[2], Saurabh Ray[2] and B. Van Hout[3], [1]Pharmerit International, York, United Kingdom, [2]Abbott Laboratories, Abbott Park, IL, [3]University Medical Centre Utrecht, Utrecht, Netherlands

Purpose: This study analyzed the impact of physical functioning (measured by the Health Assessment Questionnaire [HAQ]) on self-reported employment status over time using econometric methods that use all time-point observations over the course of a 2-year study. Data were from PREMIER, a prospective, multicenter, randomized, double-blind, active comparator-controlled, Phase III trial comparing treatment with adalimumab, methotrexate (MTX), and the combination of adalimumab plus MTX in patients with early RA.

Methods: The analysis included 664 patients who supplied self-reported responses over scheduled, unequally spaced time periods. Patients indicated whether they were employed (categorical response of employed, unemployed, or retired) and the extent to which RA had hindered work since the last observation on a continuous visual analog scale (VAS) response (0–100). Ordered, discrete categories were created by combining the discrete employment and continuous VAS responses into non-overlapping and exhaustive states (employed/VAS=0, employed/0<VAS≤25, employed/25<VAS≤50, employed/50<VAS≤100, unemployed, retired). HAQ status over time was coded as weeks spent in each HAQ category (0, 0.5, 1, 1.5, 2, 2.5, 3). An ordered logistic regression model using lagged employment status and HAQ by time interactions as explanatory variables was estimated to provide parameter/transition probability estimates to populate a Markov chain model of employment. The intuition underpinning the model is that the longer the time period, the greater the influence of HAQ state becomes relative to lagged employment state.

Results: The retired patients never switched employment categories and so were excluded from the analysis. A Somer's D of 0.81 and c value of 0.905 were indicative of a good fit and the null hypothesis that the regression coefficients were zero was rejected ($p<0.0001$). Lagged status was a significant predictor of current status ($p<0.0001$), with lagged unemployment particularly strongly associated with current unemployment. HAQ by time interactions were also statistically significant ($p<0.0001$), with weeks spent in states 0 and 0.5 leading to increased probabilities of better employment states (proportional odds ratios for 1 week in HAQ state 0 or 0.5 were 1.039 and 1.005, respectively). Time spent in HAQ state 1 or greater led to increasing probabilities of worse employment states (odds ratios=0.969, 0.944, 0.935, 0.872, and 0.658).

Conclusion: A regression model evaluating the effect of physical function on the combination of self-reported employment status and degree of work impairment demonstrated that although lagged employment state was a strong predictor of future states, HAQ status significantly changed the transition probabilities. Specifically, time spent in HAQ states ≤0.5 led to better employment states.

Disclosure: C. Bojke, None; **M. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **S. Ray**, Abbott Laboratories, 3 ; **B. Van Hout**, Abbott Laboratories, 9 .

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Changes in Health Care Utilization and Costs for Employed Patients with Rheumatoid Arthritis From 1997–2006. H. Birnbaum[1], C. Pike[1], R. Banerjee[1], T. Waldman[1] and Mary Cifaldi[2], [1]Analysis Group, Inc., Boston, MA, [2]Abbott Laboratories, Abbott Park, IL

Purpose: A retrospective analysis of claims data was used to assess changes in health care utilization and costs between 1997 and 2006 for employed patients with rheumatoid arthritis (RA).

Method: Using 2 separate administrative claims databases, 2 cohorts of employed patients with RA ("patients") and matched employed controls without RA ("controls") were identified: a 1997 cohort and a 2006 cohort. Patients in both cohorts were required to have at least 1 prior RA diagnosis, be age 18 to 64 years, have 12 months of continuous eligibility, and be employees with disability data in the index year. Patients in the 2006 cohort were matched to patients in the 1997 cohort on a 3:1 basis by age (±2 years), sex, and geographic region. Employed controls with no RA diagnosis in their claims history who had disability data and met the eligibility and age requirements were matched 1:1 to each patient cohort. Differences in comorbidities, resource utilization, health care costs, and work loss costs between patients and controls in each cohort were calculated; these relative changes were compared between the 1997 and 2006 cohorts using a difference-in-differences methodology. Costs were inflated to 2006 dollars. To assess statistical significance, paired *t*-tests were used for continuous outcomes and generalized estimating equations were used for binary and count outcomes.

Results: The 1997 and 2006 cohorts contained 279 and 837 patients, respectively, and a corresponding number of controls. There were no statistically significant differences between cohorts in the relative prevalence of non-RA comorbidities or the Charlson comorbidity index,

except for the relative prevalence of cardiovascular disease, which decreased by 11.1% from 1997 to 2006 ($p<0.05$). The relative percentages of patients seeking primary care and non-rheumatologist outpatient care decreased by 9.9% ($p<0.05$) and 16.3% ($p<0.01$), respectively. Relative number of emergency department (ED) visits decreased by 1.1 visits/patient ($p<0.01$) and days hospitalized decreased by 0.9 days/patient ($p<0.05$). Rheumatologist visits increased by 0.9 visits/patient ($p<0.01$) and other physician visits increased by 1.2 visits/patient ($p<0.01$). Relative direct costs were unchanged; drug costs rose $633/patient ($p<0.05$) but were offset by declines in medical costs/patient ($618 [p=0.68]). Relative RA-specific total costs increased by $1,432/patient ($p<0.01$) due to increases in both relative medical ($612 [$p<0.01$]) and drug ($820 [$p<0.01$]) costs/patient. Relative number of work days lost fell by 4.8 days/patient ($p=0.35$). Relative indirect costs declined by $423/patient ($p=0.32$).

Conclusion: Between 1997 and 2006, hospital days and ED visits decreased, but total health care costs were unchanged. Treatments introduced during this period may be associated with cost savings from changes in medical services utilization. Reduction in ED visits and hospital days also suggests improved quality of life.

Disclosure: H. Birnbaum, Analysis Group, 3 ; **C. Pike**, Analysis Group, 3 ; **R. Banerjee**, Analysis Group, 3 ; **T. Waldman**, Analysis Group, 3 ; **M. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1 .

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Tolerability of Non-Selective NSAIDs and Celecoxib Among Patients with Gastroesophageal Reflux Disease and Osteoarthritis or Rheumatoid Arthritis. B. Cryer[1], X. Luo[2], AR. Assaf[2] and George Sands[3], [1]University of Texas Southwestern Medical School, Dallas, TX, [2]Pfizer Inc, New London, CT, [3]Pfizer Global Pharmaceuticals, New York, NY

Purpose: Gastrointestinal (GI) symptoms are common in patients taking nonselective nonsteroidal antiinflammatory drugs (nsNSAIDS) and are often a reason for therapy discontinuation. In osteoarthritis (OA) and rheumatoid arthritis (RA), selective COX-2 NSAID use is typically associated with less dyspepsia than with nsNSAIDS. In patients with gastroesophageal reflux disease (GERD), little is known about NSAID tolerance. Therefore, we studied nsNSAID and celecoxib prescription patterns, including discontinuations, in OA/ RA patients with concomitant GERD.

Methods: This is an observational study of GERD patients with a diagnosis OA/RA using two separate databases, the PharMetrics Patient-Centric and Medstat databases, each containing longitudinal records of medical and pharmacy claims for millions of unique patients. In each database, we performed parallel and separate analyses of adult patients with their first GERD diagnosis in 2006 and who were subsequently diagnosed with OA or RA, in the same year. We excluded patients with peptic ulcer, GI bleeding, Barretts Esophagus, esophageal cancer or eosinophilic esophagitis, rendering 22,831 patients (PharmMetrics) and 29,319 patients (Medstat) with GERD and OA/RA. From these groups we next identified GERD/OA or GERD/RA patients who were first prescribed a nsNSAID or celecoxib during the 90 days following their diagnosis of OA or RA (index prescription), excluding those taking a nsNSAID, celecoxib or gastroprotective agent [GPA (H_2-blocker or proton pump inhibitor)] during the 90 days preceding the index prescription date. NsNSAID utilization and discontinuations were evaluated and Kaplan-Meier survival curves were constructed. Reasons for discontinuations are not available in these databases.

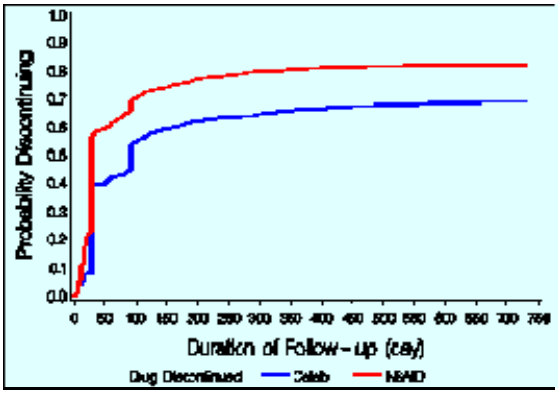
Results:

NSAID Naïve and GPA Naïve GERD/OA or GERD/RA Patients Initiating nsNSAID or Celecoxib in 2006				
	Discontinue Treatment within 60 days of Initiation			
	PharMetrics		MedStat	
	N	Probability Discontinuing	N	Probability Discontinuing
New nsNSAID Users	1680	61%	3204	56%
New Celecoxib Users	372	42%	880	33%

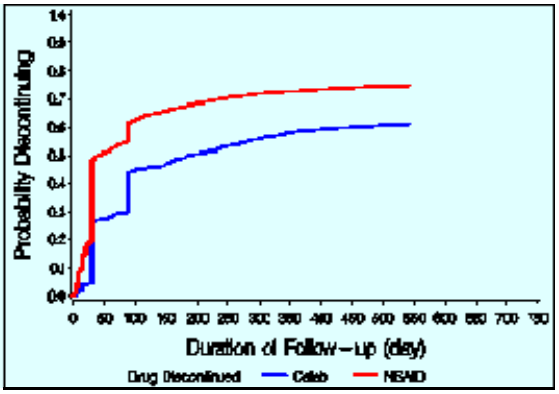
$p<0.001$ by log rank test of equality of the two survival curves in PharMetrics & MedStat

Kaplan-Meier Survival Curves: Time to Discontinuation of nsNSAIDS vs. Celecoxib.

Pharmetrics



Medstat



Most nsNSAID discontinuation occurred within 60 days of treatment initiation, but not with celecoxib. Patients who tolerated nsNSAID or celecoxib for 60 days without discontinuation were likely to continue treatment for the remainder of the evaluation period. Replication of these observations in two separate, large patient databases increases the confidence in this study's conclusion.

Conclusion: In patients with GERD/OA or GERD/RA who require antiinflammatory treatment, significantly fewer patients discontinue celecoxib when compared to those discontinuing nsNSAIDS.

Disclosure: B. Cryer, Pfizer, Astra-Zeneca, Sucampo Pharamceuticals, Pozen Inc, NiCox Inc, PLx Pharma, 5 ; **X. Luo**, Pfizer Inc, 3 ; **A. Assaf**, Pfizer Inc, 1, Pfizer Inc, 3 ; **G. Sands**, Pfizer Inc, 1 .

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The Effect of Diabetes Over the 6 Month Recovery After Total Knee Arthroplasty. C. Allyson Jones[1], Lauren A. Beaupre[1], G.S. Jhangri[1] and Marie E. Suarez-Almazor[2], [1]University of Alberta, Edmonton, AB, [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX

Purpose: Although the medical effects of diabetes on surgical outcomes has been examined for total knee arthroplasty (TKA), the impact of diabetes on pain relief and functional recovery has not been clearly delineated. Diabetes is well known for associated musculoskeletal and peripheral neurologic problems which may interfere with recovery after joint arthroplasty. We looked at the pattern of recovery for pain and function in TKA to determine whether differences existed between diabetes (DM) and nonDM patients.

Method: Longitudinal prospective inception cohort of 405 patients receiving elective primary TKA were followed within a month prior to surgery, and 1, 3, 6 months after surgery. The outcome measures, knee pain and function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Diabetes status was extracted from the chart and reported by the patient. The Center for Epidemiologic Studies-Depression (CES-D) was used to screen for depression. Social support was evaluated using the Medical Outcomes Study Social Support Survey. Measurements were repeated at each of the follow-up interviews. Linear mixed models were developed for pain and functional recovery to evaluate changes over time and between group differences (DM and nonDM) while adjusting for covariates.

Results: Patients had a mean age 68 (SD10) yrs; 249(61.5%) were female; 60(14.8%) had DM. 7% of DM and 3% of nonDM patients had surgical complications (p=0.2). Pre-operative pain (p=0.9) and function (p=0.3) scores were similar regardless of DM. After controlling for age, sex, baseline pain or function and time, DM had a significant deleterious effect (-2.7, p=0.03) along with depression (-3.1, p=0.02), kidney disease (-4.9, p=0.04) and social support (-0.05, p=0.03). No interactions were found between diabetes and depression or kidney disease. DM was not a significant factor in functional recovery (p=0.14), neither was obesity or cardiovascular disease.

Conclusion: Because patients with DM who undergo TKA may have slower pain relief over a 6 month recovery, pain management should be monitored and treated more actively in this subgroup of patients. Knowing that pain relief may take longer in this subgroup can assist clinicians in setting realistic patient expectations for recovery time.

Disclosure: C. A. Jones, None; **L. A. Beaupre**, None; **G. S. Jhangri**, None; **M. E. Suarez-Almazor**, None.

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Population-Based Estimates of Uveitis Incidence in Patients with Ankylosing Spondylitis. SM Szabo[1], Katherine Gooch[2], K.M. Johnston[1], Walter P. Maksymowych[3], Diane V. Lacaille[4], Aileen Pangan[2] and AR Levy[1], [1]Oxford Outcomes, Vancouver, BC, [2]Abbott Laboratories, Abbott Park, IL, [3]University of Alberta, Edmonton, AB, [4]University of British Columbia, Vancouver, BC

Purpose: Noninfectious uveitis is the most common extra-articular manifestation of ankylosing spondylitis (AS), with a reported lifetime prevalence of up to 40% in patients with AS. However, those prevalence estimates were based on self-report, examination, or chart review and lacked standardized definitions of uveitis. Accurate, population-based estimates of the incidence of uveitis due to AS, would be valuable for 2 reasons: first, to allow calculation of the excess risk of uveitis due to AS; second, to facilitate a more thorough quantification of the burden of illness of AS, because the impact of uveitis is not frequently included in burden-of-illness models. We compared the incidence of uveitis in patients with AS with estimates of the incidence of uveitis in the general population.

Methods: We designed a retrospective cohort study using the Régie de l'Assurance Maladie du Québec (RAMQ) databases, which contain population-based, longitudinal, patient-level, physician billing data. These data include records of physician services delivered in outpatient clinics, offices, and hospitals and patient sociodemographic data. Entry into the AS cohort was defined at first physician diagnosis of AS (ICD-9 720.0) between 1998 and 2006 with no such diagnosis in the 2 preceding years. A comparison cohort was generated using a 1% random sample of individuals from Québec without AS (no diagnosis of 720.0 within the period). Incident cases of noninfectious uveitis were identified from either cohort using ICD-9 codes 363.2, 363.3, or 364.0. Cohort members were censored at RAMQ plan deregistration or at the end of the study period (December 31, 2006). A standardized incidence ratio (SIR) was calculated comparing the 10-year incidence rate of uveitis in persons with AS vs. without AS, adjusted for age and sex.

Results: The sample included 7,663 patients with AS (Québec 2006 population: 7,631,552) diagnosed between 1998 and 2006; 4,175 (54.5%) were male. The crude 10-year incidence rate of uveitis in the AS population was 374.0/10,000 persons compared with 21.1/10,000 persons in the non-AS population. The SIR for the development of uveitis during the study period was 22.7 for those with AS vs. those without AS.

Conclusion: We found that noninfectious uveitis is much more common in patients with AS than in the general population; patients with AS have a >20-fold increased risk of developing uveitis. This study provides robust, population-based estimates of uveitis incidence that could be incorporated into AS models. As uveitis imposes a cost, both because of the need for treatment and because of its substantial negative impact on health-related quality of life, failing to incorporate uveitis incidence in AS models may underestimate the true burden of illness with AS.

Disclosure: S. Szabo, Oxford Outcomes, 3 ; **K. Gooch**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **K. M. Johnston**, None; **W. P. Maksymowych**, Abbott Laboratories, 5, Abbott Laboratories ; **D. V. Lacaille**, None; **A. Pangan**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **A. Levy**, Oxford Outcomes, 3 .

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Comparisons Between Three Work-Related Patient-Reported Outcome Instruments in Patients with Ankylosing Spondylitis. Walter P. Maksymowych[1], Katherine Gooch[2], M. Lorimer[2], H. Khong[3] and A. Boonen[4], [1]University of Alberta, Edmonton, AB, [2]Abbott Laboratories, Abbott Park, IL, [3]Vcomtech, Edmonton, AB, [4]Maastricht University Medical Centre, Maastricht, Netherlands

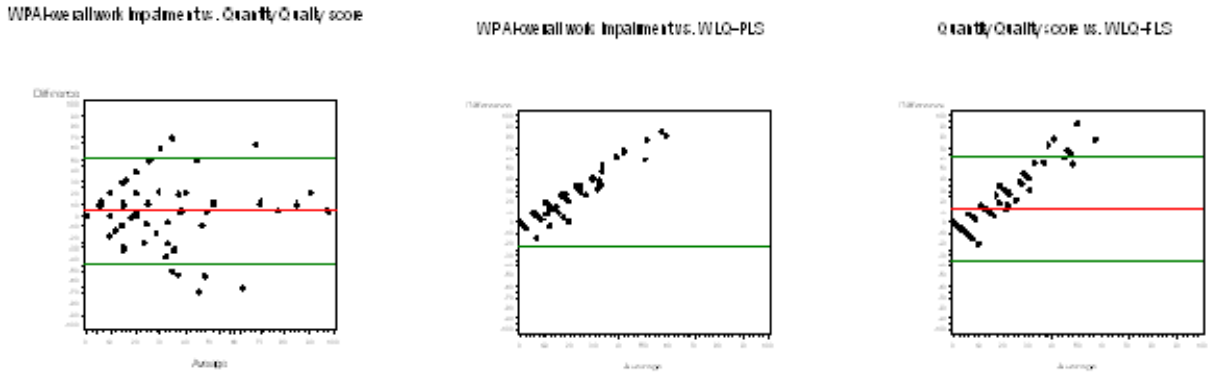
Purpose: Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory disease that results in functional limitations and impairment of health-related quality of life, typically affecting patients during their working years. OMERACT has identified the need to determine which patient-reported outcome (PRO) instruments are best suited to measure work productivity. We evaluated the agreement between 3 PRO measures of presenteeism, defined as the impact of disease on a patient's ability to perform at work.

Methods: Data were obtained from the Patient-Reported Outcomes in Employment Study (PROSE), a longitudinal, observational study of AS and work productivity. Participants diagnosed with AS completed an online patient survey that included 3 measures of work productivity: 1) the Work Productivity and Activity Impairment Questionnaire (WPAI) presenteeism score, 2) the Work Limitations

Questionnaire (WLQ-25), and 3) the Quality Quantity Method (QQ). Scores were calculated and transformed to a 0–100 scale, with greater scores indicating greater work impairment. Descriptive statistics were used to describe the complete and employed-only cohorts. Agreement between the instruments was assessed by comparing score distributions, means, Pearson's correlation coefficients (r), and Bland-Altman (BA) plots. The comparative analysis included only employed patients and baseline surveys.

Results: Of 175 surveys obtained, 77% were completed by employed patients with AS. Mean (SD) age of the employed patients was 44.1 (10.9) years; 78% of patients were men. The means of work productivity scores at baseline were WPAI, 22.55; WLQ, 5.53; and QQ, 19.37. The WPAI and WLQ were highly correlated (r=0.63), the QQ and WLQ were moderately correlated (r=0.38), and the WPAI and QQ were moderately correlated (r=0.49). Results of BA plots (figure) show that, although the mean of the difference between WPAI and QQ scores was relatively small (2.64), the limits of agreement were large (–45.61, 50.89), so WPAI and QQ scores do not have substantial agreement. The large means of differences (WPAI and WLQ [16.62] and QQ and WOQ [13.21]), large limits of agreement, and increasing dispersion as average values increase suggest that the WLQ has poor agreement with the QQ and the WPAI.

Bland-Altman Plots of Agreement Between Work Productivity Measures



Conclusion: The use of different work productivity measures may yield different work productivity loss results. These analyses suggest that the 3 instruments evaluated are not interchangeable for assessing work productivity in AS.

Disclosure: W. P. Maksymowych, Abbott Laboratories, 5, Abbott Laboratories, 9 ; **K. Gooch**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **M. Lorimer**, Abbott Laboratories, 3 ; **H. Khong**, Vcomtech, 3 ; **A. Boonen**, None.

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The Georgia Lupus Registry: Exploring Early Lupus Subtypes. Rebecca A. Speckman[1], Cristina M. Drenkard[2] and S. Sam Lim[2], [1]Rollins School of Public Health, Emory University, Atlanta, GA, [2]Emory University, Atlanta, GA

Purpose: In SLE and other diseases with a wide variety in manifestations between patients, it has been suggested that identification of subtypes (i.e., subgroups with homogeneous manifestations) may help elucidate risk factors and pathophysiology of disease. Our objective was to use formal cluster analysis techniques to explore potential early lupus subtypes.

Method: The Georgia Lupus Registry is a population-based registry designed to assess the incidence (2002-2004) and prevalence (2002) of SLE in Atlanta. 234 patients met our case definition for "early lupus" with a date of diagnosis in 2002-2004 and ≥ 4 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by the patient's rheumatologist. *K*-means is a cluster analysis method that partitions patients into mutually exclusive clusters based on their similarity to each other. *K*-means was performed using 26 clinical and 11 laboratory variables. A set of potential early lupus subtype clusters was chosen based on conservation of cluster membership.

Results: Clusters 2 and 3 appeared to be similar to the MCTD phenotype and were more likely to be Black with a lower mean age of onset. Cluster 3, with high probability of alopecia and anti-RNP and medium probability of Raynaud's syndrome, had relatively high probabilities of malar rash, discoid rash, and leukopenia. Cluster 4, characterized by high probability of proteinuria, thrombocytopenia, anti-DNA, and low complement, had an intermediate age of diagnosis and likelihood of being Black. Cluster 1 (the reference group) was characterized by arthritis and lower probability of other manifestations.

	Cluster 1	*Cluster 2*	*Cluster 3*	*Cluster 4*
Number of patients (row %)	37 (24.5)	47 (31.1)	32 (21.2)	35 (23.2)
Characteristic clinical features	arthritis	arthritis	arthritis, alopecia, Raynaud's, malar rash, mucosal ulcers, discoid rash, pleuritis	pleuritis
Characteristic laboratory features		anti-RNP, anti-DNA, (anti-Sm)	anti-RNP, anti-DNA, anti-Sm	proteinuria, lymphopenia, low complement, thrombocytopenia
Black n (column %) White OR (95% CI), for Black	22 (59.5) 15 (40.5) (ref)	40 (85.1) 7 (14.9) **3.9 (1.4, 11.0)***	27 (84.4) 5 (15.6) **3.7 (1.16, 11.7)***	28 (80.0) 7 (20.0) 2.7 (0.9, 7.8)
Mean age at diagnosis (SE)	47.0 (2.9) (ref)	**35.7 (2.3)***	**35.3 (2.9)***	40.3 (2.9)

* significant compared to Cluster 1 at $p < 0.05$

Conclusion: The characteristics of these clusters of SLE patients early in disease are putative early lupus subtypes. Our study signals the possibility of a group of Blacks with disease at a younger age that has a greater association with the MCTD-like phenotype. The exploration of risk factors for disease phenotypes suggested by cluster analysis may provide another degree of insight into SLE etiology and pathophysiology.

Disclosure: R. A. Speckman, None; **C. M. Drenkard**, None; **S. S. Lim**, None.

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Quality of Life in Patients with Systemic Lupus Erythematosus (SLE) Compared to Related Controls within a Unique African American Cohort. April L. Barnado[1], L. Wheless[2], C. Demos[2], GS Gilkeson[3] and DL Kamen[4], [1]Duke Univ SOM, Durham, NC, [2]MUSC, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC, [4]MUSC PO Box 250637, Charleston, SC

Purpose: To characterize health-related quality of life (QOL) in African Americans with SLE and assess the impact of the caregiver role among their unaffected relatives. The cohort is an African American Gullah population with a proven homogeneous genetic and environmental background, a high prevalence of multi-patient families with SLE, and a distinct cultural identity.

Methods: We collected and compared demographic and socioeconomic data, past medical history, and Short-Form 36 (SF-36), a generic measure of QOL, in SLE cases and related controls. Categorical variables were examined by chi-square test and Fisher's exact test. Differences between the means of continuous variables were tested using Student's t-test. We assessed the relationship between SF-36 and demographic and socioeconomic data and past medical history using Pearson correlation coefficient and multiple linear regression. P-values < 0.05 were considered significant.

Results: Cases (n = 60) and related controls (n = 39) are compared in Table 1. Compared to related controls, cases had a lower Physical Component Scale (PCS, 43 vs 53, p<0.01), but not Mental Component Scale (MCS, 55 vs 56, p=NS). For cases, PCS correlated negatively with disability (r = -0.38, p<0.01) and positively with employment (r = 0.43, p<0.01). For related controls, PCS correlated negatively with age (r = -0.36, p=0.03). Following adjustment for socioeconomic factors and age, PCS was still significantly lower for cases (p < 0.05). For both cases and related controls, MCS did not correlate with demographic or socioeconomic data or past medical history.

Conclusion: As expected, SLE cases had significantly lower PCS compared to related controls. This difference remained after adjustment for socioeconomic and demographic factors. In contrast, cases had a MCS similar to related controls. We hypothesize that this lack of effect of SLE on MCS may be due to disease coping mechanisms interplaying with cultural and religious factors unique to the African American Gullah population. We did not find a negative impact of the cases' SLE on the related controls. Older age was associated with lower QOL scores in related controls but not cases, again suggesting coping mechanisms developing in the cases.

Table 1. Characteristics of African American SLE cases compared to related controls.

Characteristics	**SLE cases (n = 60)**	**Related controls (n = 39)**	**P value§**
Mean age (years)	40.4	43.1	0.43
Sex (% female)	93	85	0.16
Currently working (%)	28	69	<0.01
Medical coverage* (%)	72	87	0.09
Disabled† (%)	43	0	<0.01
Dialysis (%)	17	0	<0.01
PCS‡	43	53	<0.01
MCS+	55	56	0.57

***** Includes private insurance, Medicare, Medicaid, and military benefits.
† Includes currently accepting disability payments.
‡ Physical Component Scale, range (0-100)
+ Mental Component Scale, range (0-100)
§ Chi square/t-test

Disclosure: A. L. Barnado, None; **L. Wheless**, None; **C. Demos**, None; **G. Gilkeson**, None; **D. Kamen**, Genentech and Biogen IDEC Inc., 2 .

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Utility-based Outcomes Made Easy: The Number Needed Per QALY Gained (NNQ)-Observational Study of TNF Blockade in Inflammatory Arthritis. A. Gülfe[1], L.E. Kristensen[1], Ingemar F. Petersson[1], Lennart TH Jacobsson[2], Tore Saxne[1] and P. Geborek[1], [1]Lund University, Lund, Sweden, [2]Lund University, Malmö, Sweden

Purpose and Background: Funding agencies or tax payers incur great costs due to new treatment modalities in arthritis care. The outcome measures used are not always intuitive for the clinician or easy to understand for the layman.

Objectives: 1. To develop a simple, utility based outcome measure, the NNQ (number needed to gain 1 quality adjusted life year, QALY) that can assist judging to what extent a therapeutic intervention may be worth while;

2. To apply it in a cohort of patients with established rheumatoid arthritis (RA), psoriatic arthritis (PsA) or spondarthritis (SpA) treated with TNF blockers in a "real life", clinical setting.

Method: Patients: 1st and 2nd anti-TNF treatment courses for RA, PsA and SpA patients having utility data at baseline and at least once more during 12 months were retrieved from the South Swedish Arthritis Treatment Group (SSATG) registry of patients receiving biologic drugs. Patients were enrolled 2002-2006.

NNQ: Utility is a measure of health related quality of life (0=death, 1=perfect health) often derived from preference based, generic instruments, e g EuroQoL-5-dimensions, EQ-5D. Economic models utilize quality adjusted life years (QALYs); a year spent in perfect health yields 1 QALY, a year in a state with utility 0.5 yields 0.5 QALY, etc. The number needed to gain 1 QALY, NNQ, is the number of patients one has to subject to an intervention to gain 1 QALY. We obtained mean QALY gain as the mean utility gain from baseline over 1 year. By inverting this value, one gets the NNQ.

Results: There were 1001 eligible 1st anti-TNF courses for RA, 241 for PsA and 255 for SpA. The NNQ for 1st and 2nd courses are given in Table 1. NNQ was calculated based on mean QALY gain for all courses assuming 1 year duration of therapy (not time corrected – LOCF approach) and on each course contributing QALYs only for the actual time on treatment (time corrected).

Not time corrected	**RA**	**PsA**	**SpA**
1st course	4.5 (4.1-5.0)	4.5 (3.8-5.6)	4.1 (3.6-4.9)
2nd course	6.4 (5.3-7.9)	4.2 (3.2-6.2)	4.3 (3.2-6.8)
Time corrected			
1st course	4.7 (4.3-5.2)	4.8 (4.0-5.9)	4.4 (3.8-5.3)
2nd course	6.7 (5.7-8.2)	4.7 (3.6-6.9)	4.5 (3.3-6.8)

Table 1. NNQ (mean[95% CI]) for anti-TNF treatment of RA, PsA and SpA.

Conclusion: NNQ was easy to calculate and relate to the "real world" clinical situation. Correcting for actual time on treatment increases NNQ somewhat, as expected, due to lower QALY gain for courses <1 year. EQ-5D was found to perform well across 3 different diagnoses. In our setting, NNQ in RA was found to be higher in 2nd than in 1st anti-TNF courses, maybe due to selection of treatment resistant patients. By contrast, NNQ was about the same in 1st and 2nd anti-TNF treatment of PsA and SpA. The latter finding must be interpreted cautiously because of limited cohort size.

Disclosure: A. Gülfe, None; **L. E. Kristensen**, None; **I. F. Petersson**, None; **L. T. Jacobsson**, None; **T. Saxne**, None; **P. Geborek**, None.

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Impact of Specialty Pharmacy Management On Medication Compliance, Medical Utilization and Costs for Patients with Rheumatoid Arthritis. Jane Barlow[1], Wenyi Wang[1], Richard Faris[2], Susan O'Connor[1], Susan Garavaglia[1] and Ronald Aubert[1], [1]Medco Health Solutions, Inc., Franklin Lakes, NJ, [2]Medco Health Solutions, Inc., Memphis, TN

Purpose: Specialty pharmacy serves the medication needs of patients with complex chronic conditions, such as rheumatoid arthritis (RA). In addition to prescription fulfillment and coordination of coverage and payment, specialty pharmacy provides comprehensive therapy management. This includes programs to promote patient adherence and help the patient improve his/her quality of life, clinical services to assist the patient under the supervision of his/her physician in implementing the prescribed course of treatment, and 24 hour telephonic access to specially trained pharmacists and registered nurses.This study evaluates the impact one specialty pharmacy's management of RA patients who use either adalimumab or etanercept.

Method: A retrospective cohort study using integrated pharmacy and medical claims to compare RA patients who had specialty pharmacy management from 2006 to 2008 to patients who filled claims only in retail pharmacy during the same period. The study sample includes a total 4,388 patients between age 18 and 62 with a documented RA diagnosis in 2005 or 2006. The study group consisted of 3,054 patients who filled at least one adalimumab or etanercept prescription through a specialty pharmacy in 2006 and refilled the prescription through the specialty pharmacy in 2007 or 2008. The Control group consisted of 1,334 patients who filled at least one prescription of these drugs through retail pharmacy in 2006 and refilled the prescription only through a retail pharmacy in 2007 or 2008. Compliance, medical services and cost

outcomes were compared between the study and control groups each year from 2006 to 2008 by controlling age, gender and comorbidities. Generalized linear regression models were used to estimate the adjusted compliance rates and costs. Logistic regression models were used to estimate the likelihood of patients having hospitalizations, outpatient visits, and ER visits.

Results: After 2 years follow-up, compared to the control group, patients who filled RA medications through a specialty pharmacy had 16.0% higher compliance rate ($p<0.0001$); per patient per year drug cost (AWP) was $4000 higher ($p<0.0001$) and overall medical expenses per patient per year was $1,534 lower ($P<0.01$). The study group had a lower percent of patients using medical services: office visits (82.5% vs. 88.4%, $p< 0.001$) and ER visits (13.4% vs. 15.7%, $p=0.0219$). The study group also had lower hospitalization rates and shorter length of hospital stay, but both were not statistically significant.

Conclusion: Patients who received their RA medication from a specialty pharmacy were more likely to be compliant than those who received their medication from a retail pharmacy. For overall medical and cost outcomes, these patients used less medical services and overall had lower medical expenses. Use of specialty pharmacy may be associated with higher compliance to RA treatment and lower utilization and costs of medical services.

Disclosure: J. Barlow, Medco Health Solutions, 3, Medco Health Solutions, 1 ; **W. Wang**, Medco Health Solutions, Inc., 3, Medco Health Solutions, Inc., 1 ; **R. Faris**, Medco Health Solutions, Inc., 1, Medco Health Solutions, Inc., 3 ; **S. O'Connor**, Medco Health Solutions, 3, Medco Health Solutions, 1 ; **S. Garavaglia**, Medco Health Solutions, Inc., 3, Medco Health Solutions, Inc., 1 ; **R. Aubert**, Medco Health Solutions, Inc., 1, Medco Health Solutions, Inc., 3 .

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Predictors of Quality of Life (QOL) in Rheumatoid Arthritis (RA) Patients. S. C. Bae[1], Soo-Kyung Cho[1], Yoon-Kyoung Sung[1], Hyeseon Lee[1], Kyounghee Jung[1] and Tae-Jong Kim[2], [1]Hanyang Univ Medical Center, Seoul, South Korea, [2]Chonnam National University Medical School, Gwangju, South Korea

Purpose: To identify the predictors for health-related quality of life (HR-QOL) in RA patients according to their disease activities.

Method: Two hundred twenty three RA patients diagnosed with the American College of Rheumatology criteria were recruited from the Hospital for Rheumatic Diseases in Hanyang University, Seoul, Korea (from Hanyang University Medical center Arthritis Network, HUMAN). Their health status was measured with European quality of life (EQ-5D). Multiple regression analysis was used to investigate associations between the dependent variable (HR-QOL) and independent variables (health assessment questionnaire [HAQ], DAS28 score, age, disease duration, VAS, co-morbidity, operation history, and demographic features). Then, RA patients were divided into three subgroups according to their disease activity: remission (DAS28 $\leq$2.6), low and moderate disease activity (2.6<DAS28$\leq$5.1), and high disease activity (DAS28>5.1). Predictors for HR-QOL in each group were also identified.

Results: HAQ ($p<0.001$), disease duration ($p=0.024$) and patient assessed pain-VAS ($p=0.001$) were significant predictors of EQ-5D utility in multiple stepwise regression models. In patients with remission (n=34), QOL was affected by pain-VAS ($p=0.011$) and age ($p=0.03$) ($R^2=0.868$). For patients with low and moderate disease activity (n=152), HAQ ($p<0.001$) and pain-VAS ($p=0.004$) were predictors for HR-QOL ($R^2=0.439$). Among high disease activity patients(n=37), co-morbidity ($p=0.006$), recent operation history ($p=0.002$) and disease duration ($p=0.004$) in addition to pain-VAS ($p=0.01$) affected QOL ($R^2=0.937$), while HAQ was not associated with QOL in this group($p=0.108$).

Conclusion: There were differences in predictors of QOL according to the disease activity of RA patients. Pain was a major predictor for QOL in RA patients and HAQ was important in patients with low and moderate disease activity. However, in patients with high disease activity, co-morbidity and operation history are more important predictors for QOL than HAQ. It might be important for physicians to notice that different factors are influencing the QOL in RA patients as their disease activities.

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Converting MHAQ, MDHAQ and HAQII Scores Into HAQ Scores Using Models Developed with 59,281 RA Patients. Jaclyn K. Anderson[1], F. Wolfe[2] and Kaleb D. Michaud[1], [1]University of Nebraska Medical Center and NDB, Omaha, NE, [2]National Data Bank, Wichita, KS

Purpose: The Stanford Health Assessment Questionnaire Disability Index (HAQ) is the gold standard functional status questionnaire in rheumatology, but is lengthy with 41 questions. Three prominent and much shorter versions, multidimensional HAQ (MDHAQ), modified HAQ (MHAQ), and HAQII, are often used in outcomes research as HAQ substitutes without demonstrated equivalence. Due to differing psychometric properties of each measure, we seek to develop a method of conversion between these three versions and the original HAQ.

Method: Utilizing previously collected data from the National Data Bank for Rheumatic Disease (NDB) long-term outcomes study from 1998-2008, analysis was limited to comparison in rheumatoid arthritis (RA) patients at a random observation at which the HAQ was asked in conjunction with the MHAQ, MDHAQ, and HAQII. Univariate linear regression analyses were performed with 30 explanatory variables believed to be important indicators of the HAQ score with variables not contributing to the model excluded from further analysis. The developed models were limited to 80% of the data with the remaining 20% used to test the model fit. Predicted values were constrained to the 0 to 3 range of the HAQ. Graphical fits are presented in lowess curves.

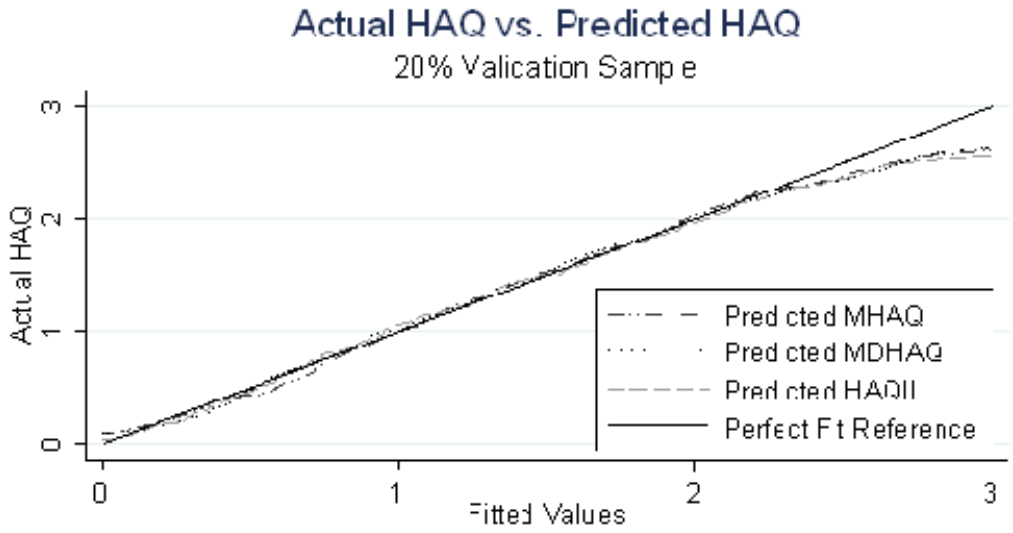
Results: The number of unique RA patients completing the HAQ and alternatives were: 29,686 MHAQ, 13,666 MDHAQ, and 19,117 HAQII. Table 1 displays coefficients (standard error [SE]) for the final models. The square root of MHAQ was more closely correlated with HAQ than the untransformed variable (0.881 vs. 0.857), improved the R^2 modestly (ΔR^2=0.042), and was included in the final model. Addition of pain VAS, number of years smoked, and patient global severity improved R^2 by 0.013 but were not included in favor of parsimony. Transformed versions of the MDHAQ and HAQII did not significantly improve model fit. Including age and sex in the HAQII model produced a nonsignificant improvement (ΔR^2=0.002). For each measure both the 80% development sample and 20% validation sample closely approximated the fitted HAQ values and demonstrate nearly identical lines (Figure 1).

Conclusion: We have developed conversion formulas between the MDHAQ, MHAQ, and HAQII and HAQ in a large sample of RA patients. We feel the models we have developed are useful for conversion of the measures in the research setting with application to the individual patient inappropriate.

Table 1. Model Coefficients.

Model	Measure (SE)	AGE (SE)	SEX (SE)	Constant (SE)	√MHAQ (SE)	R^2 20% Validation Sample
MHAQ	0.380(0.012)	0.006(0.000)	-0.240(0.005)	-0.068(0.010)	1.085(0.015)	0.816
MDHAQ	1.113(0.005)	0.004(0.000)	-0.206(0.007)	0.053(0.014)	-	0.802
HAQII	0.993(0.004)	-	-	0.044(0.005)	-	0.838

Figure 1. Fitted vs. Predicted MHAQ, MD-HAQ, and HAQ-II.



Disclosure: J. K. Anderson, None; **F. Wolfe**, None; **K. D. Michaud**, None.

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HRQoL Domain Coverage of the Patient Generated Index in Patients with Systemic Sclerosis: An Application of the PROMIS Framework. S. de Achaval[1], M. Kallen[1], V. Cox[1], M. Mayes[2] and Marie E. Suarez-Almazor[1], [1]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [2]U.Texas Houston, Houston, TX

Purpose: Systemic sclerosis (SSc) is a multifaceted disease severely impacting patient health-related quality of life (HRQoL). Available instruments assessing SSc patient HRQoL inadequately capture the wide spectrum of symptoms and burden SSc patients experience. The Patient Generated Index (PGI) assesses HRQoL from the subjective view of factors deemed important per individual patient. We mapped the range of HRQoL issues reported by SSc patients on the PGI onto currently established PROMIS (Patient Reported Outcomes Measurement Information System) domains to investigate PGI domain coverage. PROMIS, an NIH initiative, currently proposes a framework to comprehensively measure patient-reported symptoms and outcomes.

Methods: A cross-sectional study was performed with 62 SSc participants. The PGI was completed in 4 stages: 1) patients identified the 5 most important life areas affected by SSc, 2) they scored each area using a 0 (bad as could be) to 6 (good as could be) scale, with “last month” as time reference, 3) with 10 points “to spend” they distributed points per life area to indicate most-to-least important areas, 4) they ranked their life areas. All identified life areas from PGI stage 1 were then categorized into one general and 2 specific PROMIS framework domains. Descriptive statistics were calculated for patient characteristics and the self-reported HRQoL life areas. Correlations between PGI score and standardized instruments used in SSc patient assessment (e.g., HAQ-DI, SF-36, Symptom Burden Index (SBI)) were obtained to assess validity of the PGI in this patient population.

Results: Patients were mostly female (87%), English-speaking (87%), white (69%), and had a mean age of 53 years. Mean disease duration was 8 years; 63% had diffuse disease. A total of 279 individual life area responses were recorded, 53% of which were in the general domain social health, particularly in the specific domains of social function and relationships. Another 20% were in the general domain physical

health, most in the specific domains of physical function, symptoms, sleep/wake function, and sexual function. Some 17% were categorized in the general domain mental health, with a majority in the specific domains of emotional distress and psychological function. Ten percent overlapped 2-3 domains. Patient responses were found to be distributed across 8 of 9 specific domains in the current PROMIS framework. Statistically significant correlations ranging in absolute value from 0.26-0.50 were observed between the PGI and HAQ-DI, both SF-36 component scores, 7 of 8 SF-36 subscales, and 7 of 9 SBI components.

Conclusion: The social health domain was reported as most affected by SSc. The PGI is an individualized, wide-spectrum HRQoL instrument for SSc patients. Implementation of this single instrument may allow for a more comprehensive coverage of the multiple HRQoL areas affected by SSc.

Disclosure: S. de Achaval, None; **M. Kallen**, None; **V. Cox**, None; **M. Mayes**, None; **M. E. Suarez-Almazor**, None.

ACR Poster Session A

Fibromyalgia and Soft Tissue Disorders

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Validation of the Skin Extensibility Test in Joint Hypermobility. Adam Farmer[1], H. Douthwaite[1], Qasim Aziz[1] and Rodney Grahame[2], [1]Wingate Institute of Neurogastroenterology, London, United Kingdom, [2]Univ College Hospital, London, United Kingdom

Purpose: Generalised joint hypermobility (JHM) is common and is a feature of many of the hereditary disorders of connective tissue (HDCTs), including the benign joint hypermobility syndrome (BJHS) and Ehlers-Danlos syndrome (EDS). JHM can be evaluated using the Beighton score [1]. Skin hyperextensibility, too is a feature of HDCTs and forms part of the Revised 1998 Brighton diagnostic criteria for BJHS [2]. There is a paucity of data in the literature examining the use of paraclinical methods for determining skin extensibility as a function of connective tissue deficiency. We aimed to evaluate skin extensibility and skin thickness in a cohort of healthy volunteers.

Methods: 250 healthy volunteers, without BJHS, had their demographics and Beighton score recorded. Skin extensibility was measured by placing 2 dots (applied with a Pilot V5 Hi-Techpoint 0.5 ball-point pen) on the dorsum of the right hand overlying the space between the 2nd and 3rd metacarpals, approximately 10mm apart, and the distance between them was measured accurately (to +/-0.01mm) using an electronic caliper. A lateral stretching force was applied to the dots until the skin was taut and the increase in distance between the dots was noted and transformed into a percentage increment based on the initial measurement. Skin fold thickness was measured using a Harpenden caliper [3]. A corrected skin extensibility score (CSES) was calculated by multiplying the percentage increment by skin thickness (skin fold/2).

Results: 250 healthy volunteers (131 female) with a median age of 31 years (range 18 - 89 years) were studied. The prevalence of JHM of 17.6% as assessed by using the Beighton score = > 4/9. Skin thickness negatively correlated with age ($p<0.0001$ $r=-0.49$). Male gender and those who had JHM had thicker skin ($p=0.003$, $p=0.0002$ respectively). Asians were significantly more hypermobile than caucasians and afro-caribbeans ($p<0.05$). CSES was positively correlated with Beighton score, $r=0.48$, $p<0.0001$. The mean CSES was 23.84 (SEM +/- 0.84) in the hypermobile group vs. 13.55 (SEM +/- 0.34) in the normal mobility group, $p<0.0001$. Using a CSES>18 as the cut off for a positive test, sensitivity was 0.85, specificity 0.84, negative predicted value 0.96, positive predicted value 0.53. Using the receiver operator characteristics for the test, the area under the curve was 0.91, 95% confidence interval 0.87-0.96.

Conclusion: The CSES represents a useful adjunct in the clinician's armamentarium for the evaluation of tissue laxity in healthy subjects without BJHS. It provides an objective measure of skin extensibility corrected for skin thickness with excellent sensitivity and specificity. Further work is now warranted to validate this test in a cohort of patients with BJHS and EDS. References: 1.Beighton P et al. Ann Rheum Dis 1973;32:413-8. 2.Grahame R et al. J Rheumatol 2000;27:1777-9. 3.Tanner JM et al. Am J Phys Anthropol 1955;13:743-6.

Disclosure: A. Farmer, None; **H. Douthwaite**, None; **Q. Aziz**, None; **R. Grahame**, None.

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GH-IGF1 Axis in Severe Fibromyalgia Patients: Screening Data From the CT27560 Trial. C. Alegre[1], G. Cuatrecasas[2], J. Cabrera[3] and Fernandez-Sola Joaquim Sr.[4], [1]Rheumatology, Barcelona, Spain, [2]Endocrinology, Barcelona, Spain, [3]Merck S.L., Madrid, Spain, [4]HOSPITAL CLINIC, Spain

Purpose: Fibromyalgia syndrome (FM), defined by tender points and weakness is becoming widespread. Some studies have shown disturbances in the GH axis in global FM (1), although not clear subgroup stratification according to GH secretion or resistance had been done. Two intervention studies have been published so far (2,3). CT27560 compares GH +triple therapy (2 antidepressive + opioid analgesia) vs triple therapy alone, in a low IGF-1 but normal ITT and GT responders, in a selective cohort of severe FM. We present screening data of the pre-selected patients for the trial.

Methods: All patients (n=164 women) had>16 tender points and FIQ scale>75. Mean age was 50± 9,4 years and mean BMI was 27,2±4,1 Kg/m2. They had 2 basal GH and IGF-1 determinations (IGF-1<150 uU/ml corresponded to-2SD and <250 uU/ml to-1 SD according to control population), insulin-tolerance test (ITT) or glucagon test for the GH secretion analysis,(cut-off 5 ng/ml) and a modified generation test (GT) for the insensitivity analysis (cut-off >50% IGF-1 response) . IGF1 was measured by chimioluminiscensce or RIA depending on the center.

Results: 19/164 (12,75%) had IGF-1>150 ug/l and 4/164 had IGF-1>250 ug/l (2,68%). 7/95p had an ITT<3ng/ml (7,36% of the total),15/95 had an ITT<5 ng/ml (15,7%), criteria for AGHD. 5 patients were retested, previous withdrawal of the antidepressant drug, 1 normalized its response (glucagon test). 9/95 had basal GH>5 ng/ml (9,4%), 8/95 had a GT<50% IGF-1 response (8,4%), criteria for GH insensitivity. No correlation was found between basal GH or IGF-1 and GT response. No statistical differences were seen between the centers when analyzing IGF-1, % of itt non-responders and % of GT non-responders (Student t test).

Conclusion: Severe fibromyalgic syndromes have a high prevalence of GH axis disfunction. Some patients show classic biochemical patterns of AGHD and might be candidates for substitution treatment. The majority stands with normal-low IGF-1 but correct secretion test, suggesting certain GH insensitivity in this disease. This seems to be confirmed by the % of non responders to the GT

Disclosure: C. Alegre, Pfizer Inc, 5 ; **G. Cuatrecasas**, Merck España SA, 5 ; **J. Cabrera**, Merck SL Spain, 3 ; **F. S. Joaquim**, None.

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Accuracy of Physical Examination in the Evaluation of Subacromial Impingement Syndrome. Lucía Silva, José-Luis Andreu, Pilar Muñoz, Teresa Otón, Alejandro Prada, José Campos, Mónica Fernández-Castro, Jesús Sanz, Carmen Barbadillo and Juan Mulero, Rheumatology Department. Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain

Purpose: Shoulder pain due to subacromial impingement syndrome (SIS) is a common presenting complaint in rheumatology units. Physical examination (PE) of the shoulder includes several manoeuvres that explore subacromial space (SAS). High resolution ultrasonography (HRUS) has been advocated as a precise tool in the diagnosis of painful shoulder since it can evaluate the dynamic signs of impingement. The objective of this study is to compare PE findings with HRUS changes of subacromial space in patients with painful shoulder.

Method: Consecutive patients with painful shoulder referred to our unit were included in the study. After obtaining a signed informed consent, in the same day, a pre-defined physical examination was done separately by two rheumatologists, and a HRUS examination (GE Logic-5 Pro) was carried out by a third rheumatologist, blinded for the clinical findings. Sensitivity, specificity, positive and negative predictive values, and precision of the different PE manoeuvres for the diagnosis SAS pathology were calculated.

Results: Fourteen men and sixteen women were included. Mean ± SD age was 54.87 ± 13.8 years and the median duration of symptoms was 97.5 days. Sensitivity for Neer's manoeuvre was 100% and precision was 41%. Hawkins' test achieved a sensitivity of 67% and a precision of 34%. For Yocum's manoeuvre, sensitivity was 67% and precision 31%. For impingement manoeuvre values were: sensitivity, 67% and precision, 24%. Jobe's manoeuvre obtained a sensitivity of 100% and a precision of 38%. For Patte's manoeuvre sensitivity was 100% and precision 59%; and for resisted abduction 33% and 31% respectively. No test obtained a high positive predictive value for the diagnosis of SIS, although Neer, Jobe and Patte manoeuvres had a negative predictive value of 100%.

Conclusion: Most of PE manoeuvres detect reasonably well subacromial impingement of the shoulder, although only Patte manoeuvre has an acceptable accuracy.

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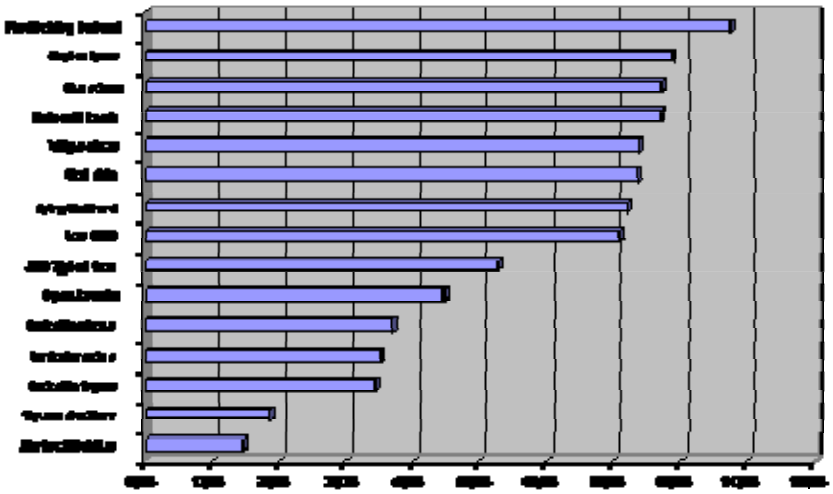
Signs and Symptoms of Joint Hypermobility Syndrome to Consider When Diagnosing This Condition. Jaime F. Bravo[1] and Carlos Wolff[2], [1]San Juan de Dios Hospital, Santiago, Chile, [2]University of Chile, Santiago, Chile

Purpose: To facilitate the diagnosis of Joint Hypermobility Syndrome (JHS), a frequent form of Ehlers-Danlos Syndrome (EDS) that for most authors is the same as EDS type III, which usually goes undiagnosed.

Methods: We have studied 1395 JHS patients during the last 8 years, in our adult Rheumatology Clinic, in Santiago, Chile. In this study, the Beighton score (BSc), the Brighton Criteria (BC) and a checklist for frequent signs and symptoms of JHS were used. Age range: 16 - 87 y/o. Average age: 45.9. Females 78.1%. Patients were grouped by ages. Group A (226 patients; 16.2%) less than 30 y/o, Group B, (571; 40.9%) and Group C. (598; 42.9%) 50 y/o or older. Chi square test was used for statistical analysis.

Results: In the total group we found: negative BSc 56.9%; Marfanoids 14.6%; Light blue sclera 77.2% (M 56.0%, F 83.1%); Dysautonomia (Dys) 44.6% (M 23.8%, F 50.5%). Frequency of Dys in M by groups: A 52.0%, B 27.7%, C 10.6%; In F: A 80.2%, B 61.8%, C 27.8%. Low BMD, Osteopenia and Osteoporosis (O), was present in 70.9% (M 79.3%, F 69.1%). Frequency of low BMD in M by groups: A 66.7%, B 74.4%, C 86.7%. In F: A 68.6%, B 63.2%, C 73.4%. Frequency of O: M 25.6%, F 23.1%. O: in M by groups: A 16.7% B 16.3%, C 35.0%, in F: A 17.6%, B 14.5%, C 30.2%. Frequency of other signs studied are noted as follows:



Conclusion: The following signs and symptoms were frequent enough (≥ 45%) to feel that they are important when considering the diagnosis of JHS: Hand holding the head; elephant paw; light blue sclera; horizontal thumb: valgus elbow; soft skin; flying bird hand; typical JHS face; low BMD and Dys. There was no significant difference between sexes regarding low BMD at all ages. Dys was significantly more noticeable in women than in men at all ages. All patients had a positive BC, since this is required by the JHS definition. As noted in our previous studies, the BSc was again negative, (56.9%). This is important since in some studies, many JHS patients are not included when applying only the BSc rather than the BC. We suggest preparing a checklist similar to the one used here to facilitate JHS diagnosis.

Disclosure: J. F. Bravo, None; **C. Wolff**, None.

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An in Vitro Model of Human Tenocytes to Investigate the Effectiveness of a Novel Formulation for the Prophylaxis and Treatment of Tendinopathies. Anna Torrent[1], Ramon Ruhí[1], Cristina Martínez[2], Mar Cid[2], Constanze Csaki[3] and Mehdi Shakibaei[3], [1]BIOIBERICA S.A., Palafolls (Barcelona), Spain, [2]BIOIBERICA S.A., Barcelona, Spain, [3]Ludwig-Maximillians-University, Munich,Germany

Purpose: Clinically, tendinopathies pose a major problem as they require lengthy treatment protocols and the tendon often heals unsatisfactorily. Tendons have a limited capacity for self-repair due to low cell density and little mitotic activity. Pro-inflammatory cytokines such as interleukin-1β (IL-1β) have been identified as the main initiators of tendinopathies, stimulating inflammation, apoptosis and extracellular matrix (ECM) degradation. The aim of this study was to evaluate the potential effectiveness of a novel formulation (BIS-033) including mucopolysaccharides, in an *in vitro* model of tendon inflammation.

Method: In monolayer cultures primary human tenocytes were either treated with BIS-033, non-stimulated or stimulated with IL-1β, stimulated with IL-1β and BIS-033 or pre-stimulated with BIS-033 followed by co-treatment with BIS-033 and IL-1β. Cell viability, adhesion, proliferation and production of ECM were analysed with light microscopy and transmission electron microscopy (TEM). Immunofluorescence was used to evaluate production of type I collagen, the main extracellular matrix protein produced by tenocytes. We also studied the expression of the signal transduction and adhesion molecule β1-integrin. Western blotting (WB) was performed to evaluate expression of apoptotic and inflammatory markers (MMP-1, Cox-2, Caspase-3).

Results: BIS-033 had a potent stimulatory effect on human tenocyte proliferation and ECM production. BIS-033 was able to suppress the catabolic, apoptotic and inflammatory effects induced by IL-1β in human tenocytes. This was demonstrated by the suppression of IL-1β-induced expression of MMP-1, Cox-2 and Caspase-3 and up-regulation of type I collagen and β1-integrin.

Conclusion: The methodology and results demonstrate that this *in vitro* model is useful for evaluating the potential effectiveness of new compounds and formulations on tendon disorders. The results presented also suggest that this formulation inhibits catabolic and inflammatory processes in an *in vitro* model of tendonitis. BIS-033 may therefore be used on prophylaxis and treatment of tendinopathies to stimulate tendon healing, regeneration and repair.

Disclosure: A. Torrent, BiOIBERICA S.A., 3 ; **R. Ruhí**, BIOIBERICA S.A., 3 ; **C. Martínez**, BIOIBERICA S.A., 3 ; **M. Cid**, BIOIBERICA S.A., 3 ; **C. Csaki**, BIOIBERICA S.A., 5 ; **M. Shakibaei**, BIOIBERICA S.A., 5 .

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The Instability of Fibromyalgia Diagnosis: Associations with Measures of Severity. F. Wolfe[1], Daniel Clauw[2], MA Fitzcharles[3], Don L. Goldenberg[4], KA Harp[1], RS Katz[5], PJ Mease[6], KD Michaud[7], Anthony S. Russell[8], lJ Russell[9], JB Winfield[10] and MB Yunus[11], [1]National Data Bank, Wichita, KS, [2]University of Michigan, Ann Arbor, MI, [3]MGH, Montreal, QC, [4]Newton-Wellesley Hosp, Newton, MA, [5]Rheumatology Associates, Chicago, IL, [6]Seattle Rheumatology, Seattle, WA, [7]U Neb Med Cntr and NDB, Omaha, NE, [8]U Alberta, Edmonton, AB, [9]U TX Hlth Sci Ctr, San Antonio, TX, [10]UNC, Chapel Hill, NC, [11]U IL Coll of Med, Peoria, IL

Purpose: To determine the percent of patients diagnosed with Fibromyalgia (FM) who do not satisfy American College of Rheumatology (ACR) criteria; to determine the comparative characteristics of these patients, and to investigate the use of ACR criteria among rheumatologists.

Methods: As part of a two-phase multicenter study to develop simple clinical criteria for fibromyalgia, we evaluated 920 FM patients and pain controls. FM patients were consecutive FM patients seen during routine practice who carried a diagnosis of FM made previously by the examining rheumatologist. Patients underwent a detailed interview and examination, including TP examination and assessment of the extent of widespread pain using a widespread pain index (WPI). Physicians enrolled 258 valid patients in Phase I whose clinical diagnosis was fibromyalgia and 256 who were control subjects. We report here on the Phase I study because it also included patients' self-report data.

Results: 25.4% of patients being treated for FM did not satisfy ACR criteria. We called this group "prior fibromyalgia." In addition, rheumatologists had not used ACR criteria in 36.4% of fibromyalgia diagnoses. There was a clear difference in clinical findings and symptom severity among the groups, with prior fibromyalgia generally occupying the midpoint between current fibromyalgia and controls (Table 1). With respect to diagnostic variables, the TP count (15.9 vs. 7.9) and the WPI (11.4 vs. 7.2) were significantly less abnormal in prior FM than in ACR (+) patients. These differences also extended to non-criteria severity measures such as fatigue, unrefreshed sleep, somatic symptoms, cognition, function, and pain medications. No set of class variables could be found that could adequately separate prior FM from ACR (+) FM or control subjects.

Conclusion: ACR criteria do not adequately diagnose or describe the characteristics of all FM patients in clinical practice. ACR criteria are not used by a third of rheumatologists diagnosing fibromyalgia, and 25.5% of patients being treated for fibromyalgia by rheumatologists do not satisfy these criteria. Current FM criteria aggregate and confound diagnostic status and symptom severity, features that should be separated to enable more adequate FM evaluation and management.

Variable	Current FM	Prior FM	Control
	Mean (SD)	Mean (SD)	Mean (SD)
MD Widespread pain index (0-19)	11.4 (4.1)	7.2 (3.9)	3.3 (2.5)
Tender point count (0-18)	15.9 (2.3)	7.9 (4.1)	2.5 (3.0)
MD global severity, categorical (0-3)	2.1	1.5	1.1
MD Somatic symptoms (0-3)	2.3 (0.7)	1.9 (0.7)	1.2 (0.5)
Patient VAS unrefreshed sleep (0-10)	7.3 (2.7)	5.2 (3.4)	3.1 (3.0)
Patient VAS pain (0-10)	6.5 (2.3)	4.9 (2.7)	4.1 (2.8)
Patient VAS fatigue (0-10)	7.0 (2.4)	5.0 (3.1)	3.3 (2.9)
Patient cognition, categorical (0-3)	1.7	1.3	0.6
HAQ-II (0-3)	1.3 (0.6)	1.0 (0.7)	0.7 (0.6)
Number of pain medications	3.3 (2.3)	2.5 (1.4)	1.9 (1.9)

Disclosure: F. Wolfe, None; **D. Clauw**, Pfizer Inc, 2, Forest Laboratories , 2, Cypress Biosciences Inc, 5, Lilly , 5, Pfizer Inc, 5, Forest Laboratories, 5, UCB, 5, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **M. Fitzcharles**, None; **D. L. Goldenberg**, Forest Laboratories, , 8, Lilly, 5, Pfizer Inc, 8 ; **K. Harp**, None; **R. Katz**, None; **P. Mease**, None; **K. Michaud**, None; **A. S. Russell**, None; **L. Russell**, None; **J. Winfield**, None; **M. Yunus**, None.

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Comparison Between Pressure and Thermal Conditioning Stimuli in the Evaluation of Descending Noxious Inhibitory Control (DNIC) in Fibromyalgia Patients and Healthy Controls. Rachel K. Harrison[1], Craig Urwin[1], Rupal Bhavsar[1], Richard E. Harris[1], Daniel Clauw[2] and Steven E. Harte[1], [1]U. Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI

Purpose: Endogenous pain modulation is commonly evaluated using DNIC testing paradigms. These procedures incorporate a conditioning stimulus (a noxious stimulus that evokes DNIC activation) and a test stimulus (a noxious stimulus used to evaluate the analgesic response to the conditioning stimulus). DNIC paradigms vary greatly in regards to experimental parameters, including the type of noxious stimuli employed. It is not clear, however, if certain parameters affect DNIC outcomes differently. Previous studies indicate that individuals with fibromyalgia (FM) have attenuated DNIC compared to pain-free controls. Therefore, we compared the effects of 2 different conditioning stimuli on DNIC activation in FM patients and healthy controls (HCs) to determine if different stimuli produce different DNIC effects.

Method: Right-handed females (FM = 18, HC = 15) underwent DNIC testing with pressure as the test stimulus, and either noxious pressure or cold water as the conditioning stimulus. Baseline intensity of the test stimulus was rated during 30-s of continuous pressure applied to the left thumbnail on a 0-100 rating scale. DNIC was induced 5-min later by applying 60-s of continuous pressure to the right thumbnail. Alternatively, subjects immersed their right hand into a 12 degree Celsius water bath for 60-s. Parallel to the last 30-s of pressure or cold water conditioning, the same test stimulus was reapplied to the left thumbnail and rated. DNIC was evaluated as the difference in pain rating of the test stimulus applied before and during the conditioning stimulus.

Results: Differences in DNIC between groups were assessed with separate repeated measures general linear models, one for pressure and one for cold water. Preliminary data indicate a significant GROUP X DNIC interaction when pressure was used as the conditioning

stimulus, p = 0.038. Ratings of the test stimulus taken before and during application of the pressure conditioning stimulus revealed DNIC-induced analgesia in HCs (Mean ± SD, 57.83 ± 18.07 vs. 40.17 ± 24.90). In contrast, FM patients exhibited hyperalgesia during concomitant pressure stimulation (57.70 ± 26.32 vs. 64.00 ± 24.90). When cold water was used as the conditioning stimulus, modest differences in DNIC were observed between HCs (58.17 ± 22.19 vs. 39.03 ± 21.81) and FM patients (60.10 ± 20.95 vs. 51.00 ± 27.09), however no significant GROUP X DNIC interaction was found, p > 0.30.

Conclusion: These data suggest that DNIC testing using pressure as both a conditioning and test stimulus identifies attenuated DNIC in FM. The cold water conditioning stimulus led to less robust differences between FM patients and HCs. In contrast to other DNIC paradigms that either use sophisticated and/or expensive test stimuli (e.g. thermal probes), or very noxious conditioning stimuli that individuals may be reluctant to undergo repeatedly, this paradigm can be performed longitudinally in nearly any setting.

Disclosure: R. K. Harrison, None; **C. Urwin**, None; **R. Bhavsar**, None; **R. E. Harris**, None; **D. Clauw**, UCB, 5, Forest Laboratories, 5, Pfizer Inc, 5, Lilly , 5, Cypress Biosciences Inc, 5, Forest Laboratories , 2, Pfizer Inc, 2, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **S. E. Harte**, None.

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Severity of Anger, and Not Clinical Pain, Correlated with Nociceptive Flexion Reflex Threshold in Fibromyalgia: An Exploratory Analysis. Dennis C. Ang[1], Rafael Chakr[1], Steven A. Mazzuca[1] and Christopher France[2], [1]Indiana University, Indianapolis, IN, [2]Ohio University, Athens, OH

Purpose: While the exact cause of fibromyalgia (FMS) is yet to be fully understood, the phenomenon of central sensitization (CS) is thought to play a major pathogenetic role. CS, associated with hyperexcitability of spinal cord dorsal horn neurons, is manifested by below-average endogenous pain-inhibitory capacity and above-average pain sensitivity. In addition, well-studied psychological features of FMS, such as catastrophizing and anger regulation, may exert their harmful effects by direct amplification of the central nervous system's processing of pain, as part of CS. As an objective CS assessment tool, the nociceptive flexion reflex (NFR), via elicitation of a spinal reflex of the lower extremity after stimulation of a sensory nerve, might overcome the self-report bias of other CS assessment tools. Therefore, our goal was to study the correlations between self-report clinical pain, anger, and catastrophizing with NFR.

Method: Cross-sectional analyses of women with FMS that completed survey questionnaires on pain, anger, depression and catastrophizing were performed. Using a previously validated protocol, NFR test was performed to all participants. The protocol-derived NFR threshold was the main outcome measure. The secondary outcome was the first reflex NFR threshold.

Results: The 36 female participants had a mean age of 47± 11 years and mean disease duration of 12 ± 6 years. The mean fibromyalgia impact questionnaire (FIQ) score was 62 ± 16, suggesting a moderate-to-severely ill patient population. On bivariate analyses (table), anger out expression consistently correlated with the two NFR measures (r= -0.39 to -0.37, p<0.05). There was a trend for current pain, for bodily pain inventory (BPI) pain intensity and catastrophizing to correlate with first reflex NFR threshold (r=-0.33, p=0.06; r=-0.30, p=0.08; and r=-0.32, p=0.06, respectively). In multiple regression analyses, only anger out correlated with protocol-derived NFR threshold (r=-1.4, p=0.02).

Conclusion: Our study showed a consistent association between anger out expression and NFR threshold, an objective measure of nociception. Self-report clinical pain and catastrophizing did not correlate with NFR threshold. The exploratory nature of our study warrants confirmation in larger studies to better understand the potential link between the psychological and biological mechanisms of fibromyalgia.

Table: Pearson's correlation coefficients between objective and self-report variables

	Protocol-derived NFR threshold	First reflex NFR threshold
BPI pain intensity	-0.26	-0.30†
Current pain	-0.23	-0.33†
Pain catastrophizing	-0.24	-0.32†
Anger out	-0.37*	-0.39*

NFR: nociceptive flexion reflex; BPI: Brief Pain Inventory
*p<0.05

†p<0.10

Disclosure: D. C. Ang, None; **R. Chakr**, None; **S. A. Mazzuca**, None; **C. France**, None.

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Neuroimaging of Evoked Pain in Individuals with Fibromyalgia and Healthy Controls. Eric Ichesco[1], Rupal Bhavsar[1], Richard Harris[1], Daniel Clauw[2], Richard Gracely[3] and David A. Williams[1], [1]U. Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]U. North Carolina, Chapel Hill, NC

Purpose: Prior neuroimaging studies in fibromyalgia (FM) have identified augmented neuronal activity in response to evoked pain when compared to healthy controls (HC). Affected regions are largely contained within the pain matrix (e.g., insula, thalamus, primary and secondary somatosensory cortex, anterior cingulate and the inferior parietal lobe). To date, the majority of the functional magnetic resonance imaging (fMRI) studies in FM have been on a relatively small scale. Heterogeneity within FM as a disease state however suggests the need to replicate earlier findings in a larger sample.

Methods: 57 individuals (mean age 45) satisfying American College of Rheumatology criteria for FM and 20 HC (mean age 42) were studied. During a 10 min fMRI scan, 2 Kg. of pressure (mild pressure) was applied three times to the left thumbnail in random sequence for 25s. A 3-Tesla GE Sigma Scanner with neuro-optimized gradients (FOV = 22cm, T2* weighted, single shot, reverse spinal acquisition, GRE, TR = 2500, TE = 30, FA = 90, 64 x 64) was used to acquire fMRI data. Pre-processing and analysis of BOLD signal was performed using SPM2. Group level T statistical images were generated and uncorrected voxel level threshold of $p<0.002$ was used to identify significant activations.

Results: In FM, 2 Kg. of pressure resulted in significant neural activity in insula (Z = 3.21). bilateral inferior parietal lobes (BA 40, Z = 4.48-4.81), primary somatosensory cortex (Z = 4.03) and secondary somatosensory cortex (Z = 4.69), putamen (Z = 3.27) and caudate (Z = 3.24). Additional activations were observed in the cerebellum (Z = 4.95) and the middle frontal gyrus (Z = 4.37). HC's only had significant activation in the contralateral inferior parietal lobe (BA 40, Z = 3.18) using the same stimulus intensity.

Conclusion: In contrast to HC, mild pressure stimuli resulted in more extensive activation of pain matrix regions in individuals with FM. This study reconfirms an augmented involvement of the "pain matrix" in the processing of evoked pain in FM and supports the role of central mechanisms being responsible for the pain of FM.

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Best Websites for Fibromyalgia. Robert S. Katz[1], Lauren Kwan[2] and Jessica L. Polyak[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

Purpose: Patients with fibromyalgia usually turn to the Internet to gain a better understanding of their illness and for recommended treatment. Finding accurate, reliable information on the Internet can be difficult for patients trying to learn more about their illness. We created a rating system for health care professionals to assess the quality of these websites. We reviewed 20 Internet sites to determine which appear to be the best regarding accurate and comprehensive patient information.

Method: We assessed the top 20 sites using the Google search engine under the term fibromyalgia. We rated each site using the following criteria to assess: accuracy, no promotion, graphics, ease of use, links, and comprehensive information. We assigned numbers from zero to 10 and then added them to determine the total sum for the six categories.

Results: The top four websites were webmd (55 of possible 60 points); medlineplus (53 points); mayoclinic (52 points); and fmaware.org (52 points). Each of these sites provided pt with accurate, user-friendly, comprehensive information, which was reviewed and rated by health care professionals specializing in Rheumatology. By determining which sites are the best resources we can better help our patients to understand Fibromyalgia and provide them with additional learning tools.

Conclusion: Finding reliable information on the Internet can be difficult for patients who seek additional learning tools and resources about their illness. By assessing the top 20 websites we are able to provide useful, informative information to our patients. Internet based research is another method to provide patient education outside of the healthcare setting.

	Accuracy	**Not Promoting**	**Graphics**	**Ease of Use**	**Links**	**Comprehensive**	**Total**
FibromyalgiaRx.Treatment.com	2	1	2	2	8	5	**20**
PatientsLikeMe.com	5	8	5	8	8	8	**42**
Webmd	10	5	10	10	10	10	**55**
Mayoclinic	10	6	6	10	10	10	**52**
Wikipedia	6	5	6	6	6	6	**35**
Fmnetnews.com	8	9	4	10	8	8	**47**
Fmaware.org	8	10	5	10	10	9	**52**
Fibromyalgia.com	8	1	1	10	1	1	**22**
medline plus	9	10	10	6	10	8	**53**
medicine net	9	1	10	7	7	8	**42**
Health.com	6	1	2	3	4	5	**21**
myalgia.com	7	1	2	6	6	7	**29**
treatingandbeating.com	5	1	2	8	1	3	**20**
yourtotalhealth.ivillage.com	4	1	7	6	6	5	**29**
afsafund.org	10	9	5	8	6	8	**46**
emedicine	5	5	4	8	6	5	**33**
neurologychannel.com	8	5	4	8	10	7	**42**
familydoctor.org	8	1	2	7	10	7	**35**
healthcentral.com	8	1	10	8	8	8	**43**
prohealth.com	8	5	4	7	5	6	**35**

10 is the best

Disclosure: R. S. Katz, None; **L. Kwan**, None; **J. L. Polyak**, None.

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A Tale of Two Cities – The Effect of Low Intensity Conflict On Prevalence and Characteristics of Musculoskeletal Pain Associated with Chronic Stress. Jacob Ablin[1], Hagit Cohen[2], Daniel Clauw[3], Ronit Shalev[4], Eti Ablin[4], Lily Neumann[5] and Dan Buskila[6], [1]Rheumatology institute, Tel Aviv, Tel Aviv, Israel, [2]Ben-Gurion University, Beer Sheva, Israel;, Beer Sheva, Israel, [3]University of Michigan, Ann Arbor, MI, [4]Haifa University, Haifa, Israel, [5]Ben-Gurion University, Israel, [6]Soroka Medical Center, Beer Sheva, Israel

Purpose: Although both acute and chronic stress lead to pain, the precise characteristics of this association have not been defined. Sderot is an Israeli town exposed to repeated missile attacks. Ofakim, a town of similar demographic and socioeconomic characteristics, had not been targeted, as of the period of our study. We examined the occurrence and characteristics of pain and related symptoms in Sderot and Ofakim.

Method: The study was conducted as a population survey. 1750 households were contacted by telephone in Sderot and 1939 in Ofakim, with a 59% and 52% participation respectively. A total of 2,030 interviews were conducted.

1024 individuals in Sderot and 1006 in Ofakim were interviewed regarding pain, somatic symptoms, mood, trauma - exposure, and general health status.

Results: Significantly higher levels of trauma-related symptoms and somatic symptoms were noted in Sderot compared with Ofakim ($p<0.001$). Chronic widespread pain (CWP) was more common in Sderot (11.1%) than Ofakim (8.3 %; OR 1.37, $p=0.038$). Women were more likely (13.9% vs. 9.3%; OR 1.45, $p=0.06$) than men (8.9% vs.7.3%, OR 1.24, $p=0.37$) to experience CWP in Sderot vs. Ofakim. Amongst males, Chronic Regional Pain was more common in Sderot (19.2%) than in Ofakim (14.2%; $p=0.036$). Pain Severity in Sderot was significantly higher than in Ofakim ($p<0.001$).

Conclusion: In the current study we have demonstrated the effect of ongoing missile attacks on the civilian population of the Israeli town of Sderot, compared with the town of Ofakim. Significantly increased rates of somatic complaints, including pain, fatigue and IBS-like symptoms, were reported by individuals in Sderot, as well as significantly higher rates of trauma-related symptoms. Widespread pain was reported significantly more frequently by inhabitants of Sderot compared with Ofakim but was not independent of increased self-reported depression. These results strengthen the relationship between low - intensity military conflict and the development of "unexplained" somatic complaints and draw attention to the need for medical resource - allocation to such areas, in order to meet these needs. The results highlight the contribution of external "environmental" factors such as stress to the occurrence of chronic pain as part of a spectrum of related somatic and affective symptoms. It remains to be investigated to what extent these external factors may interplay with a genetic predisposition in the pathogenesis of this symptom array.

Disclosure: J. Ablin, None; **H. Cohen**, None; **D. Clauw**, Cypress Biosciences, Inc, 5, Forest Laboratories, 5, Lilley, 5, Pfizer Inc, 5, Wyeth Pharmaceuticals, 5 ; **R. Shalev**, None; **E. Ablin**, None; **L. Neumann**, None; **D. Buskila**, None.

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Serum Hydrogen Peroxide Levels Are Elevated in Fibromyalgia Syndrome. I. Jon Russell, Yangming Xiao, Wanda L. Haynes and Joel E. Michalek, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Purpose: The fibromyalgia syndrome [FMS] is perceived as a disorder of central sensitization. Proposed initiating factors include genetic predisposition, physical trauma, and infection, but free radical-mediated oxidative stress, and inflammatory cytokines may also play important roles in its pathogenesis. Previous studies have reported oxidative stress in the patients with FMS, but the results were inconsistent. The present study was designed to measure serum hydrogen peroxide [H2O2] and total antioxidant capacity in patients with FMS and whether they correlated with FMS symptom severity.

Method: Primary FMS patients [1990 ACR Criteria] and healthy normal controls [HNC] were demographically matched 1:1. Clinical measures were assessed at the time of phlebotomy using validated methods. Total H2O2 [µmol] was measured by the colorimetric method of Alindag using aliquots of frozen [-70°C] serum. Serum total antioxidant capacity [mmol Trolox equil] was measured as directed [Sigma, Cat# CS0790]. The oxidative stress index [OSI] was calculated as [total H2O /total antioxidant capacity level] x100.

Results: Twenty three FMS and 1:1 matched HNC were studied. FMS serum exhibited significantly higher levels of serum total H2O2 and higher oxidative stress index than HNC. However, serum total antioxidant capacity of FMS patients did not differ from HNC. There was no significant correlation between H2O2 or oxidative stress parameters and clinical measures.

Variables	FMS	HNC	P-value

	[mean ± SD]	[mean ± SD]	
Number	23	23	
Age [years]	48.6 ± 8.0	48.1 ± 10.8	>0.05
Gender [%F]	96	96	>0.05
Ethnicity [%C]	70	70	>0.05
APT	3.3 ± 0.8	5.1 ± 0.6	<0.001
TPI	39 ± 7.7	2.9 ± 8.4	<0.001
CESD	44.2 ± 20.6	34.1 ± 11.6	<0.001
Zung-A	44.2 ± 7.6	34.1 ± 5.2	<0.001
Total hydrogen peroxide [μM]	14.60 ± 5.67	11.10 ± 3.56	0.016
OSI	1.34 ± 0.57	1.06 ± 0.34	0.043
Total antioxidant capacity [mM]	1.10 ± 0.13	1.07 ± 0.17	0.25

APT=Average Pain Threshold, TPI=Tender Point Index, CESD = center for epidemiologic studies depression scale, Zung-A=Zung Anxiety Scale Score, and OSI = oxidative stress index.

Conclusion: These findings support the hypothesis that FMS is subject to increased oxidative stress. We hypothesized that an imbalance of pro-oxidant and antioxidant systems could generate an excess of reactive oxygen species capable of reacting with cellular lipids, proteins, and DNA to cause neuronal cell injury. If this mechanism contributes importantly to the pathogenesis of FMS, it may herald the first preventive therapy for this condition.

Disclosure: I. J. Russell, None; **Y. Xiao**, None; **W. L. Haynes**, None; **J. E. Michalek**, None.

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The Effect of Somnolence On Pain, Function, and Sleep Responses to Pregabalin in Patients with Fibromyalgia. Lynne Pauer[1], Gary Atkinson[2], Danielle Lauren Petersel[3], Bernhardt G. Zeiher[4] and Alison Gagnon[5], [1]Pfizer Inc, New London, CT, [2]Pfizer Global Research and Development, Sandwich, United Kingdom, [3]Pfizer Global Research and Development, New York, NY, [4]Pfizer Inc., New London, CT, [5]UBC Scientific Solutions, Southport, CT

Purpose: Somnolence is one of the more common adverse events (AEs) associated with pregabalin therapy. In fibromyalgia studies, somnolence was reported in 19.2% of pregabalin patients and 4.6% of placebo patients. The objective of this report was to evaluate whether somnolence influenced the treatment response to pregabalin in fibromyalgia patients by comparing pain, function, and sleep outcomes between patients reporting somnolence on study and those not reporting somnolence.

Methods: Data from 3 similarly designed randomized, double-blind, placebo-controlled studies of pregabalin in fibromyalgia were pooled for this analysis. Patients meeting ACR criteria for fibromyalgia for ≥3 months with pain visual analog scale score ≥40 mm were treated for 13–14 weeks with pregabalin at doses of 300 (n=551), 450 (n=555), and 600 (n=564) mg/day or placebo (n=558). Efficacy outcomes of endpoint mean pain score, endpoint mean Fibromyalgia Impact Questionnaire (FIQ) total score, Medical Outcomes Survey-Sleep Scale (MOS-SS) sleep disturbance and sleep problems index scores, and sleep quality diary mean score were analyzed using least square means and analysis of covariance with effects for treatment, somnolence, and treatment by somnolence interaction. The mean changes from

baseline were compared between patients who reported AEs of somnolence at any time (n=366) during the study and those who did not (n=1861). The covariate of baseline quantity of sleep was used for analysis of pain and sleep outcomes and baseline FIQ total score for analysis of function.

Results: The changes from baseline with pregabalin treatment for each of these endpoints were similar regardless of whether somnolence was reported (pain: no somnolence, –1.55 to –1.76 vs somnolence reported, –1.79 to –2.05; FIQ: –11.57 to –14.07 vs –12.04 to –14.71; sleep disturbance: –18.23 to –23.84 vs –22.41 to –25.49). No significant treatment by somnolence interaction was observed for endpoint mean pain score (*P*=0.785), FIQ (*P*=0.497), sleep disturbance (*P*=0.308), sleep problems index (*P*=0.190), or mean sleep score (*P*=0.891). The placebo-corrected differences in response (pregabalin − placebo) for each endpoint showed that patients without somnolence had a somewhat greater improvement with pregabalin treatment (pain: no somnolence, –0.46 to –0.59 vs somnolence reported, –0.17 to –0.43; FIQ: –1.89 to –4.39 vs 0.04 to 2.72; sleep disturbance: –7.48 to –13.09 vs –4.00 to –7.07).

Conclusion: The magnitude of pregabalin treatment response on pain, function, and sleep outcomes was comparable between fibromyalgia patients reporting somnolence and not reporting somnolence. No statistically significant interaction of treatment by somnolence was observed. Therefore, the benefits observed with pregabalin treatment cannot be attributed to the occurrence of somnolence.

Disclosure: L. Pauer, Pfizer Inc, 3 ; **G. Atkinson**, Pfizer Inc, 3 ; **D. L. Petersel**, Pfizer Inc, 3 ; **B. G. Zeiher**, Pfizer Inc, 3 ; **A. Gagnon**, UBC Scientific Solutions, 3 .

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Test-Retest Reliability of the Mental Clutter Scale in Individuals with Fibromyalgia. Robert S. Katz and Frank Leavitt, Rush University Medical Center, Chicago, IL

Purpose: Defining and measuring fibrofog is central to an understanding of cognitive disability in fibromyalgia (FMS). Factor analysis of a new 16-item measure of fibrofog known as the Mental Clutter Scale (MCS), revealed a two dimension construct of cognition and mental clarity. This study aimed to evaluate the test-retest reliability of the MCS and its two subscales in patients with FMS.

Method: A total of 32 patients with fibromyalgia filled out the Mental Clutter Scale on two separate test sessions. The first Mental Clutter Scale was completed at a medical office visit according to a standard protocol. The second MCS was completed by mail. The interval between test sessions ranged from 4 days to 2 weeks. The median interval was 5 days.

Results: FMS patients were predominantly female (84.4%) with a mean age of 48.7±12.7 years and a mean level of education of 14.9±2.2 years. The MCS quantifies cognitive status along the dimensions of cognition and mental clarity. The eight items representing Cognition are displayed in Table 1. The eight items representing the Mental Clarity domain are displayed in column 2. Test-retest correlations (Pearson r) for the Full Scale as well as the two subscales were 0.93, 0.88 and 0.92 respectively. Differences were not significant at the $p<0.05$ level. Variations in mean measurement due to chance fluctuations from Test 1 to Test 2 were minimal as displayed in Table 2.

Table 1. Two Subscales of the Mental Clutter Scale.

Cognition Scale	**Mental Clarity Scale**
Concentration	Spaciness
Memory	Haziness
Staying Focused	Confusion
Multitasking	Cluttered Thinking
Expressing Self	Fogginess
Thinking Clearly	Rushing Thoughts
Perceptual Clarity	Fuzzy Headedness

Mental Speed	Information Overload

Table 2. Comparison of Immediate and Retest Reliability Scores.

	TEST (mean)	(sd)	RETEST (mean)	(sd)
Full Scale	4.36	2.22	4.39	2.26
Cognition Scale	4.71	2.27	4.49	2.21
Mental Clarity Scale	4.09	2.40	4.29	2.41

Conclusion: The MCS and its two subscales (Cognition and Mental Clarity) have excellent test-retest reliability for time intervals ranging from 4 days to 2 weeks. With respect to reproducibility, the MCS is an acceptable measure for use in individuals with fibromyalgia. High reliability allows changes in the fibrofog condition to be tracked with a fair degree of precision.

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

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Hyperalgesia of Fibromyalgia Patients Is Maintained by Muscle Afferent Input: A Randomized, Double-Blind, Placebo Controlled Study. Roland Staud, Susann Nagel, Michael E. Robinson and Donald D. Price, Univ of Florida, Gainesville, FL

Purpose: Fibromyalgia syndrome (FM) is characterized by pain and widespread hyperalgesia to mechanical, thermal, and electrical stimuli. Despite convincing evidence for central sensitization of nociceptive pain pathways, the role of peripheral tissue impulse input in the initiation and maintenance of FM is unclear. In contrast, peripheral impulse input has been found to contribute to pain in irritable bowel syndrome (IBS) and complex regional pain syndrome (CRPS). Because of the considerable overlap between FM and IBS, similar pain mechanisms may be operant in both chronic pain syndromes.

Method: This randomized, double-blind, placebo-controlled trial of 22 normal female controls (NC) and 28 female FM subjects tested the effects of trapezius muscle (TrapM) tender point injections with 1% lidocaine (50 mg) on local pain thresholds as well as on remote heat hyperalgesia at the forearm. Prior to muscle injections shoulder pain was standardized by tonic mechanical muscle stimulation, resulting in local pain ratings of 4.0 ± 0.5 VAS units. Tonic muscle stimulation was interrupted for the TrapM injections but continued afterwards at the same level. Mechanical pain thresholds were tested at the shoulders using an electronic algometer. Heat hyperalgesia at the forearm was determined using 10 sec sensitivity adjusted stimuli between 45 and 49 ^{0}C.

Results: NC as well as FM subjects experienced significant increases of TrapM pressure pain-thresholds from lidocaine but not placebo injections ($p < .001$). Additionally, heat-hyperalgesia of FM participants was significantly reduced at areas remote from the injection site (forearm) by lidocaine but not placebo ($p = .02$). Neither lidocaine nor saline injections significantly affected clinical FM pain ratings, a result most likely due to the very low dose of lidocaine (50 mg) used in this trial. The subjects were unable to estimate which study drug they received, thus maintaining allocation concealment.

Conclusion: Lidocaine injections increased local pain-thresholds and decreased remote secondary heat hyperalgesia in FM patients, emphasizing the important role of peripheral impulse input in maintaining central sensitization in this chronic pain syndrome; similar to other persistent pain conditions like IBS and CRPS.

Disclosure: R. Staud, Jazz Pharmaceuticals, 2 ; **S. Nagel**, None; **M. E. Robinson**, None; **D. D. Price**, None.

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Determinants of the Quality of Life in Patients with Fibromyalgia: a Structural Equation Modeling Approach. Shin-Seok Lee[1], Seong Ho Kim[2], Seong-Su Nah[3], Ji Hyun Lee[4], Seong-Kyu Kim[5], Yeon-Ah Lee[6], Seung-Jae Hong[6], Hyun-Sook Kim[7], Hye-Soon Lee[8], Hyoun-Ah Kim[9] and Chung-Il Joung[10], [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Dongguk University College of Medicine, Gyeongju, South Korea, [3]Soonchunhyang University College of Medicine, Cheonan, South Korea, [4]Maryknoll Medical Center, Busan, South Korea, [5]Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]School of Medicine, Kyung Hee University, Seoul, South Korea, [7]College of Medicine, Chosun University, Gwangju, South Korea, [8]Hanyang Univ Medical Center, Seoul, South Korea, [9]Ajou University School of Med, Suwon, South Korea, [10]Konyang University Medical School, Daejeon, South Korea

Purpose: Health-related quality of life (HRQOL) in patients with fibromyalgia (FM) is lower than in patients with other chronic diseases and the general population. Although various factors affect HRQOL, including socioeconomic status, no studies have examined a casual model of HRQOL as an outcome variable in FM patients. We examined the relationships between sociodemograhpic status, physical function, social and psychological factors, and HRQOL, and the effects of physical, psychological, and social influences on HRQOL were assessed in a hypothesized causal model using a structural equation modeling (SEM) approach.

Method: HRQOL was measured using the SF-36, and a Korean version of the Fibromyalgia Impact Questionnaire (FIQ) was used to assess the physical dysfunction. Social and psychological status were assessed using the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), the Self-Efficacy Scale, and the Social Support Scale. SEM analysis was used to test the structural relationships of the model using AMOS software, with the maximum likelihood ratio as the method of estimation.

Results: Of the 336 patients, 301 (89.6%) were women with an average age of 47.9±10.9 years (mean±SD). The mean scores of the physical (PCS) and mental (MCS) component summary of the SF-36 were 35.9±7.5 and 33.7±11.8, respectively. The SEM results supported the hypothesized structural model ($\chi^2 = 2.336$, df = 3, p = 0.506). The final model showed that PCS was directly related to self-efficacy and inversely related to FIQ, and MCS was directly related to social support and inversely related to FIQ, BDI, and STAI.

Conclusion: In our causal model of FM patients, HRQOL was affected by physical, social, and psychological variables. In these patients, higher levels of physical function and self-efficacy can improve the physical component of HRQOL, while physical function, depression, anxiety, and social support affect the mental component of HRQOL.

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Measures of Tenderness as Predictors of Clinical Pain in Patients with Fibromyalgia. Roland Staud, Jamie Goldman, Susann Nagel, Michael E. Robinson and Donald D. Price, Univ of Florida, Gainesville, FL

Purpose: Fibromyalgia (FM) patients complain of widespread pain, tenderness, and distress. Although tender points (TP) are part of the 1990 ACR Criteria for FM, they represent better predictors of distress than tenderness in this pain population. Since tenderness not only represents a risk factor for chronic pain, but correlates with clinical and experimental pain intensity, other methods than TP are needed to characterize FM. Therefore we used painful heat stimuli at TP areas to characterize the widespread hyperalgesia of FM patients. Mechanical pain threshold testing at TP sites was used for comparisons.

Method: 32 normal controls (NC) and 30 FM patients received 5sec heat-stimuli of 45 and 47^{0}C to 16 body areas corresponding to TP-locations. The participants rated experimental and clinical pain using a visual analogue scale (VAS). In addition mechanical pain-thresholds (MPT) were obtained at the same TP areas using an electronic algometer..

Results: NC and FM patients had 4.5 and 16.3 TP, respectively. FM patients' clinical pain ratings were 4.3 VAS units. Average pain ratings at all TP sites for MPT, 45 and 47^{0}C heat stimuli, were 522.2kPa, 2.2VAS, and 3.5VAS units for NC and 227.8kPa, 4.1VAS and 5.8VAS units for NC and FM subjects, respectively. These group differences were all highly significant (p<.001). A Pearson's product moment correlation between TP, MPT, and suprathreshold heat pain ratings was significant for TP count and MPT (r=-0.7; p<.001) as well as TP count and 45^{0}C heat pain ratings (r=0.05; p=.008) in FM patients. Although NCs' correlations of TP count with MPTs were significant (r=-0.63; p <.001), correlations between TP and heat pain ratings were not (p > .05). Correlations of clinical FM pain with MPT and heat pain ratings ranged between r=-0.5 (p< .02) and r=0.4 (p=.04), respectively.

Conclusion: These results show not only that mechanical and heat-pain tenderness are significantly different between FM and NC but also that these measures can be used to characterize the abnormally widespread tenderness of FM patients. As hypothesized MPT and suprathreshold heat pain ratings may also be useful for prediction of clinical FM pain.

Disclosure: R. Staud, Jazz Pharmaceuticals, 2 ; **J. Goldman**, None; **S. Nagel**, None; **M. E. Robinson**, None; **D. D. Price**, None.

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Treatment of Fibromyalgia with Pindolol: A 12-Week, Open-Label, Fixed Dose Escalation, Observational Study. Patrick B. Wood[1] and Andrew J. Holman[2], [1]LSUHSC-Shreveport, Shreveport, LA, [2]Pacific Rheumatology Assoc, Renton, WA

Purpose: Fibromyalgia(FM) is an enigmatic, musculoskeletal disorder associated with varied symptom domains often inadequately responsive to current pharmacotherapeutic options. Objective abnormalities associated with the disorder include dysautonomia and increased responsiveness of cortical neurons to painful stimulation. As a novel choice, pindolol, a lipophilic mixed beta1/beta2 receptor antagonist with intrinsic sympathetic activity, was evaluated in a pilot study. Its potential therapeutic benefit in FM may relate either to reduction of a beta-adrenergic dependent sensitization of peripheral nociceptors or attenuation of stress-induced cortical hyper-excitability.

Method: In a tertiary, FM referral clinic, pindolol response was evaluated in an open-label, fixed dose escalation trial design in subjects meeting 1990 ACR criteria for FM. Subjects continuing concomitant medications were evaluated at baseline (visit 1) and began pindolol at 2.5 mg po qhs continued for 7 days after which they increased the dose to 5 mg po qhs. Two follow up visits were conducted at 4 weeks (Visit 2) and 12 weeks (Visit 3). The primary outcome measure was reduction in total score on the Fibromyalgia Impact Questionnaire (FIQ). Secondary outcomes included total score on the Fibromyalgia Symptom Inventory (FSI), tender point count (TPC) and tender point score (TPS) calculated as the sum of 18 tender points scored as 0 for painless, as 1 for classic 4 kg tenderness, as 2 for tenderness with grimace and as 3 for pain with withdrawal. Response to treatment was operationally defined as $\geq$ 30% reduction in total FIQ score. A repeated measures ANOVA was used to evaluate outcomes.

Results: Over a five month period, 22 female patients (mean age 51.1 [range 26-74], mean BMI 31.7) began pindolol as described and continued therapy for a mean pindolol exposure of 105.2 ± 18.0 days. Overall, FIQ decreased from a baseline of 50.3 ± 12.4 to 42.6 ± 19.1 ($p = 0.008$). Similar statistically significant outcomes were found for change in FSI ($p=0.001$), TPC ($p=0.009$) and TPS ($p=0.016$). Seven of 22 patients (31.7%) were defined as responders by FIQ. Among responders, FIQ decreased from a baseline of 47.7 ± 14.4 to 21.4 ± 11.5 (-55%; $p=0.002$), FSI decreased from 47.9 ± 12.0 to 30.4 ± 9.8 (-36%; $p=0.007$), TPC decreased from 15.1 ± 1.8 to 10.9 ± 4.6 (-28%; $p=0.028$) and TPS decreased from 25.9 ± 6.7 to 15.9 ± 8.0 (-38%; $p=0.006$). Responders and non-responders did not differ at baseline in terms of clinical parameters. Regression analysis demonstrated correlation between patient age and improvements on both FIQ total score and TPS (FIQ: $r2= 0.268$, $p=.014$; TPS: $r2=0.289$, $p<.01$). Side effects were mild and consisted of increased diaphoresis (n=9) and increased frequency/intensity of dreams (n=5), which are in accordance with product labeling.

Conclusion: This pilot study suggests that pindolol, a generic, inexpensive and familiar medication, is safe and efficacious in a subset of patients with FM. Further studies are indicated to confirm these results and elucidate pindolol's mechanism of action in patients with FM.

Disclosure: P. B. Wood, None; **A. J. Holman**, Jazz Pharmaceuticals, 2 .

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Sustained Depletion of Biogenic Amines Causes Chronic Muscular Pain and Tactile Allodynia Accompanied by Depression: A Putative Animal Model of Fibromyalgia. Tomoya Oe, Yukinori Nagakura, Toshiaki Aoki and Nobuya Matsuoka, Astellas Pharma Inc., Tsukuba, Japan

Purpose: Fibromyalgia (FM) is a musculoskeletal syndrome characterized by chronic widespread pain, tenderness to palpation, and various concomitant symptoms, including depression. Although exact pathogenesis of FM remains to be elucidated, dysfunction of biogenic amine-mediated central nervous system (CNS) pain control may underlie the pathophysiology of FM. To establish new treatments for pain-centered FM symptoms, the development of animal models which mimic the features of human FM patients is an urgent issue. In the present study, we developed an FM animal model by using reserpine (long-acting depletor) or tetrabenazine (short-acting depletor) to deplete biogenic amines in the CNS.

Method: Male and female SD rats were used in the present study. Reserpine (1 mg/kg) was subcutaneously administered to animals once daily for 3 consecutive days, while tetrabenazine (20 mg/kg) was given as a single intraperitoneal dose. Muscle pressure threshold (to the gastrocnemius muscle) and tactile response threshold were determined using the Randall-Selitto apparatus and von Frey filaments, respectively. Biogenic amine (dopamine, norepinephrine, and 5-hydroxytriptamine) content in the brain and spinal cord was measured using HPLC. Immobility time in the forced swim test (index of depression) was assessed using an automated swimming behavior analysis system. The effect of drug administration (pregabalin, duloxetine, pramipexole, and diclofenac) on pain thresholds was evaluated 5 days after the last injection of reserpine.

Results: Reserpine significantly reduced muscle pressure and tactile response thresholds, and these effects were sustained for 1 week or more in both male and female rats. In contrast, tetrabenazine did not produce significant decreases in these thresholds. Reserpine administration decreased the content of dopamine, norepinephrine, and 5-hydroxytriptamine in the spinal cord, thalamus, and prefrontal cortex for over a week. Further, reserpine significantly increased immobility time in the forced swim test. Pregabalin (10, 30 mg/kg, p.o.), duloxetine (30 mg/kg, p.o.), and pramipexole (0.3, 1 mg/kg, s.c.), but not diclofenac (1 - 10 mg/kg, p.o.), significantly attenuated the reserpine-induced decrease in muscle pressure threshold.

Conclusion: Sustained depletion of biogenic amines caused FM-like pain symptoms accompanied by depression in rats. The validity of the use of this reserpinized animal as an FM model is demonstrated from three different aspects: face validity (manifestation of chronic pain and comorbid symptoms), construct validity (involves dysfunction of biogenic amine-mediated CNS pain control), and predictive validity (similar responses to treatments used in FM patients). This animal model will contribute to the better understanding of FM pathophysiology and evaluation of anti-FM drugs.

Disclosure: T. Oe, Astellas Pharma Inc., 3 ; **Y. Nagakura**, Astellas Pharma Inc., 3 ; **T. Aoki**, Astellas Pharma Inc., 3 ; **N. Matsuoka**, Astellas Pharma Inc., 3.

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Hand Joints and Tendons Involvement in Antiaromatase Users: a Follow-up Clinical and Ultrasonographic Study (D5392L00013). K. Briot[1], B. Lecoq[2], A. Fontana[3], F. Debiais[4], T. Schaeverbeke[5], M. Licour[6] and C. Roux[1], [1]Cochin hospital, Paris, France, [2]CHU Caen, Caen, France, [3]Hopital Edouard Herriot, Lyon, France, [4]CHU Poitiers, Poitiers, France, [5]CHU Bordeaux, Bordeaux, France, [6]Astra Zeneca, Rueil Malmaison, France

Purpose: Aromatase inhibitors (AIs) are standard adjuvant endocrine-therapy in postmenopausal women with hormone-sensitive breast cancer, but can cause musculoskeletal symptoms. The pathogenic and anatomic features of AI-induced pain have not been clearly delineated. Previous studies showed that hand is the most common site of these symptoms.

The objective of the study was to describe the 6-month changes in clinical rheumatologic and ultrasonographic (US) examination of hands in anastrozole users.

Method: 106 postmenopausal women (mean age 62.9 ±6.9 years) were included in a 6-month prospective open study. All of them were naïve of AI and tamoxifen treatment and began anastrozole. Rheumatologic and US examination (mode B and power Doppler) of hands (wrists and fingers) were assessed at baseline and 6 months. Synovitis was graded on a scale of 0–3 according to a semiquantitative scale and Power Doppler was graded as positive (PD+) or negative (PD-).

Results: At baseline, 27 (25.5%) patients described hands pain which are associated with one tenosynovitis but no clinical synovitis whereas US evaluation showed synovitis in 15 patients (55.6%), with PD+ in 7 patients (25.9%) and tenosynovitis in 3 patients (11.1%) with PD+ in 2 patients (7.4%). After 6 months of treatment, 24 patients had still pain associated with one clinical synovitis and no tenosynovitis.

Among the 79 women (74.5 %) without baseline hands pain, physical evaluation found no synovitis and one tenosynovitis. US exam revealed synovitis in 39 patients (49.4%) with PD+ in 15 patients (19%) and tenosynovitis in 13 patients (16.5%) with PD+ in 4 patients (5.1%). At 6 months, 25 patients (31.6%) reported hands pain with clinical synovitis (n=2, 2.5%) and tenosynovitis (n=2, 2.5 %).

The results of US examination at 6 months are reported in the table

	Patients with hand pain at baseline (n=27)	Patients without hand pain at baseline (n=79)

	N (%)	N (%)
Synovitis at baseline	15 (55.6)	39 (49.4)
PD+	7 (25.9)	15 (19.0)
Synovitis at M6	15 (55.6)	38 (48.1)
Yes	14 (51.9)	34 (43.0)
Grade 1	8 (29.6)	21 (26.6)
Grade 2	2 (7.4)	6 (7.6)
Grade 3	7 (25.9)	17 (21.8)
PD+		
Tenosynovitis at baseline	3 (11.1)	13 (16.5)
PD+	2 (7.4)	4 (5.1)
Tenosynovitis at M6	5 (18.5)	13 (16.5)
PD+	3 (11.1)	9 (11.5)

Among patients without pain before initiation of anastrozole, who experienced hands pain (n=25), US examination showed 16 synovitis (64%) with PD+ in 9 (36%) and 8 tenosynovitis (32%) with PD+ in 6(24%).

Conclusion: This prospective study suggests that 30% of women without hands pain before beginning anastrozole experienced hands pain which are not associated with a significant increase in US synovitis, and that structural changes in joints of the hand are frequent in postmenopausal women with symptoms or not.

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Is Sleep Quality a Bookmark of Clinical Severity in Fibromyalgia? Casanueva Fernández B[1], Belenguer Prieto R[2,] Peña Sagredo JL[3], González-Gay MA[4],1- Rheumatologist. Rheumatology Services at the Specialist Clinic of Cantabria. Santander. Cantabria, Spain, 2- 9 d'Octubre Hospital, Valencia, Spain, 3- Rheumatology Services at Valdecilla Hospital, Santander, Cantabria, Spain, 4- Rheumatologist, Rheumatology Services at Xeral Hospital, Lugo, Spain.

Purpose & Background: The aim of the present study is to analyze if the quality of sleep, assessed with the Pittsburgh Sleep Quality Index (PSQI), has influence over pain symptoms, fatigue, anxiety, depression, psychological pattern, coping, impact of the illness, stress, quality of life and invalidity, in patients with fibromyalgia (FM).

Methods: A total of 510 patients (480 women and 30 men) with a diagnosis of FM (ACR criteria) were included. The delay in diagnosis, work activity, granting of disability, questionnaire about 75 symptoms, analysis of pain, catastrophic thinking, fatigue, anxiety, depression, psychological pattern, coping, impact of fibromyalgia, state of health, stress, quality of life, handicap, and sleep analysis were reviewed for all patients. After applying the PSQI the patients were classified into four groups. The first group contained 15 patients whose total score in the PSQI was ≤ 5; they were considered good sleepers (GS). A second group consisted of 41 patients whose score in the PSQI was between 6 and 8; this group was termed slightly bad sleepers (SBS). A third group was made up of 105 patients, with a score oscillating between 9 and 11, and who were considered moderately bad sleepers (MBS). Finally, there was a fourth group, made up of 349 patients who scored ≥ 12, and considered to be very bad sleepers (VBS). The SPSS 15 statistical package for Windows was used for the statistical analysis of the data.

Results: In our sample, 68% of the patients show severe sleep alterations and only 3% could consider themselves good sleepers. The VBS patients showed statistically significant differences with respect to GS, SBS and MBS in the number of symptoms, pain, fatigue, depression, anxiety, quality of life, impact of FM, state of health and stress level. The SBS showed statistically significant differences with respect to the MBS in pain levels, fatigue, impact of FM, catastrophic thinking, physical function, and self perception of general health and vitality.

Conclusion: The degree of sleep change, evaluated with the PSQI, permits the differentiation of four groups of patients who present not only significant statistical differences regarding quality of sleep but also relating to severity of pain, fatigue, depression, anxiety , impact of FM and quality of life. Thus, beyond merely evaluating the quality of sleep, the PSQI does serve as a bookmark of global clinical severity in patients with FM.

Disclosure: B. Casanueva Fernandez, None.

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Medical Resource Utilization and Workdays Lost in a European Survey of Patients with Fibromyalgia. Joris Kleintjens[1], Pascale Peeters[2], Anke van Engen[1], Gavin Taylor-Stokes[3], Katell le Lay[4] and Charles Taieb[5], [1]Quintiles Consulting, WT Hoofddorp, Netherlands, [2]Quintiles Consulting, Levallois-Perret, France, [3]Adelphi Group, Macclesfield, Cheshire, United Kingdom, [4]Pierre Fabre, Boulogne-billancourt, France, [5]PFSA, Boulogne, France

Purpose: Fibromyalgia or fibromyalgia syndrome (FMS) is characterized by chronic widespread muscular pain and generalized tender points, often accompanied often accompanied by a number of associated symptoms such as fatigue, sleep disturbance, psychological distress. The objective of this study was to assess the medical resource utilization (MRU) and workdays lost (WDL) of FMS patients according to their health status defined by level of pain and fatigue.

Method: The Adelphi Fibromyalgia Disease Specific Programme is a cross-sectional survey among 2,159 FMS patients in France, Germany, Italy, Spain and the UK. The survey included one questionnaire filled in by the patient and one by the physician. Patient health states were defined on the basis of items 15 and 16 (100mm VAS scales) of FIQ (Fibromyalgia Impact Questionnaire).

Results: From the pool of 2159 FMS patients, 802 patients (<40mm; 37.1%) presented with mild pain, 729 with moderate pain (40-70mm; 33.8%), and 628 with severe pain (>70mm; 29.1%). Most patients with moderate (80.5%) or severe pain (95.5%) also suffered from fatigue. A total of 1341 patients had significant fatigue (cut off: 50mm), associated with mild (N=154), moderate (N=587) or severe (N=600) pain. In these patients, the annual number of physician visits per patient (5.71, 6.14 and 7.47 respectively), co-medication costs per 4 weeks (£3.66, £5.48 and £8.11), as well as the annual hospitalisation rate (2.6%, 5.6% and 7.5%) and length of stay per patient per year (0.42, 1.69 and 1.95 days, respectively) increased following the level of pain. Similarly, the percentage of patients on sick leave and its duration were larger in patients with fatigue and moderate (11.9% and 40 weeks) or severe (20.0% and 44 weeks) pain, compared to patients with mild pain (8.4% and 33 weeks).

Conclusion: In FMS patients who present with significant fatigue, medical resource utilization and workdays lost increase with respect to the level of pain.

Disclosure: J. Kleintjens, Pierre Fabre, 5 ; **P. Peeters**, Pierre Fabre, 5 ; **A. van Engen**, Pierre Fabre , 5 ; **G. Taylor-Stokes**, Pierre Fabre, 5 ; **K. le Lay**, Pierre Fabre, 3 ; **C. Taieb**, None.

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SELDI-TOF Proteomic Whole Saliva Profiling in Fibromyalgic Patient. Camillo Giacomelli, Laura Bazzichi, Federica Ciregia, Chiara Baldini, Francesca Sernissi, Laura Giusti, Arianna Consensi, Claudia Ferrari, Antonio Lucacchini and Stefano Bombardieri, University of Pisa, Pisa, Italy

Purpose: Fibromyalgia (FM) is a chronic non inflammatory musculoskeletal disorder characterised by widespread pain and by the presence of at least 11 out of 18 specific tender points on physical examination. Currently no validated laboratory biomarkers are available for FM and the diagnosis of the disease remains exclusively clinical. The aim of the present study was to perform a proteomic analysis of FM patients' saliva with surface-enhanced laser desorption/ionization time-of-flight/mass spectrometry (SELDI-TOF/MS).

Method: In the first step we enrolled 40 females (mean age 43.60±11.30 yrs, M±SD) all fulfilling the ACR criteria for FM and 35 healthy controls with similar demographic characteristics. In order to confirm these preliminary results, in the second step, we performed other independent experiments on a validation set composed by 26 FM subjects and 16 healthy controls. Whole saliva samples are centrifuged to remove undissolved material. Aliquots of resulting supernatants are analysed by SELDI-TOF/MS. Saliva is applied to the spots of Protein Chip Arrays (CM10, Q10, H50). After an incubation period (1h), unbound proteins and other contaminants are washed off the spots using buffers as required by the array chemistry; only proteins interacting with the chemistry of the array surface are retained for analysis. Finally matrix (sinapinic acid-SPA) is applied to each spot to facilitate laser desorption and ionization. The statistical analysis was performed using cluster analysis, and the difference between two groups was underlined using t-student test.

Results: The analysis of the obtained spectra on three chips, after validation, allowed us to observe 14 peaks (ranging from 3374 and 24087 *m/z*) differently expressed in FM patients ($p<0.05$) with respect to the controls. The preliminary results obtained by SELDI-TOF analysis were compared with those obtained in an our previous work (work submitted) performed in whole saliva of FM patients by using two-dimensional electrophoresis (2DE) and matrix-assisted laser/desorption ionisation time-of-flight (MALDI-TOF-MS). The m/z of two peaks increased in FM patients (11040, 22961) well overlap with the molecular weight of calgranulin A and C (11 kDa) and Rho GDP-dissociation inhibitor 2 (23 KDa), found up-regulated in FM patients with 2DE. Further studies could be useful to confirm these data and identify other significant peaks detected.

Conclusion: These preliminary results showed the possibility to identify a salivary biomarker through salivary proteomic analysis with SELDI-TOF in FM patients. This study demonstrated that 2DE-MALDI-TOF-MS and SELDI-TOF-MS might be valid complementary techniques able to identify the potential novel diagnostic biomarkers for FM.

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What Is the True Cost of Fibromyalgia to Our Society: Results From a Cross-Sectional Survey in the United States. Don L. Goldenberg[1], Caroline Schaefer[2], Kellie Ryan[2], Arthi Chandran[3] and Gergana Zlateva[3], [1]Newton-Wellesley Hosp, Newton, MA, [2]Covance Market Access Services, Gaithersburg, MD, [3]Pfizer Inc, New York, NY

Purpose: Patients with fibromyalgia (FM) report persistent, widespread pain, fatigue, and significant functional limitations. While several retrospective studies have documented that FM is associated with substantial direct and indirect health care costs[1], patient-level research has not been reported in the US. The objective of this study is to assess direct and indirect costs associated with FM in routine clinical practice in the US.

Method: This cross-sectional, observational study recruited 203 FM subjects from 20 community-based physician offices. Subjects completed questions about pain, health-related quality-of-life, productivity, and out-of-pocket expenses related to FM; site staff recorded subjects' treatment and medical resource use based on a review of medical records. Annual costs from a societal perspective were calculated in 2009 US dollars.

Results: Subjects had a mean (SD) of 6.1 (8.2) FM-related office visits over the past 3 months with a mean (SD) of 4.2 (4.5) visits to physicians, corresponding to 24.4 office visits and 16.8 physician office visits per year. Most subjects (92%) were taking at least one, and over half (54%) were taking 3 or more prescription FM medications. The highest proportions of subjects were prescribed anti-depressants (56%), analgesics other than anti-inflammatories (52%) and anti-epileptics (38%). Subjects employed full- or part-time (40% of sample) reported missing a mean (SD) of 1.8 (3.9) days of work to FM over the last 4 weeks, corresponding to 23.4 days of work missed due to FM per year. Among subjects not employed, 38% reported being disabled due to FM and 34% reported being unemployed or retired early due to FM. The mean (SD) annual direct costs per subject for FM were $7,973 ($7,341), including physician office visits $1,528 ($1,953), diagnostic tests $435 ($1,859), prescription medications $3,419 ($3,667), emergency room visits $43 ($323), and out-of-pocket costs incurred by subjects for FM treatments $1,798 ($3,056) and home healthcare services $750 ($1,756). The mean (SD) annual indirect costs per subject for FM were $10,697 ($20,463), including $1,228 ($4,904) related to absenteeism and $9,470 ($20,446) related to disability due to FM, including both disability payments and the opportunity cost of not working. These figures do not include additional substantial indirect costs related to FM, including reductions in work schedule or early retirement for patients, and lost productivity for caregivers due to FM.

Conclusion: FM imposes a significant economic burden on society. Consistent with other studies, there are substantial direct and indirect costs associated with FM, with indirect costs due to lost productivity accounting for the largest proportion of costs.

[1]White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. J Occup Environ Med 2008;50:13-24.

Disclosure: D. L. Goldenberg, Pfizer Inc, 9 ; **C. Schaefer**, Pfizer Inc, 5 ; **K. Ryan**, Pfizer Inc, 5 ; **A. Chandran**, Pfizer Inc, 1, Pfizer Inc, 3 ; **G. Zlateva**, Pfizer Inc, 3.

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Telephone-Delivered Cognitive Behavioral Therapy (CBT) On Clinical Symptoms and Nociceptive Responding in Fibromyalgia (FM) – A Pilot Study. Dennis C. Ang[1], Rafael Chakr[1], Steven A. Mazzuca[2] and Christopher France[3], [1]Indiana University, Indianapolis, IN, [2]Indiana Univ Sch of Med, Indianapolis, IN, [3]Ohio University, Athens, OH

Purpose: Traditional CBT (face-to-face) has been shown to improve the clinical symptoms of FM. However, due to cost and scarcity of skilled therapist, practical application of CBT is limited. More importantly, although various psychological models have been theorized to explain CBT's beneficial effects, the biological mechanisms of CBT have been unexplored. Thus, we sought to determine the effects of telephone-delivered CBT on self-reported pain, physical function and nociceptive responsivity (i.e., nociceptive flexion reflex/NFR). NFR is a neurophysiological tool that measures responsivity to noxious stimulation via elicitation of a spinal withdrawal reflex upon stimulation of a sensory nerve.

Method: FM patients with Fibromyalgia Impact Questionnaire (FIQ)-pain score ≥ 4 and FIQ-physical impairment (FIQ-PI) score ≥ 2 were randomized to 6 sessions of telephone-delivered CBT or usual care (UC). CBT was delivered from week 0 to 6. Assessments were done at baseline, week 6 and 12. Study endpoint was the change from baseline in NFR threshold (milliamperes/mA). Clinical endpoints were the changes from baseline in the FIQ-PI, FIQ-pain; and the proportion of subjects achieving a clinically meaningful reduction (i.e. 14%) in the total FIQ.

Results: The 28 female participants had a mean age of 47 ± 11 years, mean disease duration of 12 ± 6 years, and were 80% white, and 83% with > high school education. At study entry, 15 (53%) were on narcotics and 19 (68%) were on antidepressant other than tricyclics. There were no differences in the demographics, depression severity, and medication usage between the treated and the usual care groups.

Baseline Characteristics

	CBT (n=15)	**UC** (n=13)
Nociceptive Responsivity		
NFR threshold (mA†)	32.5 ±15	37.6 ± 10
Clinical Outcomes		
FIQ-PI (0-10*)	5.6 ± 1.8	5.4 ± 1.7
FIQ-pain (0-10*)	7.6 ± 1.8	7.8 ± 1.4
Total FIQ (0-100*)	62.2 ± 15	67.8 ± 12

†Lower values reflect higher responsivity to electrical stimulation.

***Higher scores reflect more severe symptoms.**

Mean Changes from Baseline to Week 12

	CBT (n=15)	UC (n=13)	Mean Difference	P value
Nociceptive Responsivity				
NFR threshold	7.3 ± 9.2	-5.4 ± 13.5	-12.7 ± 11.4	0.006
Clinical Outcomes	-0.6 ± 2.3	0.5 ± 1.2	1.1 ± 1.9	0.13
FIQ–PI				
FIQ-pain	-0.6 ± 1.6	-0.3 ± 1.7	0.3 ± 1.7	0.6

Compared to usual care, CBT resulted in marginal improvements in clinical outcomes (table) and in the percent of patients with clinically meaningful improvements in total FIQ score (33% vs. 15%, p=0.3). However, CBT also resulted in a significant lowering of nociceptive responding, as evidenced by an increase in the NFR threshold, relative to controls.

Conclusion: This small pilot study was powered primarily to detect an effect of CBT on the NFR threshold. These data indicate the need for a larger study to confirm that changes in central sensitization, as reflected in the NFR, may underlie the benefits of CBT in FM patients.

Disclosure: D. C. Ang, None; **R. Chakr**, None; **S. A. Mazzuca**, None; **C. France**, None.

ACR Poster Session A

Human Etiology and Pathogenesis

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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OAZ Interfere with the Production of Antinuclear Antibody in Patients with Systemic Lupus Erythematosus. Xuebing Feng[1], Ronliang Li[2], Jing Huang[2], Betty P. Tsao[3] and Lingyun Sun[1], [1]the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [3]Division of Rheumatology, UCLA, Los Angeles, CA

Purpose: To study whether gene expression levels of OAZ (Olf1/EBF associated zinc finger protein, a transcription factor encoded by a positional SLE candidate gene) and its possible downstream gene, ID3 (inhibitor of differentiation 3), play a functional role in the pathogenesis in SLE.

Method: Gene expression levels in peripheral blood cells (PBLs) measured using quantitative real-time quantitative PCR (qPCR) were assessed for association with disease activity and the presence of specific autoantibodies. Peripheral blood mononuclear cells (PBMCs) from 5 SLE patients were incubated with specific siRNAs for 3 days, then cells were harvested for measuring mRNA levels using qPCR, and supernatants for levels of secreted cytokines, chemokine, and antinuclear antibodies (ANA) using ELISA. Indirect immunofluorescence was also applied for ANA detection.

Results: OAZ and ID3 gene expressions in PBLs from 30 SLE patients were significantly increased than PBLs from 20 normal controls ($p < 0.01$). In SLE patients, OAZ and ID3 transcripts were positively correlated with SLEDAI score ($r = 0.74$ and 0.69, $p < 0.0001$) and OAZ expressions were higher in those positive for IgG antibodies to dsDNA or RNA-containing proteins ($p < 0.05$). Co-culturing with OAZ siRNAs reduced mRNA levels of OAZ and ID1-3 by 73.5%, 68.7%, 70.2% and 67.7% respectively as compared to those co-cultured with non-targeting siRNA. Compared to negative control groups, OAZ silencing resulted in reduced ANA (shown in Figure 1), IFN-gamma, IL-10, IL-12 and IL-21, and elevated CCL2 levels in culture supernatants ($p < 0.05$). The declined ANA levels correlated with the ratio of OAZ inhibition ($r = 0.88$, $p = 0.05$), reduced IL-21 levels ($r = 0.99$, $p < 0.01$), and elevated CCL2 levels ($r = -0.98$, $p < 0.01$).

Conclusion: OAZ, a new lupus candidate gene, is highly expressed in SLE PBLs, which may act through the regulation of ID genes as well as cytokines and chemokines to increase the ANA secretion. Our data show a role of OAZ-ID pathway in the pathogenesis of SLE.

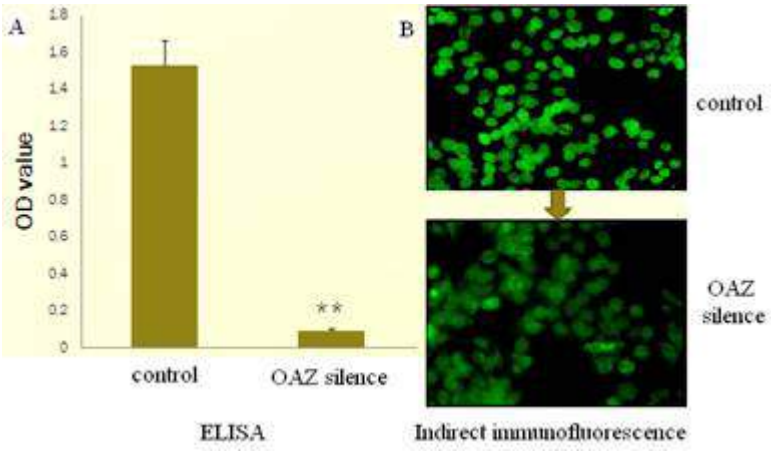

Figure 1 Decreased ANA production after OAZ silence as detected by ELISA and indirect immunofluorescence.

Disclosure: X. Feng, None; **R. Li**, None; **J. Huang**, None; **B. P. Tsao**, None; **L. Sun**, None.

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The Epigenome of SLE. Kathleen E. Sullivan[1], Zhe Zhang[2] and Michelle Petri[3], [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Bioinformatics, Philadelphia, PA, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Systemic lupus erythematosus is a polygenic disorder where recent data have implicated interferons in the pathogenesis of the disease. The expression of many genes downstream of interferons are regulated at the level of histone modifications. We examined whether the disease process could significantly alter histone modifications at multiple gene loci and in turn alter the competence for expression of genes relevant to the SLE disease process.

Method: We examined H4 acetylation and gene expression in monocytes from patients with systemic lupus erythematosus to define alterations to the epigenome. Monocytes from 14 controls and 24 SLE patients were used for analysis by chromatin immunoprecipitation for H4 acetylation and gene expression arrays. Primary monocytes treated with a-interferon were used as a comparator. Data were analyzed for concordance of H4 acetylation and gene expression. Network analyses and transcription factor analyses were performed to identify potential pathways.

Results: H4 acetylation was significantly altered in monocytes from patients with systemic lupus erythematosus. Sixty three percent of genes with increased H4 acetylation had the potential for regulation by IRF1. IRF1 binding sites were also upstream of nearly all genes with both increased H4 acetylation and gene expression. a-interferon was a significant contributor to both expression and H4 acetylation patterns but the greatest concordance was seen in the enrichment of certain transcription factor binding sites upstream of genes with increased H4 acetylation in SLE and genes with increased H4 acetylation after a-interferon treatment.

Conclusion: Monocytes have been significantly altered as a consequence of the disease process. Alterations to the epigenome can be long lived and can contribute to sustained pathologic cell behavior.

Disclosure: K. E. Sullivan, None; **Z. Zhang**, None; **M. Petri**, None.

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RFX1 Regulates the Expression of CD11a and CD70 in CD4+ T Cells of Patients with Systemic Lupus Erythematosus. Ming Zhao[1], Fei Gao[1], Xiaoyan Wu[1], Jinling Tang[1], Yongqi Luo[1], Yimin Sun[2], Bruce C. Richardson[3] and Qianjin Lu[1], [1]The Second Xiangya Hospital, Central South University, Changsha, China, [2]Tsinghua University School of Medicine, Beijin, China, [3]University of Michigan, Ann Arbor, MI

Purpose: Abnormal T lymphocyte activation plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). CD11a and CD70 are overexpressed in $CD4^+$ T cells of patients with SLE, contributing to T cell autoreactivity and autoantibody production, respectively. To understand why these genes are overexpressed, we sought to identify key transcription factors involved in CD11a and CD70 regulation.

Method: Peripheral blood mononuclear cells from 35 patients with SLE and 30 healthy controls were isolated by Ficoll-Hypaque density gradient centrifugation, and the CD4+ subpopulation was extracted using Miltenyi beads. Transcription factor activity and expression levels were assessed using oligonucleotide array-based assays, real-time RT-PCR and Western blot. RFX1-expressing and RFX1 siRNA constructs were transfected into $CD4^+$ T cells using Human T cell Nucleofector kits. CD11a and CD70 transcription levels were measured by RT-PCR, and IgG levels were measured by ELISA. The promoter region of CD11a and CD70 were cloned into pGL3 vectors. The binding and regulatory activity of RFX1 was determined by ChIP and luciferase assays. Protein interactions with RFX1 were examined by immunoprecipitation.

Results: Compared to healthy controls, the activity of several transcription factors, including RFX1, MIF1 and SRF was downregulated in $CD4^+$ T cells from SLE patients . The reduction in RFX1 expression was confirmed by quantitative RT-PCR ($p<0.01$) and Western blot ($p<0.05$). Transfecting lupus CD4+ T cells with RFX1 led to significant decreases in CD11a and CD70 expression and B cell stimulation. In contrast, knocking down RFX1 expression with RNAi induced CD11a and CD70 overexpression in normal CD4+ T cells, and significantly increased IgG production by autologous B cells. Moreover, we found that RFX1 could directly regulate the expression of CD11a and CD70 by binding to their promoter regions, as shown by ChIP and luciferase reporter assays. In addition, IP revealed that the regulatory activity of RFX1 in $CD4^+$ T cells was dependent on the recruitment of co-repressors, such as the acetylation factor HDAC1 and the methylation factor DNMT1.

Conclusion: Our data suggest that overexpression of CD11a and CD70 in $CD4^+$ T cells of SLE patients is caused at least in part by the downregulation of RFX1. Reduced RFX1 may decrease the recruitment of HDAC1 and DNMT1 to the promoter regions of CD11a and CD70, facilitating their expression and promoting autoimmune responses.

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Disclosure: M. Zhao, None; **F. Gao**, None; **X. Wu**, None; **J. Tang**, None; **Y. Luo**, None; **Y. Sun**, None; **B. C. Richardson**, None; **Q. Lu**, None.

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Analysis of SLAM Family Receptors in SLE. Jong R. Kim[1], Rahul K. Patel[1], Stephen O. Mathew[1], Raymond M. Pertusi[2] and Porunelloor Mathew[1], [1]University of North Texas Health Science Center, Fort Worth, TX, [2]Harvard Vanguard Medical Associates, Boston, MA

Purpose: The SLAM family receptors play a critical role in activation and regulation of immune function.SLAM family receptor genes are also located on chromosome region 1q23, a region linked in genetic studies of systemic lupus erythematosus. Here, we investigated the expression and alternative splicing of 2 SLAM family receptors, 2B4 and CS1, in patients with systemic lupus erythematosus.

Methods: 45 patients with SLE and 30 healthy controls were studied. SLEDAI scores of SLE patients were calculated at the time of enrollment. Peripheral blood mononuclear cells (PBMC) were isolated and studied for 2B4 and CS1 expression on T, B, NK, and monocytes by flow cytometry. Total RNA was isolated from PBMC and reverse transcriptase PCR (RT-PCR) was performed for 2B4, CS1. Single-stranded conformational polymorphism (SSCP)-heteroduplex mobility shift assay (HMA) was conducted for analysis of 2B4 and CS1 polymorphisms.

Results: Overall proportions of 2B4+ and CS1+ PBMCs were comparable in SLE and control subjects. However, frequency of 2B4+ cells was significantly decreased in CD56+ NK cells and CD14+ monocytes from patients with SLE compared to healthy controls ($p<0.05$). Also, increased CS1+ expression was noted in B cells of SLE patients vs. healthy controls. This increased CS1+ expression was associated with increased percentage of CD19 low B cells. The proportion of CS1 expressing cells in T cells, NK cells and monocytes was not

significantly different between healthy controls and SLE patients. Two patients with SLE showed increased expression of h2B4-B splice variant over h2B4-A isoform, while 2 other SLE patients showed more predominance of h2B4-A over 2B4-B than healthy controls. However, there was no direct correlation between differential expression ratio of h2B4-A over h2B4-B and SLEDAI. Healthy individuals as well as most of SLE patients expressed similar or higher level of CS1-L isoform over CS1-S. However, the CS1-S isoform was overexpressed in 2 SLE patients.

Conclusion: These findings suggest a role for the differential expression of SLAM family receptors 2B4 and CS1 in systemic lupus erythematosus. In particular, we found decreased 2B4+ expression in NK cells and monocytes and increased CS1+ expression in B cells of SLE patients versus controls, as well as differential isoform expression in some SLE patients. Further functional studies and downstream signaling studies may be warranted to help confirm these findings and characterize their contribution to immune dysregulation in SLE.

Disclosure: J. R. Kim, None; **R. K. Patel**, None; **S. O. Mathew**, None; **R. M. Pertusi**, None; **P. Mathew**, None.

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Association Study of a Polymorphism of the CD244 Gene with Susceptibility to Systemic Lupus Erythematosus and with Clinical Features. Yuko Ota, Yasushi Kawaguchi, Manabu Kawamoto, Katsunori Ikari, Yasuhiro Katsumata, Takahisa Gono, Kae Takagi, Masako Hara and Hisashi Yamanaka, Tokyo Women's Medical University, Tokyo, Japan

Purpose: CD244 belongs to a signaling lymphocyte activation molecule (SLAM) family and is expressed on all NK, γ α, and memory CD8+ (αβ) T cells. Recent findings on the molecular mechanisms of CD244 have indicated their important roles in the immune system in NK cells and T cells. It is possible that SLAM family proteins contribute to the development in autoimmune disorders, because a causal variant of a murine lupus model was identified in Ly108 gene, another member of the SLAM family. In human, a family-based association study of UK and Canadian families with systemic lupus erythematosus (SLE) revealed variants in the promoter and coding region of SLAMF7 and LY9, which were situated adjacent to CD244. The strongest association was detected in exon 8 of LY9. Those evidences suggest that CD244, one of the SLAM family, may be involved in disease susceptibility to SLE. Recently, it was reported that a single nucleotide polymorphisms (SNPs) in CD244 gene was significantly associated with susceptibility to RA. They did not replicate association of the LY9 gene with susceptibility to SLE in a Japanese population and very recent report did not replicate the association in 16 collections from 9 European countries, either. In the present study we explored the association of a single nucleotide polymorphism (SNP) of the CD244 gene with susceptibility to systemic lupus erythematosus (SLE) and with clinical manifestations of SLE in the Japanese population.

Method: Two hundred forty-three patients with SLE and 756 healthy controls (HC) were enrolled in this study. Two SNPs (rs6682654 and rs3766379) in the CD244 gene were determined by allelic discrimination with the use of a specific TaqMan probe.

Results: Only a SNP at rs3766379 of the CD244 gene was significantly associated with susceptibility to SLE (P = 0.023, odds ratio 1.3 [95% confidence interval 1.0-1.6]). The association was preferentially observed in subsets of SLE patients with nephritis and neuropsychiatric (NP)-lupus. The frequency of allele at rs6682654 was strongly associated with nephritis (P = 0.00065, odds ratio 2.0 [95% confidence interval 1.3-3.0]) and NP-lupus (P = 0.00000016, odds ratio 3.5 [95% confidence interval 2.1-5.7]), and the frequency of allele at rs3766379 was strongly associated with nephritis (P = 0.0014, odds ratio 1.9 [95% confidence interval 1.3-2.7]) and NP-lupus (P = 0.00000026, odds ratio 3.2 [95% confidence interval 2.0-5.0]).

Conclusion: In this study, the CD244 gene was one of susceptibility-genes in patients with SLE. Especially, there was a strong association in SLE patients with nephritis and NP-lupus, suggesting that this genetic marker could predict the involvement of those severe complications.

Disclosure: Y. Ota, None; **Y. Kawaguchi**, None; **M. Kawamoto**, None; **K. Ikari**, None; **Y. Katsumata**, None; **T. Gono**, None; **K. Takagi**, None; **M. Hara**, None; **H. Yamanaka**, None.

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Differential MicroRNA Expression and the Contribution of MiR-126 to CD4+ T Cell DNA Hypomethylation in Systemic Lupus Erythematosus. Sha Zhao, Yu Wang, Yusheng Liang, Hai Long, Shu Ding, Ming Zhao, Heng Yin and Qianjin Lu, The Second Xiangya Hospital, Central South University, Changsha, China

Purpose: Epigenetic alterations, particularly DNA hypomethylation, play essential roles in the pathogenesis of systemic lupus erythematosus (SLE). MicroRNA (miRNA) genes are also implicated in autoimmune disorders, and are known to be differentially expressed in SLE patients. Here we investigated the expression of miRNAs in $CD4^+$ T cells from patients with SLE, as well as the effect of miRNA-126 upregulation on T cell DNA hypomethylation.

Method: Total RNA was extracted from $CD4^+$ T cells of 12 patients with SLE and 10 age- and gender-matched controls, and analyzed by miRNA microarray. Expression levels of miR-126 and miR-142-3p were further confirmed by stem-loop qPCR for 30 SLE patients and 20 healthy controls. DNMT1 expression was determined by Western blotting in 8 SLE and 7 normal $CD4^+$ T cell samples. Control CD4+ T cells were transfected with a plasmid encoding miR-126 and a negative control plasmid. 48h after transfection, miR-126 and DNMT1 expression were detected by stem-loop qPCR and Western blotting, respectively. Phosphorylated and total PKC-δ and ERK1/2 were quantified by Western blotting. The methylation status of CpG pairs within CD11a and CD70 promoter regulatory elements was detected by sodium bisulfite sequencing, and the expression of CD11a and CD70 was determined by flow cytometry.

Results: Of the 900 miRNAs analyzed by microarray, 11 were significantly upregulated or downregulated in SLE CD4+ T cells relative to controls, four of which, miR-126, miR-142-3p, miR-142-5p and miR-638, putatively target epigenetic regulation-associated genes. The upregulation of miR-126 and downregulation of miR-142-3p were confirmed by stem-loop qPCR ($p<0.001$, $p<0.05$, respectively). DNMT1 expression was decreased in SLE $CD4^+$ T cells, compared to normal controls ($p<0.05$), and negatively correlated with miR-126 expression ($r=-0.628$, $p=0.012$). 48h after transfecting $CD4^+$ T cells with a miR-126-encoding plasmid, DNMT1 expression and the phosphorylation of PKC-δ and ERK1/2 were decreased ($p=0.014$, $p= 0.048$, $p=0.003$, respectively). Additionally, methylation levels of the CD11a and CD70 promoter regions were significantly decreased (p=0.008, p=0.025, respectively), whereas both CD11a and CD70 expression levels were increased (p=0.002 and 0.007, respectively) compared to negative controls.

Conclusion: Our data suggest that differential expression of a set miRNAs in $CD4^+$ T cells contribute to the pathogenesis of SLE. Specifically, by inhibiting DNMT1 expression as well as PKC-δ and ERK1/2 phosphorylation, miR-126 may trigger DNA demethylation in $CD4^+$ T cells of patients with SLE.

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Disclosure: S. Zhao, None; **Y. Wang**, None; **Y. Liang**, None; **H. Long**, None; **S. Ding**, None; **M. Zhao**, None; **H. Yin**, None; **Q. Lu**, None.

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Increased Proximal B Cell Receptor Signaling in the Naive B Cell Population of SLE Patients. Nan-Hua Chang[1], Julie Kim[2], Elaheh Aghdassi[1], Dafna Gladman[3], Murray Urowitz[3], Paul R. Fortin[3] and Joan E. Wither[3], [1]University Health Network, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: SLE patients have an increased proportion of activated B cells in their peripheral blood. This may be due to B cell hyper-responsiveness, as supported by studies demonstrating increased calcium flux and tyrosine phosphorylation following IgM crosslinking of the B cells. However, in many of these studies, the precise B cell subsets that mediate this altered response have not been identified. In this study, PhosFlow was used to address this question.

Method: Patients (N=26) satisfying at least 4 ACR criteria, taking ≤ 20 mg of prednisone, and between the ages of 18-44 yrs were recruited from the University of Toronto Lupus Clinic. Healthy controls (N=16) without a family history of systemic autoimmune disease were also recruited. PBMCs were isolated over a Ficoll gradient, rested for 1 hr at 37°C, and stimulated with goat anti-human IgM $F(ab')_2$ Ab for 2 or 10 min. The cells were then fixed and frozen at -80°C. Upon thawing the cells were stained with various combinations of labeled mAb to identify specific B cell subsets, permeabilized with methanol, and then stained with Ab directed against phospho (p)-SYK, p-PLCγ2, and p-ERK.

Results: SLE patients have increased basal levels p-SYK and p-ERK in the $CD20^+IgD^+CD27^-$ naïve B cell subset as compared to controls. Basal levels of p-SYK, but not p-ERK, significantly correlated with the proportion of activated $CD86^+$ cells in this subset, but not with disease activity, as measured by the SLEDAI-2K. The naïve B cell subset of SLE patients also demonstrated increased levels of p-SYK following IgM crosslinking at 2 and 10 min as compared with controls (mean ± SD increased % above background; 2 min , controls = 9.75 ± 7.69, patients = 17.64 ± 13.71, p=0.022; 10 min, controls = 5.48 ± 4.09, patients = 11.49 ± 9.54, p= 0.0088). Similar trends to increased

proportions of p-PLCγ2^{+} and p-ERK^{+} cells were also seen but did not achieve statistical significance. There was a significant correlation between the proportions of p-SYK^{+} and p-PLCγ2^{+}, but not p-ERK^{+}, cells in SLE patients. There was no correlation between the levels of these signaling molecules following activation and their basal levels, disease activity, or treatment. In the transitional B cell subset, CD38^{++}IgM^{high} subset of the naïve B cell population, basal levels of p-SYK or p-ERK were not elevated; yet, there was an increase in the levels of p-SYK following IgM crosslinking (mean ± SD increased % above background; 2 min, controls = 33.04 ± 9.86, patients = 60.32 ± 16.34, p<0.0001; 10 min, controls = 18.37 ± 11.98, patients = 33.18 ± 17.28, p= 0.0029).

Conclusion: The naïve B cell compartment of SLE patients is hyper-responsive to IgM crosslinking and can be seen earlier in transitional B cells. The altered expression of p-SYK suggests that this results from differences in proximal signaling events.

Disclosure: N. H. Chang, None; **J. Kim**, None; **E. Aghdassi**, None; **D. Gladman**, None; **M. Urowitz**, None; **P. R. Fortin**, None; **J. E. Wither**, None.

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Elevated Levels of Cytokines and Chemokines in Patients with SLE in a Multi-Center, Multi-Ethnic, US Multi-Institutional Cohort.

Alan M. Seif[1], Gerald Mc Gwin II[2], Renan Aguilar-Valenzuela[1], Laura Aline Martinez-Martinez[1], Elizabeth Papalardo[1], Jigna Liu[2], John D. Reveille[3], Luis M. Vila[4], Neha Dang[1], Ellis Doan[1], Graciela S. Alarcon[2] and Silvia S. Pierangeli[1], [1]University of Texas Medical Branch, Galveston, TX, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Texas Health Science Center Houston, Houston, TX, [4]Univ of PuertoRico Schl of Med, San Juan, PR

Purpose: Studies have proposed that certain cytokines, chemokines and cellular adhesion molecules, are associated with SLE but whether these biomarkers are elevated in plasma of SLE patients and their association with disease activity is not clearly known. Objectives: a) To examine whether the levels of cytokines/chemokines are elevated in SLE patients and whether they correlate with disease activity (SLAM-R) and with damage accrual (SLICC-ACR Damage Index, SDI).

Method: Sera/plasma from 56 SLE patients (ACR criteria) from a multi-ethnic, multi-center cohort were assessed. Patients that were on more than 10 mg prednisone/day or on other immunosuppressive therapy were excluded; likewise patients that were on either statins or hydroxycholoroquine. In the SLE group (n=56, age range 16-67), 87% were females. In the control group (n=32 with no evidence of autoimmune or inflammatory diseases; age range: 18-65), 85% were females. Levels of IL1b, IL-6, IL-8, IFN- α, IP-10, MCP-1. VEGF, TNF- α, VEGF were measured in serum using a Millipore Millliplex™ Multiplex Assay, anticardiolipin antibodies (aCL), sE-sel, sVCAM-1 and sTF were detected by ELISA, and hsCRP by nephelometry.

Results: aCL IgG, aCL IgM and hsCRP were elevated in 64%, 13% and 50%of the SLE subjects, respectively. Other results in table below.

Biomarker	# of SLE samples elevated/(%)	p values SLE vs. controls
IL1b	18/56 (32)	0.1067
IL-6	32/56 (57)	<0.0001
IL-8	19/56 (32)	0.5552
TNF-α	31/56 (55)	<0.0001
VEGF	43/56 (77)	0.0002
IFN-α	43/56 (77)	<0.0001
MCP-1	17/56 (30)	0.0919
IP-10	53/56 (94)	<0.0001

sCD40L	51/56 (91)	<0.0001
sTF	12/14 (86)	<0.0001
sE-sel	10/21(48)	<0.0001

The levels of IFN-α correlated with SLAM-R scores but statistical significance was not reached (p=0.0546); the levels of IL1-b and sVCAM-1 correlated with SDI scores (p=0.0476 and 0.0009, respectively).

Conclusion: Significant number of SLE patients' samples had elevated levels of IgG aCL, hsCRP, IL-6, TNF-α, VEGF, IFN-α, IP-10, sTF, E-sel, sCD40L and their titers were significantly different from controls. IFN- α levels correlated with disease activity (SLAM-R scores) and IL-1b and sVCAM-1 levels correlated with SDI scores. This study underscores the importance of identifying biomarkers of disease that may help predict disease activity and/or damage and possibly improve the treatment strategies of patients with SLE.

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IL-21R Expression and IL-21/IL-21R Interaction On B and T Cell Subsets From Lupus Patients and Controls. Vinh Nguyen[1], Christelle Samen[2] and Violeta Rus[1], [1]University of Maryland Sch of Medicine, Baltimore, MD, [2]University of Maryland at Baltimore County, Baltimore

Purpose: IL-21 plays an important role in the development of autoimmunity in murine models of lupus. Recent studies have revealed a strong association between genetic polymorphisms in IL-21 and IL-21R and SLE. Our group and others have reported increased expression of IL-21 in CD4 cells and serum of patients with active SLE. While these data suggest that IL-21 blockade may be an attractive therapeutic target, limited data currently available have shown that IL-21R expression and IL-21 induced proliferative responses are decreased in B cells from SLE patients, suggesting that IL-21 blockade might not be suitable in SLE patients. To address this question we set to characterize the expression of IL-21R and the effect of IL-21/IL-21R interaction on subsets of T and B cells from SLE patients and controls.

Methods: PBMC were obtained from 20 patients with SLE and 18 controls. IL-21R expression was determined by RT-PCR from purified CD4 and CD19 cells and by flow cytometry of unstimulated and stimulated naïve and memory CD4 T cells and B cells. The proliferative response of stimulated CD4 and CD19 cells to IL-21 was determined by [^{3}H] -Thymidine incorporation. IL-21 induced plasma cell (PC) differentiation, STAT3 activation, IgG and IL-10 production was determined by immunostaining and ELISA.

Results: IL-21R mRNA expression did not differ in CD4 and CD19 cells from SLE patients and controls. Surface expression of IL-21R was detected at low levels on unstimulated CD4 cells from SLE patients and controls (MCF 16.7±7 and 15.9±7, respectively) and was upregulated to a similar extent with anti-CD3/CD28 stimulation in both groups (MCF 19.8±7 and 19.4±7, respectively). IL-21R expression was higher on unstimulated and stimulated memory CD4 compared to naïve CD4 cells. CD4 cells from both patients and controls proliferated in a dose dependent fashion in response to IL-21. The stimulation index was significantly decreased in lupus patients compared to controls at lower but not higher IL-21 doses. IL-21R expression on lupus B cells displayed a trend toward upregulation at baseline (MCF:51± 20 for patients vs. 43±18 for controls) which was further upregulated with anti-CD40 stimulation (MCF: 58±15 for patients vs. 48±12 for controls). Furthermore, IL-21 enhancement of anti-CD40 induced B cell proliferation displayed a trend for higher responsiveness in lupus patients at the highest dose of IL-21. PC differentiation was enhanced to a similar extent by IL-21 in both patients (from 7%±3% to 19%±10%) and controls (from 5%±3% to 16%± 6%). Similarly, levels of IL-21 induced STAT3 activation, IgG and IL-10 production were comparable in B cells from patients and controls.

Conclusion: IL-21R expression and the responsiveness of B cells to IL-21 are comparable in lupus patients and controls. Increased IL-21 production by CD4 T cells may promote the generation of T cell dependent B cell responses in human SLE. Therapeutic targeting of IL-21 could be beneficial in patients with SLE.

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Autoantibodies to Angiotensin Converting Enzyme 2 in Patients with Rheumatic Diseases. Yuko Takahashi, Shiori Haga, Hiroyuki Yamashita, Yukihito Ishizaka and Akio Mimori, International Medical Center of Japan, Tokyo, Japan

Purpose: Angiotensin-converting enzyme 2 (ACE2), a homologue of ACE, degrades angiotensin (Ang) II to Ang-(1-7). Recent studies have indicated that ACE2 plays a vasoprotective role in cardiovascular pathophysiology. We explored the hypothesis that serum autoantibodies to ACE2 predispose patients with rheumatic diseases to vasculopathies.

Methods: Serum samples were obtained from 30 patients with systemic lupus erythematosus (SLE), scleroderma, or mixed connective tissue disease, and 30 normal control subjects. Of these, 9 patients had vasculopathies including pulmonary arterial hypertension (PAH) (n=4), progressive digital ischemia (n=2), or cutaneous vasculitis (n=3). The sera were assessed for anti-ACE2 antibodies by enzyme-linked immunosorbent assay (ELISA) using purified recombinant human ACE2.

Results: Serum anti-ACE2 antibodies were detected in all of the 9 patients with vasculopathies and were negative in the remaining patients and healthy subjects. A patient with active SLE and ischemic digital gangrene (case 1) and a scleroderma patient with lethal PAH of rapid progression (case 2) showed extremely high serum levels of anti-ACE2 antibodies. The sera of case 1 and case 2 showed a deficient peptidase activity of ACE2. Digital ischemia in case 1 resolved after combination therapy with a steroid, vasodilating drugs, and plasmapheresis. The serum tests in case 1 after therapy showed that the ELISA score of anti-ACE2 antibodies was markedly reduced ($p<0.05$) and ACE2 activity had recovered significantly ($p<0.05$) compared to those before therapy. The serum ACE2 protein levels assessed by immunoblotting were similar between before and after therapy for case 1. These results suggested that anti-ACE2 antibodies inhibited enzymatic activity of ACE2.

Conclusion: Serum autoantibodies to ACE2 may be associated with vasculopathies in patients with rheumatic diseases.

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Proteomic Analysis of Autoantigens in SLE Patients with CNS Involvement. Nobuko Iizuka[1], Kazuki Okamoto[2], Reiko Matsushita[1], Mitsumi Arito[2], Kouhei Nagai[2], Manae S. Kurokawa[2], Naoya Suematsu[2], Kayo Masuko[2], Shunsei Hirohata[1] and Tomohiro Kato[2], [1]Kitasato University School of Medicine, Kanagawa, Japan, [2]St.Marianna University Graduate School of Medicine, Kawasaki, Japan

Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects multiple organs. Involvement of central nervous system (CNS) in SLE (CNS Lupus) indicates poor prognosis. The molecular mechanism of CNS Lupus has not been clarified yet. Several reports suggest that patients with CNS Lupus have anti-neuronal cell antibodies in cerebrospinal fluid (CSF) which possibly cause CNS manifestations. Further, the anti-neuronal cell antibodies can be a diagnostic marker for CNS Lupus when their target antigens are identified. Thereby, using proteomics analysis, we tried to identify candidate autoantigens for the anti-neuronal cell antibodies.

Method: Serum samples were prepared from 30 patients with CNS Lupus (CNS Lupus group) and 30 patients with SLE but not CNS involvement (non CNS-SLE group). Proteins, extracted from cultured human neuroblastoma (SK-N-MC) cells, were separated both by SDS-PAGE (1-DE) and two-dimensional electrophoresis (2-DE). The separated proteins were transferred to PVDF membranes and autoantigenic proteins were detected by western blot using the serum samples. Then, the detected autoantigenic proteins were identified using matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry and the subsequent protein date base searching.

Results: On the 1-DE western blot analysis, 4 protein bands (B1-B4) were positively reacted more frequently (p-value <0.02) in the CNS Lupus group than in the non CNS-SLE group. In the 2-DE, we detected 3 spots which corresponded to the B1 band, one spot for the B2 band and 2 spots for the B3 band. We could not detect the spots which corresponded to the B4 band. We identified 3 proteins for the B1 band which were NADH dehydrogenase ubiquinone iron-sulfur protein 3 (NDUFS3), heat shock protein beta-1 (HSPB1) and peroxiredoxin-4 (PRDX4). To identify the antigenicities of these 3 proteins, we prepared PRDX4 recombinant protein and commercially obtained NDUFS3, HSPB1 recombinant proteins as antigens for western blot. All of the 5 serum samples which reacted to the B1 band reacted to only PRDX4 but not NDUFS3 nor HSPB1. We also identified ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) from one spot in the B2 band and histon H2A type1 were identified from both of 2 spots for the B3 band.

Conclusion: We identified 3 candidate autoantigens for anti-neuronal cell antibodies which can be a useful marker specific for CNS Lupus.

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Expression Profiling of the Vascular Endothelium in Patients with SLE Using a Novel Methodology: Human Endothelial Sampling Coupled with Microarray Analysis. Diana Goldenberg[1], Mikhail Olferiev[1], Duygu Onat[2], Mary K. Crow[1], Paolo Colombo[2] and Jane E. Salmon[1], [1]Hospital for Special Surgery, New York, NY, [2]Columbia University College of Physicians and Surgeons, New York, NY

Purpose: Systemic inflammation is considered causative of endothelial dysfunction and thereby accelerates atherosclerosis in Systemic Lupus Erythematosus (SLE). In humans, determination of endothelial function relies on measurement of endothelium-dependent vasodilation and circulating endothelial progenitor cells (EPCs). Both techniques have disclosed fundamental abnormalities in SLE; however, neither can identify the molecular events underlying these abnormalities. Herein, we introduce endothelial cell (EC) sampling coupled with gene expression profiling as a new method to characterize the pathophysiology of endothelial dysfunction in SLE.

Methods: Seven ambulatory adult patients meeting American College of Rheumatology criteria for SLE (4 males, 3 females) were studied (29.7 ± 8.2 yrs, mean SLEDAI score 9.3) and 6 age-matched healthy subjects were studied. ECs were collected from arm veins using endovascular wires. ECs were purified; amplified RNA was hybridized with Affymetrix HG-U133 2.0. Data was analyzed using GeneSpring GX 10.0 software. Samples were normalized to the baseline median level according to the MAS5 algorithm. Student T test analysis for multiple samples was performed. Differentially expressed genes with >2.0 fold expression and $p<0.05$ were selected.

Results: No adverse events were observed. A total of 2108 genes were differentially expressed between the SLE patients and controls. Functional analysis identified genes linked to apoptosis (TRAF2, AIFM3 and CASP12), cellular adhesion (EED), stress and immune response (SOCS2), inflammation (CES1), interferon (IFIT2, IFNAR1, OAS2, PRKRA and STAT6) and the insulin-like growth factor (IGF) pathways (PAPP-A, IGF-1, IGF-1 receptor, IGFBP3 and IGFBP4).

Conclusion: We documented feasibility, safety, and potential clinical relevance of endothelial expression profiling in SLE. This novel approach may identify processes relevant to the pathophysiology of endothelial dysfunction in SLE, disclose yet unrecognized biologic pathways, and generate novel hypotheses to be tested further.

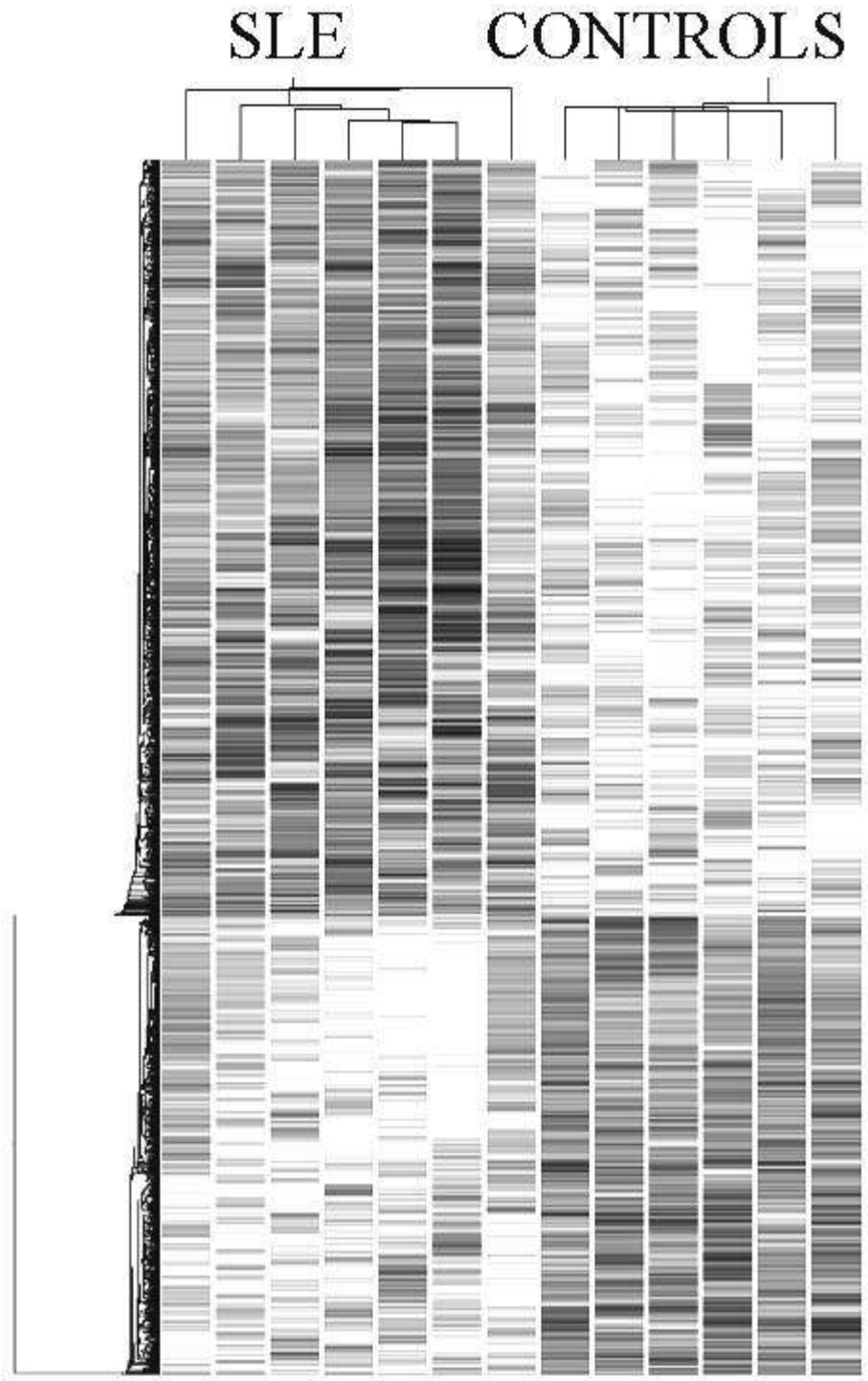

Figure 1. Hierarchical cluster of endothelial gene expression. Black represents upregulation in SLE compared with controls and white represents downregulation in SLE compared with controls.

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Cyclophilin A Is High Expressed in Active SLE and Induced Increased CD147 and Interferon Gamma Production in Jurkat T Cells.
Yile Ren, Wenfeng Tan, Xiaohua Liu and Miaojia Zhang, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Purpose: It has been reported that high expression of CD147 and interferon gamma (IFN-γ) in activated T lymphocytes may contribute to development of SLE , but the exact mechanism remains unclear. Recently, the accumulated evidence shown that Cyclophilin A(CyPA) might act as a bridge between T lymphocytes and SLE and play an important role in SLE pathogenesis, which prompted us to test the relationship between CyPA, CD147 and IFN-γ.

Method: Sera were collected from 37 active SLE, 20 inactive SLE and 30 normal controls and CyPA levels were detected by ELISA. After Jurkat T cells were treated with CyPA(0.2 μg/ml)for 24 h, the expression of CD147 was measured by flow cytometry. Jurkat T cells were also treated with CyPA(2 μg/ml), PHA(5 μg/ml)and CyPA(2 μg/ml)plus PHA(5 μg/ml)for 6h or 24h, respectively, and the expression of IFN-γ mRNA and protein in supernatant were detected by RT-PCR and ELISA.

Results: The mean serum CyPA level was significantly higher in active SLE patients (2.72ng/ml) compared to in inactive SLE patients (0.81ng/ml) or in normal controls (0.34ng/ml)($p < 0.05$). After stimulated with CyPA for 24h, the positive rate of CD147 in Jurkat T cells significantly increased (Stimulated group vs non-stimulated: 52.01% vs. 40.67%, $p<0.05$). The higher expression of IFN-γ mRNA only be detected in Jurkat T cells after treated with CyPA plus PHA for 6h. IFN-γ protein level also shown a significant increase in supernatant of Jurkat T cells after treated with CyPA plus PHA compared to with CyPA or PHA alone. (CyPA plus PHA vs CyPA vs PHA: 16.51pg/ml vs 2.04pg/ml vs 2.74 pg/ml, $p<0.05$).

Conclusion: Cyclophilin A was high expressed in active SLE and induced a increased CD147 and IFN-γ production in Jurkat T cells, which suggested that CyPA might contribute to SLE disease activity by triggering T lymphocytes activation.

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Dual Effect of *MIF* Gene Polymorphisms On the Development and the Severity of SLE.
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Purpose: SLE is a complex autoimmune disease and its etiology remains unknown. Functional polymorphisms in the gene for Macrophage Migration Inhibitory Factor (MIF) have been associated with several autoimmune disorders, and we hypothesized that *MIF* expression may influence the development or the clinical severity of SLE. There are two polymorphic sites in the *MIF* promoter that correlate with MIF production in vivo: a -173 G/C SNP and a -794 $CATT_{5-8}$ repeat. In the latter case, increasing repeat number leads to higher *MIF* expression. We studied the association of *MIF* gene polymorphisms and MIF plasma levels with SLE susceptibility and severity.

Method: The study consisted of 1369 patients and 1826 controls from the US, Sweden, and Argentina, and focused on 2 ethnic groups: Caucasians and African-Americans. The frequencies of high expression *MIF* genotypes (-173*C or -794 $CATT_7$) and high expression haplotypes (-173*C/-794 $CATT_7$) were compared between patients and controls, and in the same SLE cohort, between patients with severe end-organ involvement and those without. We also compared the frequency of low expression -794 $CATT_5$-containing genotypes between those groups. Plasma MIF was measured in 200 patients and controls and analyzed in relation to *MIF* polymorphisms.

Results: The frequency of high expression -173*C-containing genotypes was lower in the African-American patients than controls (49.7% vs 64.2%, p=0.007), whereas the frequency of high expression -794 $CATT_7$-containing genotypes was lower in the Caucasian patients as compared to controls (21% vs 24%, p=0.05). Both Caucasians and African-Americans with -173*C/-794 $CATT_7$ haplotypes had lower SLE

incidence (OR 0.63 [0.53, 0.89], p=0.001 in Caucasians, and OR 0.46 [0.23, 0.95], p=0.012 in African-Americans). MIF levels were lower in patients than in controls and reflected the low frequency of high expression *MIF* polymorphisms in the patient group. In contrast, Caucasian patients with nephritis, serositis, and males with cerebritis had reduced frequencies of low expression genotypes (-794 $CATT_5$) compared to patients without organ involvement (36% vs 64%, p=0.023 for nephritis, 42% vs 58% p=0.005 for serositis, and 11% vs 89%, p=0.04 for cerebritis).

Conclusion: MIF plays a dual role in the pathogenesis of SLE. High expression *MIF* genotypes lower the susceptibility to SLE, however once SLE develops, low expression *MIF* genotypes confer protection from end-organ damage. These data highlight the complex relationship between immune cytokine activation and SLE. Since MIF is expressed upstream of cytokines such as TNF, these results support long-standing observations suggesting that TNF is protective with respect to SLE initiation.

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Dysregulated Balance of Th17 and Th1 Cells in Systemic Lupus Erythematosus. Kamini M. Shah, Won-Woo Lee, Seong Wook Kang, Sang-Hyun Kim, Seung-Hyun Lee, Joe Craft and Insoo Kang, Yale University School of Medicine, New Haven, CT

Purpose: To analyze the balance of T helper (Th)17 and Th1 cell responses in peripheral blood from patients with systemic lupus erythematosus (SLE) and healthy subjects.

Method: Peripheral blood mononuclear cells from 25 adult patients with SLE and 26 healthy subjects were stimulated for 4 hours *ex vivo* with phorbol myristate acetate and ionomycin. The frequency of CD4+ T cells producing IL-17 and/or IFN-γ was measured using flow cytometry. The expression of Th17 cell-associated chemokine receptors CCR4 and CCR6 on CD4+ T cells as well as plasma levels of Th17-polarizing cytokines were assessed.

Results: Patients with SLE had an increased frequency of IL-17+CD4+ T cells (mean ± SD, 1.8 ± 1.26% vs. 0.6 ± 0.27%, $P < 0.001$) and CCR4+CCR6+CD4+ T cells (7.32 ± 7.27% vs. 2.18 ± 2.16%, $P = 0.021$) compared to healthy subjects. However, the frequency of IFN-γ+CD4+ T cells was similar between the two groups, indicating the altered balance of Th17 and Th1 cell responses in SLE. The frequency of IL-17+CD4+ T cells and CCR4+CCR6+CD4+ T cells correlated with disease activity ($r = 0.576$, $P = 0.003$ and $r = 0.645$, $P = 0.013$, respectively). Plasma levels of Th17-polarizing cytokine IL-6 was higher in patients with SLE than in healthy subjects (4421.95 ± 3608.13 pg/ml vs. 2803.08 ± 955.82 pg/ml, $P = 0.029$).

Conclusion: We demonstrate an enhanced Th17 cell response that correlates with disease activity in patients with SLE, proposing a potential role for IL-17 in the pathogenesis of lupus. Our data suggest that the mechanism involved in balancing Th17 and Th1 cell responses as well as in producing IL-6 are dysregulated in SLE, leading to the increased Th17 cell response. The utilization of CCR4 and CCR6 as markers for disease activity as well as therapy blocking IL-17 may be considered in SLE.

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Mutations in Complement Regulatory Proteins Predispose to Preeclampsia in Patients with Lupus or Antiphospholipid Antibodies. Jane E. Salmon[1], Veronique Fremeaux-Bacchi[2], M. Kathryn Liszewski[3], Michael Triebwasser[3], Celia Fang[4], Marta Guerra[1], Lubka Roumenina[2], Michael D. Lockshin[1], Michelle Petri[5], D. Ware Branch[6], Carl A. Laskin[7], Joan T. Merrill[8], David Kavanagh[9], Jill P. Buyon[10] and John P. Atkinson[3], [1]Hospital for Special Surgery, New York, NY, [2]Hôpital Européen Georges Pompidou, Paris, France, [3]Wash Univ, St. Louis, MO, [4]S F VA Med Center, San Francisco, CA, [5]Johns Hopkins Univ, Baltimore, MD, [6]Univ of Utah, Salt Lake City, UT, [7]Mt. Sinai Hosp, Toronto, ON, [8]Okla Med Res Found, Oklahoma City, OK, [9]Univ Newcastle, Newcastle, United Kingdom, [10]NYU School of Medicine, New York, NY

Purpose: Pregnancy in women with SLE or antiphospholipid antibodies (APL) is associated with an increased risk for preeclampsia (PE). Our studies in pregnant mice indicate that complement activation targeted to placenta drives angiogenic imbalance, placental insufficiency

and endothelial injury. In normal pregnancies, excessive complement activation is prevented by complement regulatory proteins that are highly expressed on trophoblasts [including membrane cofactor protein (MCP), DAF, and CD59], as well as circulating complement regulatory proteins [complement factor H (CFH) and complement factor I (CFI)]. Loss-of-function mutations occur in CFH, MCP and CFI leading to undesirable complement activation in patients with atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy not unlike that seen in PE, APS and SLE. Here we use the PROMISSE Study (**P**redictors of p**R**egnancy **O**utcome: bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic lupus **E**rythematosus), a prospective study of 250 pregnant patients with SLE and/or APL, to test the hypothesis that impaired capacity to limit complement activation predisposes to PE.

Method: Genes for MCP, CFH, and CFI were sequenced in the 40 patients enrolled in PROMISSE who developed PE or had PE in a previous pregnancy. PE was defined as hypertension (>140 syst or >90 diast) and proteinuria (≥1+). PE patients were matched by age and ethnicity to 34 patients without PE [SLE and/or APL (disease controls, DC) and healthy controls (HC)] and MCP, CFH and CFI were sequenced.

Results: We discovered heterozygous mutations in 7 of 40 patients (18%) with PE: 4 in MCP, 2 in CFI and 1 in CFH. Five of these patients had complications in previous pregnancies. We did not find mutations in patients without PE (19 HC, 15 DC) (7/40 vs 0/34, $p<0.02$). Five of these 7 mutations were previously identified in aHUS: 3 with MCP A304V (associated with deficient control of alternative pathway activation) and 2 with CFI IVS12+5 G>T. Two patients had novel mutations: MCP K32N which is the first MCP mutation that exclusively causes impaired ability to bind and regulate C4b, and CFH S40A which enhances C3b binding.

Conclusion: The first genetic variants associated with PE in SLE and/or APL patients are in complement regulatory proteins. That mutations in complement regulatory proteins were present in 18% of PROMISSE patients with PE underscores the importance of complement in PE, defines likely mechanisms for increased risk in patients with SLE and/or APL, and suggests new targets for treatment.

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Tuning of Adenosine-to-Inosine Editing in UCTH Gene Transcripts of Systemic Lupus Erythematosus (SLE) T Lymphocytes. Dama Laxminarayana[1], Kenneth O'Rourke[2] and Irene Olorenshaw[2], [1]Wake Forest Univiversity School of Medicine, Winston-Salem, NC, [2]Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: Adenosine deaminases that act on RNA (ADARs) edit gene transcripts by the site specific conversion of adenosine to inosine by hydrolytic deamination at C6 of the Adenosine (A). The translation machinery reads inosine (I) as guanosine (G), leading post transcriptional A to G changes in the gene transcripts. Such alterations in the primary sequences of RNA molecules lead to increasing the flexibility of eukaryotic gene expression and alter the function of the affected RNAs. We and other investigators demonstrated the up-regulation of type I IFN inducible transcript editing gene, 150-kDa (ADAR), in SLE T lymphocytes. Such up-regulation of the 150-kDa ADAR1 alters the ratio of ADAR1 versus ADAR2 expression in SLE T cells. *Ubiquitin Carboxyl-Terminal Hydrolase (UCTH)* is a deubiquitinating enzyme and plays an important role in cellular functions. Therefore, the goal of these experiments is to identify and compare A to I editing in novel *UCTH* gene transcripts of healthy controls and SLE patients.

Methods: The *UCTH* gene transcripts are edited by ADAR enzymes. Therefore, we assessed the role of altered ADAR enzymes expression in editing of *UCTH* gene transcripts of SLE T cells. The base position numbers of *UCTH* gene transcripts reported here are used from the accession number AF056490. The UCTH gene transcripts from normal and SLE T cell samples were amplified and cloned into pCR2.1-TOPO vectors and analyzed for transcript editing. A total of 159 clones from eight control T cell samples and 200 clones from ten SLE patients were sequenced using T7 and M13 primers and an automated ABI-377 sequencer.

Results: Two hot spots for A to I editing were observed in the *UCTH* gene transcripts of SLE T cells and termed as site1 and 2. The site 1 consists of known edited bases and well documented as a substrate for ADARs. Seventy two percent of A to G discrepancies observed in *UCTH* gene transcripts of control samples are clustered in site 1. The frequency of such editing in this site of SLE samples is 43.3%, which indicates substantial reduction of editing at this site of SLE patients ($p<0.001$). The second hot spot consists of novel edited bases between nucleotides 39707 to 39718, and the frequency of editing in this site in SLE samples is 30% and 2.3% in control samples. About 13 folds increase in editing frequency has been observed at this site in SLE patients compared to controls ($p<0.001$). The other important

finding of this study is the compensatory alteration of A to I editing frequencies at hot spots in *UTCH* gene transcripts of SLE. In general these results demonstrate altered and site selective editing in UCTH gene transcripts of SLE patients.

Conclusion: Based on these results, it is proposed that altered transcript editing contributes to the modulation of gene expression and immune functions in SLE patients and play an important role in the initiation and propagation of SLE pathogenesis. .

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Disclosure: D. Laxminarayana, None; **K. O'Rourke**, None; **I. Olorenshaw**, None.

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Genetic Risk Factors for Thrombosis in An Ethnically Diverse Systemic Lupus Erythematosus (SLE) Population. R. Kaiser[1], Y. Li[2], M. Chang[2], J. Catanese[2], A.B. Begovich[3] and L.A. Criswell[1], [1]UCSF, San Francisco, CA, [2]Celera, Alameda, CA, [3]Roche Diagnostics, Pleasanton, CA

Purpose: Thrombosis is a devastating SLE complication. Established risk factors such as antiphospholipid antibodies (aPL) do not completely explain this increased thrombosis risk. We investigated whether previously described and novel single nucleotide polymorphisms (SNPs) recently associated with risk for thrombosis in the general (non-SLE) Caucasian population help explain the increased risk of thrombosis in an ethnically diverse SLE population.

Methods: Subjects were enrolled in a large SLE cohort through diverse recruitment sources, completed an extensive questionnaire, and had thrombosis phenotypes well-characterized. We genotyped 1513 SLE subjects for established and novel SNPs recently suggested to be associated with deep venous thrombosis in the general Caucasian population. Each SNP was tested for association with thrombosis in bivariate analysis. Statistically significant results from bivariate analyses ($p \leq 0.05$) were evaluated in a logistic regression model that included aPL, disease duration, ever history of smoking, and medication treatment history as covariates. In sensitivity analyses, thrombosis subgroups were analyzed as distinct outcomes because certain SNPs have been shown to be risk factors specifically for arterial or venous thrombosis.

Results: 1380 SLE patients (91%) were female, 874 (58%) Caucasian, 232 (15%) Hispanic, 190 (13%) African American and 217 (14%) Asian American. Average age at SLE diagnosis was 33.3 ± 13.4 years and average disease duration was 8.96 ± 8.2 years. 587 subjects (40%) were ever-smokers, and 841 (53%) had a history of immunomodulator therapy (cytoxan, methotrexate, etc.). 357 (25%) subjects had a total of 499 thrombotic events. 444 (31%) subjects were positive for either anticardiolipin antibodies or the lupus anticoagulant. No SNPs deviated from Hardy Weinberg Equilibrium. Table 1 summarizes multivariate genetic association results for the outcomes of arterial and venous thromboses. No SNPs were significantly associated with the combined outcome of venous and/or arterial thrombosis.

Conclusion: This is the first study to assess these genetic risk factors for thrombosis in a large, ethnically diverse SLE population and may help to identify SLE subjects at higher risk for thrombosis. Although confirmation of these findings in independent study populations is needed, the magnitude of some of these associations implies the potential for substantial clinical significance.

Table 1. Results of Multivariable Analyses

SNP	MAF* in controls	Ethnic group	Arterial thrombosis OR (95% CI)	p value	Venous thrombosis OR (95% CI)	p value
rs5030737 MBL2	0.011	AA**	8.20 (1.02-65.63)	0.047		
rs1799963 prothrombin G20210A	0.016	Caucasian	0.66 (0.34-0.98)	0.013		
rs6025 Factor V Leiden	0.024	Caucasian			2.73 (1.29-5.79)	0.008
rs1800595 Factor V R2 allele	0.024	Asian**			4.67 (1.07-19.60)	0.040
rs1801133 MTHFR C677T	0.34	Caucasian			[illegible]	[illegible]
rs1801131 MTHFR A1298C	0.34	Caucasian			1.63 (1.12-2.36)	0.011
rs6048 Factor IX	0.0832	Hispanic			11.36 ([illegible])	0.016
rs9923231 VKORC1	0.40	Asian	0.46 (0.22-0.91)	0.026		
rs9934438 VKORC1	0.40	Asian	0.45 (0.22-0.91)	0.027		
rs1613127 [illegible]	0.21	Asian	0.28 (0.09-0.91)	0.020		
rs1801690 APOH	0.089	Caucasian	2.07 (1.18-3.64)	0.011		

*MAF = minor allele frequency; **AA=African American, Asian=Asian American; [illegible] recently published in meta-analysis

Disclosure: R. Kaiser, None; **Y. Li**, Celera, 3 ; **M. Chang**, Celera, 3 ; **J. Catanese**, Celera, 3 ; **A. B. Begovich**, Celera, 1 ; **L. A. Criswell**, None.

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Novel Single Nucleotide Polymorphisms (SNP) Associated with Systemic Lupus Erythematosus (SLE). R. Kaiser[1], Y. Li[2], M. Chang[2], J. Catanese[2], Jeffrey C. Edberg[3], G. S. Alarcon[4], A.B. Begovich[5] and L.A. Criswell[1], [1]UCSF, San Francisco, CA, [2]Celera, Alameda, CA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]for the PROFILE study group, [5]Roche Diagnostics, Pleasanton, CA

Purpose: Prior work suggests that polymorphisms implicated in thrombosis risk [Mannose Binding Lectin (MBL) D allele] may also confer risk of developing SLE, a systemic autoimmune disease with a higher incidence of thrombosis that occurs at younger ages than in the general population. In a case-control analysis, we aimed to determine whether established and novel single nucleotide polymorphisms (SNP) recently suggested to be associated with deep venous thrombosis in the general population were risk factors for the development of SLE.

Methods: Subjects were enrolled in one of two North American SLE cohorts. SLE cases met American College of Rheumatology criteria. We genotyped 6909 subjects (2954 cases and 3955 controls) for 33 SNPs – some putative risk factors and many recently suggested to be associated with thrombosis in the general population. In bivariate analysis, we compared SLE subjects with thrombosis (myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, retinal vein thrombosis, recurrent miscarriages) to SLE subjects without thrombosis among the cohort for which thrombosis phenotypes were well-characterized (1452 cases and 1672 controls) as well as all SLE subjects versus healthy controls (controlling for cohort).

Results: In the overall study population, 2641 (91%) of SLE cases were female, 1500 (52%) Caucasian, 453 (16%) Hispanic, 716 (25%) African American and 217 (7%) Asian American. In the subgroup for which thrombosis phenotypes were well characterized, 360 (23%) subjects experienced at least one thrombotic event. Genetic association results are summarized in the table below, and support association of some of these genetic variants with risk of SLE. Some of these SNPs are located in genes involved in the coagulation cascade (FV and FIX) while other are involved in platelet aggregation (GP6) or in antiphospholipid antibody production (APOH). Many of these SNPs were protective for SLE in Asian-Americans. For some SNPs (FIX, GP6), odds ratios were in different directions for different ethnicities.

Conclusion: Many of the SNPs we recently demonstrated to be risk factors for thrombosis in SLE (APOH, MTHFR, FV, VKORC1) appear to be equally or more strongly associated with SLE itself. This suggests a common genetic predisposition for the development of SLE and the complication of thrombosis and may help to explain ethnic differences in SLE outcomes.

Table 1. Results of Case-Control Analyses

SNP	MAF[1] in healthy controls	SLE cases vs. non-SLE controls (n = [illegible]) OR (95%CI)	p value	SLE with thrombosis vs. SLE without thrombosis (n=[illegible]) OR (95%CI)	p value
F IX Malmö rs6048	0.16 0.0016	AA* 0.72 (0.60-0.[illegible]) Asian** 13.86 (1.76-1.10)	0.0039 0.0011	NS for p <0.05	
MBL2 rs1800450	0.031	AA 1.62 (1.12-2.35)	0.0090	NS for p <0.05	
VKORC1 rs9923231	0.088	Asian 0.33 (0.24-0.47)	8.49x10[illegible]	Asian 0.38 (0.21-0.68)	2.59x10[illegible]
VKORC1 rs9934438	0.088	Asian 0.33 (0.22-0.48)	1.07x10[illegible]	Asian 0.37 (0.22-0.63)	4.01x10[illegible]
APOH rs1801690	0.073	Asian 0.62 (0.39-0.92)	0.0217	NS for p <0.05	
CYP2C9 *3 rs[illegible]	0.064 0.014	Caucasian 1.27 (1.01-1.60) AA 2.01 (1.18-3.43)	0.040 0.0092	NS for p <0.05	
MTHFR rs1801131	0.20	Asian 0.44 (0.33-0.60)	4.40x10[illegible]	NS for p <0.05	
MTHFR rs1801133	0.37	Asian 0.44 (0.33-0.60)	1.32x10[illegible]	Asian 0.49 (0.26-0.93)	0.011
Factor V (Leiden) rs6025	--	NS for p <0.05		Caucasian 1.94 (1.04-3.11)	0.02
Factor V (R2 allele) rs1800595	0.0072	AA 2.47 (1.21-5.36)	0.0067	Hispanic 1.87 (1.03-3.26)	0.02
[illegible] rs1012[illegible]	0.12 0.0076	Hispanic 0.66 (0.50-0.88) Asian 6.17 (2.10-21.61)	0.0148 6.23x10[illegible]	NS for p <0.05	

[1]MAF = Major Allele Frequency, *AA=African American, **Asian = Asian American

Disclosure: R. Kaiser, None; **Y. Li**, Celera, 3 ; **M. Chang**, Celera, 3 ; **J. Catanese**, Celera, 3 ; **J. C. Edberg**, NIH, 2 ; **G. S. Alarcon**, None; **A. B. Begovich**, Celera, 1 ; **L. A. Criswell**, None.

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Association Analysis of *EGR2* Gene with SLE Susceptibility. Keiko Myouzen[1], Yuta Kochi[1], Kenichi Shimane[1], Akari Suzuki[1], Keishi Fujio[2], Tomohisa Okamura[2], Ryo Yamada[3], Yusuke Nakamura[4] and Kazuhiko Yamamoto[1], [1]Laboratory for Autoimmune diseases, Center for Genomic Medicine,The Institute of Physical and Chemical Research (RIKEN), Tokyo, Japan, [2]Department of Allergy and Rheumatology,Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Laboratory of Functional Genomics, Human Genome Center,The Institute of Medical science, The University of Tokyo, Toyko, Japan, [4]Laboratory of Molecular Medicine, Human Genome Center,The Institute of Medical science, The University of Tokyo, Tokyo, Japan

Purpose: Early growth response 2 (*EGR2*) gene is a zinc-finger transcription factor, whose knockout in mice has been shown to develop a lupus-like autoimmune disease. We performed case-control association study to analyze the association of *EGR2* with SLE susceptibility in Japanese population.

Method: We selected 20 tag SNPs from 80 kb region including *EGR2* and genotyped them using TaqMan assays. We compared the allele frequency of SNPs between two sets of case-control subjects in Japanese population (1st set, 376 SLE patients and 940 controls; 2nd set, 243 SLE patients and 881 controls). We analyzed the correlation between *EGR2* expression and SNP genotypes in EBV-transformed lymphoblastoid cell lines from HapMap individuals. We also performed luciferase assays to assess the transcriptional enhancer and repressor activity of DNA sequences surrounding the disease-associated SNPs.

Results: We identified a significant association of rs10761670 (A/T; T allele was susceptible allele) in the 5' flank region of *EGR2* with SLE susceptibility (1st set: p=0.049, OR=1.19 [95%CI 1.00-1.41]; 2nd set: p=0.029, OR=1.22 [95%CI 1.02-1.53] and pooled: p=0.0036, OR=1.22 [95%CI 1.07-1.39]). We also found a significant positive correlation between the number of susceptible alleles of rs10761670 and the transcriptional level of *EGR2* (R=0.23, p=0.0007). Among the SNPs in complete disequilibrium with rs10761670 (r^2=1.0), two SNPs (rs1412554 and rs1509957) affected transcriptional activity in luciferase assays, and thus they could be candidates for causal variants in this region.

Conclusion: *EGR2* is a genetic risk factor for SLE, in which increased gene expression may contribute to SLE pathogenesis.

Disclosure: K. Myouzen, None; **Y. Kochi**, None; **K. Shimane**, None; **A. Suzuki**, None; **K. Fujio**, None; **T. Okamura**, None; **R. Yamada**, None; **Y. Nakamura**, None; **K. Yamamoto**, None.

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Genetic Ancestry, Socioeconomic Status, and Disease Characteristics Among Hispanics with Systemic Lupus Erythematosus. I. B. Richman[1], J. Barton[1], L. Trupin[1], M. A. Petri[2], E. H. Yelin[1], M.F. Seldin[3] and L. A. Criswell[4], [1]UCSF, San Francisco, CA, [2]JHU, Baltimore, MD, [3]Univ. of California, Davis, [4]Univ. of California, San Francisco, CA

Purpose: Systemic lupus erythematosus (SLE) is more severe among Hispanics than among Caucasians in the U.S. The extent to which genetic and environmental factors contribute to these disparities is incompletely understood. The objective of this study was to determine whether genetic ancestry and socioeconomic status (SES) are associated with disease characteristics including renal involvement, age at diagnosis, and disease activity among Hispanic adults with SLE.

Method: This was a cross-sectional study of Hispanic adults with SLE enrolled in an ongoing study of the genetics of SLE. We confirmed SLE diagnosis and clinical characteristics by chart review. A subset of participants was enrolled in a prospective cohort study of SLE through which SES data and the Systemic Lupus Activity Questionnaire (SLAQ), a measure of disease activity, were collected. All participants were genotyped for a set of 112 single nucleotide polymorphisms informative for continental ancestry. Continental ancestry was estimated for each participant using the program STRUCTURE. We assessed the relationship between SLE characteristics and genetic ancestry using linear and logistic regression models adjusted for sex, disease duration, educational attainment, language, insurance status and type, and access to a rheumatologist.

Results: Genetic ancestry estimation for 222 Hispanic SLE cases demonstrated that participants had on average 48% European ancestry, 39% Amerindian ancestry, 8% east Asian ancestry and 5% African ancestry. Forty percent of participants (n=89) had a history of renal involvement. The mean age at diagnosis was 31 (SD 12) and the mean SLAQ score was 13 (SD 8). In multivariable analysis, participants with a larger European ancestry contribution had a lower odds of renal involvement than those with a smaller European ancestry contribution. A 25% increase in European ancestry contribution was associated with a 65% reduction in the odds of having renal disease (OR 0.35, 95% CI 0.17-0.72, p=0.004) after adjustment for covariates. European ancestry was also associated with age at diagnosis. A 25% increase in European ancestry contribution was associated with a 4.8 year increase in age at diagnosis (95% CI 1.2-8.5, p=0.009) in multivariable analysis. European ancestry was not associated with SLAQ score, but health insurance type was. Compared to those with private health insurance, those with public insurance had on average a 4.4 point (95% CI 1.0-7.8, p=0.011) higher SLAQ score after adjusting for covariates.

Conclusion: Both genetic ancestry and SES are associated with disease characteristics among Hispanic adults with SLE. Different facets of SLE may be differentially affected by genetic and environmental influences. Understanding the factors that contribute to SLE disease characteristics can help identify at-risk individuals and aid in devising targeted interventions to reduce health disparities in SLE.

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Ro60 Associated ssRNA Links Inflammation with Fetal Cardiac Fibrosis Via Ligation of Toll Like Receptors: A Potential Pathway to Heart Block. David Alvarez[1], Elena V. Komissarova[1], Jordan Swartz[1], Franck Barrat[2], Tania L. Rivera[1], Robert M. Clancy[3] and Jill P. Buyon[3], [1]NYU SOM, New York, NY, [2]Dynavax Technologies, Berkeley, CA, [3]NYU School of Medicine, New York, NY

Purpose: Exploration of pathogenic mechanisms coupling anti-Ro/La antibodies to fetal cardiac injury has focused on the protein target of the maternal immune response. The relevance of Interferon Type I and Toll like receptor (TLR) signaling in SLE supports the potential importance of Ro associated ssRNAs in the cascade to congenital heart block (CHB). Objective: To address the hypothesis that ssRNA induces macrophage activation via TLR ligation following uptake of a complex of Ro60, hY3 or mutant pre 5S (m-pre5S) RNA and anti-Ro with release of proinflammatory and profibrotic factors which result in scarring of the conduction system and endocardial fibroelastosis.

Method: In vitro conditions included evaluation of human macrophages for secretion of TNFa (inflammatory component) and transdifferentiation of human fetal cardiac fibroblasts and collagen production (fibrosing component) as well as staining of human fetal hearts.

Results: The TLR component was evaluated by transfection of ssRNA. Treatment of IFNg-primed macrophages with hY3 or m-pre5S RNA (2.5mg each) significantly stimulated TNFa release (1,121±373pg/mL p=0.02, N=14, and 1,072±338pg/mL respectively vs resting macrophages 92±40 pg/mL, p=0.01, N=14), an effect not observed with transfected ssRNA41 (control RNA) or modified hY3 RNA (base substitution of hY3, A/U). Both theTLR7/8 antagonist IRS661(32ng/mL) and chloroquine (10mM) significantly decreased TNFa release induced by either hY3 or m-pre5S RNA (IRS661: 159±77pg/mL p=0.03, N=9 for hY3, and 71±29pg/mL p=0.03, N=9 for pre-5S; chloroquine: 267±89pg/mL p=0.03, N=9 for hY3, and 180±70pg/mL p=0.03, N=9 for pre-5S). Immune complexes generated by incubation of an IgG fraction from a CHB mother with native Ro60-hY3 (CHB IgG Ro60-hY3) significantly increased TNFa secretion compared to CHB IgG Ro60-ssRNA41 or normal IgG (healthy donor absent anti-Ro) incubated with Ro60-hY3 (687±248pg/mL vs 246±103pg/mL p=0.05, N=3 vs 18±11pg/mL p<0.001, N=3). Fibrosis was evaluated using the identical supernatants (sups). Transdifferentiation of fibroblasts (SMAc staining, N=5) was markedly increased by incubation with sups generated from macrophages + hY3 or m-pre5s RNA, CHB IgG Ro60-hY3, not control ssRNAs or normal IgG Ro60-hY3. IRS661 and chloroquine each abrogated induced SMAc. Collagen secretion was stimulated by sups of macs + hY3 (766±82ng/mL, p=0.003 vs macs) compared to ssRNA41 (150±30ng/mL, p=NS vs macs) or hY3-A/U (197±27ng/mL, p=NS vs macs), and macs + CHB IgG Ro60-hY3 (650ng/mL) compared to normal IgG Ro60-hY3 (200ng/mL). TLR7 expressing mononuclear cells were observed in a CHB heart, not normal heart, and localized near the AV groove at a site enriched in fibrosis.

Conclusion: These data support a novel injury model in CHB whereby endogenous ligand, Ro60 associated ssRNA, forges a nexus between TLR ligation and fibrosis instigated by binding of anti-Ro to the target protein accessible via apoptosis.

Disclosure: D. Alvarez, None; **E. V. Komissarova**, None; **J. Swartz**, None; **F. Barrat**, None; **T. L. Rivera**, None; **R. M. Clancy**, None; **J. P. Buyon**, NIH contract N01-AR042220 and NIH grant R01 AR42455, 2 .

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Chronic Exposure to Type I Interferon Modulates CD4 T-Cell Function in Systemic Lupus Erythematosus (SLE). Wan-Sik Uhm, Jakub K. Loster, S. Sam Lim, Jorg J. Goronzy and Cornelia M. Weyand, Lowance Center for Human Immunology and Rheumatology, Atlanta, GA

Purpose: In patients with SLE, circulating IFNα levels and transcripts of IFN-induced genes are increased and correlate with disease activity and severity. Type I IFN, now considered a central pathogenic factor in SLE, regulates multiple immune pathways and critically determines T-cell development and effector functions. TNF-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily, is a quintessential IFN-induced gene. Expressed on the surface of CD4 T cells, TRAIL mediates proinflammatory and cytotoxic effector functions. Here, we have studied how chronic IFNα exposure affects TRAIL-expressing T cells in SLE.

Method: Patients with active SLE (n=77) and age-, sex-, and ethnicity-matched controls (n=77) were recruited through the SLE clinic. Spontaneous and IFNα-induced expressions of TRAIL on the surface and in the cytoplasm of CD4 T cells were examined by flow cytometry. IFNα-induced intracellular signaling events (pSTAT1, 3, 4, and 5) were quantified by phosphoflow studies. Transcripts of the IFNα-induced genes TRAIL and IFN-induced protein with tetratricopeptide repeats 1 (IFIT1) were determined by RT-PCR. TRAIL expression on CD4 T cells was studied after withdrawal from IFNα or after exposing them chronically to exogenous IFNα.

Results: Freshly isolated CD4 T cells from SLE patients expressed TRAIL at higher density (p=0.02). However, stimulation with exogenous IFNα revealed a defect in the inducibility of TRAIL on SLE T cells, both on protein (p<0.001) and transcription levels (p<0.001). Diminished responsiveness to IFN stimulation also involved IFIT2 (p<0.01), another IFN-inducible gene. This defect in IFN responsiveness could not be attributed to attenuated IFN signaling. The levels of pSTAT1 in SLE T cells after 15, 30, and 45 minutes of IFNα stimulation were even higher than in controls (p<0.05). Upregulation of pSTAT4 was indistinguishable in SLE and control T cells. Culturing of SLE T cells in IFNα-free medium restored responsiveness to an IFNα challenge. Conversely, exposure of healthy CD4 T cells to exogenous IFNα diminished TRAIL induction, resembling SLE T cells.

Conclusion: CD4 T cells from SLE patients fail to respond adequately to an IFNα challenge and express significantly lower surface levels of the effector molecule TRAIL. IFNα-low responsiveness can be induced in healthy T cells by chronic exposure to the cytokine and reverted

in SLE T cells by withdrawal of the cytokine. The adaption of SLE T cells to continuous IFNα stimulation involves a mechanism distal from STAT1 signaling and proximal from the TRAIL promoter. The inability of SLE T cells to appropriately respond to type 1 IFN may deprive SLE patients of prompt and effective anti-pathogen immunity and render them infection susceptible.

Disclosure: W. S. Uhm, None; **J. K. Loster**, None; **S. S. Lim**, None; **J. J. Goronzy**, None; **C. M. Weyand**, None.

ACR Poster Session A

Infection-related Rheumatic Disease
Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Prevalence and Characteristics of Articular Manifestations in Human Imunodeficiency Virus Infection. Paul Etau Ekwom, Kenyatta National Hospital, Nairobi, Kenya

Purpose: Articular manifestations have been reported in HIV infection with a prevalence of 2.5 to 68%. The study´s objective was to determine the prevalence, types and characteristics of articular manifestations in the HIV infected patients.

Method: This was a cross sectional descriptive study at the Comprehensive care clinic (HIV outpatient clinic) at the Kenyatta National Hospital from October 2007 to March 2008. A sample of 214 patients with HIV infection was consecutively interviewed. 21 patients were excluded due to presence of other articular/rheumatologic diseases, trauma or failure to carry out the laboratory/radiologic tests 193 patients were recruited, interviewed and examined as per the gait, arms, spine, and legs (GALS) locomotor screen. Their World Health organization (WHO) clinical stage of HIV infection was also determined.Those with abnormal GALS screen were further interviewed and examined as per the American College of Rheumatology Ad hoc committee on clinical guidelines for the initial evaluation of adults with acute musculoskeletal symptoms, their global functional status was assessed and pain was assessed by use of a four point likert scale. Blood was drawn for total blood count, erythrocyte sedimentation rate and Cluster of differentiation 4 (CD4) cell count determination. Additional uric acid, rheumatoid factor and antinuclear antibody tests were carried out for patients with arthritis. Patients with hip and alternating buttock pains had plain radiographs of the hip and sacroiliac joints done which were evaluated for features of avascular necrosis and sacroillitis respectively.

Results: Thirty three of the 193 study patients were diagnosed to have articular disease with a prevalence of articular manifestations in HIV infection of 17.1%, 95% Confidence interval of 12.1-22.1%. The type prevalence was; HIV associated arthritis; 0.5%, undifferentiated spondyloarthropathy; 1% and HIV associated arthralgia 15.6%

Characteristics of patients with articular disease:
The mean age was 36 ± 9.0 years (range 23-63 years) with 23 (69.7%) females and 10 (30.3%) males with a ratio of 1:2.3.
Majority, (65.2%), were in WHO clinical stage **III** and stage **II** of HIV infection.
Majority, (51.5%), had oligoarticular presentation with a mean duration of joint pains of 53.3 ± 75.3 days (range 2-365 days).
Majority (57.6%) of the patients, using the four point Likert pain scale, reported mild joint pains.
The mean CD4 cell count cell count was 330.4 ± 220.2 cells/mm^3. compared to 362.1 ± 223.9 cells/mm^3in those with no articular disease there being no statistically significant difference with at a p value of 0.459.
Majority (51.5%) had no impairment in their vocational activities, avocational activities or activities of daily living but six (18.2%) of the 33 patients with articular disease had missed work or school. The total hours missed from work or school was 700 hours. (Range: 2-240 hours)

Conclusion: Articular disease in HIV infection is common and is a cause of morbidity. The study did no show any correlation between CD4 cell count and articular manifestations.

Disclosure: P. E. Ekwom, None.

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Rheumatologist's Knowledge, Attitudes and Concerns Regarding Progressive Multifocal Leukoencephalopathy(PML). Leonard H. Calabrese[1], Eamonn S. Molloy[2] and Alan j. Taege[3], [1]Rheumatic & Immunologic Disease and Infectious Disease, Cleveland Clinic Foundation, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland Ohio

Purpose: PML is a highly fatal opportunistic infection classically associated with profound immunosuppression in the settings of HIV, cancer and transplantation. PML is increasingly reported with several biologic agents frequently used by rheumatologists. Though genuinely rare, biologic-associated PML has led to an aggressive risk-mitigation program for one agent (natalizumab), the voluntary withdrawal from the market of another (efalizumab) and several 'dear health care provider' letters regarding rituximab and mycophenolate. The risk of PML has added to the complexity of both physicians' and patients' shared decision making in drug selection; thus it is important to know what the level of physician knowledge is regarding this infection as well as prevailing attitudes and concerns in order to identify possible gaps in learning.

Method: A brief 10 question multiple choice survey was crafted to asses the domains of knowledge, attitudes and needs/concerns regarding PML. The survey was distributed via e-mail to a subset of clinical rheumatologists identifying themselves as members of the ACR. An open-ended question provided an opportunity to identify areas of educational need.

Results: 176 responses were analyzed representing a calculated 15% response rate. 53% of physicians identified themselves as moderately or extremely aggressive in their use of immunosuppressive and/or biologic therapies. 32% rated themselves as moderate to high in their knowledge of PML while 24% believed they were moderate to extreme in their deficiency of knowledge. When quizzed, only 16.5% could identify the correct answer on the prevalence of JC virus infection in the general population; 41% could not identify the diagnostic test of choice for PML (CSF PCR for JC). Regarding RA/SLE/CTD patients, 43% of respondents were somewhat to extremely concerned about PML as a complication for patients on TNF inhibitors, while 73% were similarly concerned when using rituximab. Only 24% and 31% of respondents felt that PML was somewhat to extremely likely to affect their use of TNF inhibitors or abatacept while 64% were similarly affected in terms of rituximab. Rheumatologists believed that 62% of their patients had somewhat to extreme concern about PML as a complication of their therapy. Finally, only 7% of rheumatologist responded that they have little or no educational needs regarding PML while over 80% felt moderate to extreme needs for education. In the open-ended question regarding specific needs, 93 of 176 responded; the majority identified needs including basic biology and mechanisms, appropriate diagnostic assessment and further understanding of risk-benefit analysis.

Conclusion: 1. Rheumatologists have important real and perceived learning gaps regarding PML. 2. Concerns regarding PML appear to affect both physician and patient decisions regarding the use of biologic agents. 3. The vast majority of rheumatologists surveyed describe strong educational needs regarding PML as a complication of anti-rheumatic therapy.

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Investigation of Possible Etiological Link Between Parainfluenza-1 and Giant Cell Arteritis. Trevor E. Davis[1], Gino Battaglioli[2], Joaquim Pinheiro[1], J. Andrew Carlson[3], Daryl M. Lamson[2] and Kirsten St. George[2], [1]Albany Medical Center, Albany, NY, [2]New York State Dept of Health, Slingerlands, NY, [3]Albany Medical Colleg, Albany, NY

Purpose: An infectious etiological trigger of Giant Cell Arteritis (GCA) is suggested by initial symptoms resembling a viral prodrome and by epidemiology which reveals both temporal and geographical clusters of GCA. The histologic hallmark of GCA is multinucleated giant cells found in temporal artery biopsies. Only a small number of human viruses are known to induce multinucleated giant cells, including respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), measles virus, Epstein Barr Virus, and herpes simplex virus. Serological testing for HPIV-1 antibodies, revealed a correlation between recent infection and GCA, but this has not yet been clearly confirmed or refuted by biopsy studies. We hypothesized HPIV-1 would be detected more frequently in GCA-positive temporal artery biopsies than in GCA-negative biopsies. Furthermore there would be no difference in frequency of detection for other common respiratory viruses including influenza A and B, RSV (1, 2, and 3), HPIV (2, 3, and 4), human metapneumovirus, enterovirus, and rhinovirus.

Method: After IRB approval, we obtained archived temporal artery biopsy samples from 80 consecutive symptomatic patients referred to Albany Medical Center for pathological examination in 2003-2007. An *a priori* power analysis indicated that the specimens available were sufficient to detect an increase in the proportion of HPIV-1 by 30% in GCA-positive biopsies, compared with negative biopsies, with a

power of 80%, and alpha of 0.05. Pathologic examination was accomplished previously by established techniques. Samples were formalin fixed and paraffin embedded. For molecular analysis, paraffin was removed using xylene and sample nucleic acid was extracted using a WaxFree extraction kit in accordance with the manufacturer's protocol. The samples were then prepared for reverse transcription polymerase chain reaction using the ResPlex II and run per protocol developed at the Wadsworth Center in collaboration with Genaco.

Results: In the 68 temporal artery biopsy samples adequate for PCR studies, 12 were previously classified, by a pathologist, as positive for GCA, and 56 were negative. No viral nucleic acid (including HPIV-1) was detected in any of the specimens, including the 12 GCA positives (proportion = 0.00, 1 sided 95% CI, 0.00-0.28). The observed number of HPIV-1 positives, 0 in 12 GCA (+) temporal artery biopsies, is significantly less ($p<0.05$ by 1-sided Fisher's exact test) than the minimum we expected *a priori*, if HPIV-1 were etiologically related to GCA.

Conclusion: Our findings do not support the role of HPIV-1 as an etiologic agent for GCA. However, it is possible that the current methodology is insufficient to confirm this relationship. For instance, if the virus is not infecting the temporal arteries directly but rather causing the pathologic changes of GCA indirectly such as through immune complex deposition or if the virus infected the tissue but is no longer present. Further investigation into a possible causative agent of GCA is necessary.

Disclosure: T. E. Davis, None; **G. Battaglioli**, None; **J. Pinheiro**, None; **J. A. Carlson**, None; **D. M. Lamson**, None; **K. St. George**, None.

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Usefulness of Procalcitonin Measurement in Differentiating Between Activity of Systemic Autoimmune Disease and Bacterial Infection. Olga Sleglova[1], Helena Dejmkova[1] and Jana Uhrova[2], [1]Institute of Rheumatology, Prague 2, Czech Republic, [2]Institute of clinical biochemistry, Prague 2, Czech Republic

Purpose: To investigate whether the determination of serum procalcitonin (PCT) in systemic autoimmune disease will help to discriminate disease flares from bacterial infection. PTC, the precursor of the calcitonin, is synthesized in the parafollicular C- cells of the thyroid. PCT in serum increases in severe bacterial and fungal infections. The first published study reported the usefulness of PTC as a screening biological tool in emergency medicine. But more than eleven years after the first publication assessing the usefulness of serum PCT dosage, its exact place in the diagnostic process remained to be defined.

Method: Patient with systemic autoimmune disease (systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, antiphospholipid syndrome and other) who were admitted to our hospital due to either a suspected deterioration of there primary diseases or an infectious disease were enrolled. Serum PCT level were measured in 113 serum samples. 76 samples were obtained from patients with disease deterioration without a detectable infection. 37 samples were obtained from patients with bacterial infections. 22 patients have systemic infections, 15 have local infections. Control group contained 80 patients without disease deterioration and without detectable infection, who came to outpatient department to routine control.

Results: 80 patients (49 female, 31 male), mean age 42 ± 19,7 in the control group and 113 patients (32 female, 26 male) mean age 46± 18,9 in the active group were enrolled. 79 of the 80 serum from the patients of control group serum PTC level were within the normal range.In 75 samples obtained from patients with disease deterioration without a detectable infection were serum PTC within the normal range in 67 samples. In the group with bacterial infection PCT level were elevated in 26 patients (19 patients with systemic and 7 with local infections). The PCT sensitivity was 84,0 % for identifying bacterial infection. Specificity was 81,4 %.

Conclusion: Serum PTC level is not elevated in patients with systemic autoimmune disease (with flare or without flare). PCT concentration offer good sensitivity for the early diagnosis of systemic bacterial infection. It can serve as a useful marker for the detection of systemic bacterial infection in patients with systemic autoimmune disease. PTC is not sufficient for ruling out localised bacterial infection.

Disclosure: O. Sleglova, None; **H. Dejmkova**, None; **J. Uhrova**, None.

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Norovirus and Influenza B Virus as Underappreciated Causes of Postinfectious Arthritis. Gita Gemulla, Normi Bruck, Manfred Gahr and Frank Pessler, Technical University Dresden Children's Hospital, 01307 Dresden, Germany

Purpose: Viruses are well-known causes of postinfectious arthritis. However, arthritis associated with noroviruses or influenza viruses has, to our knowledge, not been described in the literature. Here, we report 3 pediatric patients who developed a transient oligoarthritis of a lower extremity following infection with norovirus (n=2) and influenza B virus (n=1).

Method: Case series. Inclusion criteria: new onset synovitis in patients <16 years during or within 3 weeks of infection with a virus previously not associated with post-infectious arthritis.

Results: The patients were seen in 2008 and 2009.

Patient 1 was a 15-month-old Caucasian girl who presented to the hospital with high fever, upper respiratory symptoms, abdominal pain, vomiting, refusal to bear weight on the left lower extremity, and a swollen, warm (but not hot) left ankle joint. Ultrasound revealed an effusion in the talocrural joint. Osteomyelitis was ruled out by MRI. Cloudy synovial fluid was aspirated. The day after admission, the patient developed profuse diarrhea. Arthritis resolved with supportive treatment over several weeks. At 5 months follow up the patient has mild intermittent ankle pain and low-grade soft tissue swelling, but no joint effusion.

Patient 2 was an 11-year-old Caucasian girl who presented to the emergency room with acute painful swelling of the left knee. The week prior she had gastroenteritis with high fevers. The knee joint was swollen, warm, and painful with active and passive motion. A large joint effusion and mildly thickened synovium were seen sonographically. Joint aspiration revealed cloudy synovial fluid (cell count, 4900 cell/mm^3). In both patients, synovial fluid and blood cultures were sterile, and stool cultures for enteric bacterial pathogens and stool PCR for rotavirus were negative. However, norovirus was detected by stool PCR in both patients.

Patient 3 was a 12-year-old Caucasian girl who was seen in the pediatric rheumatology clinic because of erythema and painful swelling in the 3rd PIP and 1st MTP joint of the left foot. Two weeks prior she had the flu with high fevers, malaise, headaches, photophobia, myalgia and arthralgias. A nasopharyngial swab was positive for influenza B virus by culture and PCR, whereas extensive serological investigations for other viral or bacterial pathogens were negative. After initial improvement on treatment with ibuprofen and physical therapy, the patient returned 6 weeks later with recurrent swelling and pain in the same joints. Treatment with ibuprofen and intra-articular injection of triamcinolone hexacetonide led to resolution of symptoms in patients 2 and 3. They remain in remission at 3 months (patient 2) and 12 months (patient 3) follow up.

Conclusion: Although it is impossible to demonstrate causality in this small series, noro- and influenza viruses may constitute hitherto underappreciated causes of a transient postinfectious synovitis.

Disclosure: G. Gemulla, None; **N. Bruck**, None; **M. Gahr**, None; **F. Pessler**, None.

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Septic Arthritis: A 20-Year Review of Cases in Two Teaching Hospitals. Alejandra C. Rodriguez-Paez[1], Sherrilyn Tittermary[1], Charles H. Pritchard[2] and Lawrence H. Brent[1], [1]Albert Einstein Medical Center, Philadelphia, PA, [2]Abington Memorial Hospital, Willow Grove, PA

Purpose: Septic arthritis is a cause of considerable morbidity and mortality. Gram-positive bacteria remain the most common causative agents. The epidemiology of septic arthritis may be changing including an increase in methicillin-resistant *Staphylococcus aureus* (MRSA) and a decrease in gonococcal septic arthritis. The purpose of this study was to analyze changes in clinical features of patients with septic arthritis over time including causative microorganisms, associated co-morbidities, and outcomes of patients evaluated in two teaching institutions.

Method: Retrospective review of medical records of patients admitted to Albert Einstein Medical Center and Abington Memorial Hospital from 1988 to 2008 was performed on patients with septic arthritis. Data collected included patient demographics, clinical and laboratory features, associated co-morbidities, and disposition. The diagnosis of septic arthritis was defined as definite (inflamed joint and positive synovial fluid culture), probable (inflamed joint and negative synovial fluid culture but positive culture from another source), or possible (inflamed joint with negative cultures). Data was analyzed using SPSS 11.0 for descriptive statistics, and Chi-squared test to compare variables in the time periods 1, 2, 3 (1988-1994, 1995-2001, 2002-2008, respectively).

Results: A total of 466 patients were identified. The relative incidence of septic arthritis was stable over all time periods. Patients were younger in the time period 1 (49.3 yr) compared to time period 2 (57.4 yr, p=0.006), and 3 (55.6 yr, p=0.016). There was no difference in

gender through the different time periods. The most common etiology was methicillin-sensitive *Staphylococcus aureus* (MSSA) (27.9%), followed by MRSA (15.5%), the incidence of which did not change over time. The incidence of gonococcal septic arthritis decreased from time period 1 to period 2 and 3 (20.5% vs. 0.9% and 0.6%, p<0.001). An increased incidence over time was noted only for *Staphylococcus epidermidis* (p=0.007) and *Proteus mirabilis* (p=0.02). Comorbidities including coronary artery disease (p=0.017), cancer (p=0.04), congestive heart failure (p=0.021), diabetes mellitus (p=0.027), and liver disease (p=0.011), increased in prevalence and were significantly different among the time periods. Most patients were likely to be discharged home independently among the time periods, but the percentage decreased significantly over time (53% vs. 32.7% vs. 29.1%, p=<0.001). The mortality rate decreased overtime (7.2% vs. 5.7% vs. 4.1%, p=<0.01).

Conclusion: The microbial etiology of septic arthritis has changed over the past 20 years. While staphylococcal infections remained stable over time, gonococcal infections drastically decreased. Comorbid medical conditions increased in association with septic arthritis over time. Patients were less likely to be discharged home independently over time.

Disclosure: A. C. Rodriguez-Paez, None; **S. Tittermary**, None; **C. H. Pritchard**, None; **L. H. Brent**, None.

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NEW PPD-POSITIVE Test DURING Infliximab Treatment. María Montoro[1], C. Gonzalez[2], Francisco J. López-Longo[1], Enrique Calvo[1], E. Becerra[1], Carmen Martinez[1], D. Gerona[1], F. Aramburu[1], Carolina Marín[1], I. Monteagudo[1] and L. Carreño[3], [1]HGU Gregorio Marañón, Madrid, Spain, [2]H Gregorio Marañón, Madrid, Spain, [3]Hospital Gregorio Marañon, Madrid, Spain

Purpose: Background: Latent tuberculosis (TB) treatment is mandatory when anti-TNF treatment is indicated. However, primary TB infection may occur after anti-TNF therapy has started. **Objectives:** To evaluate PPD test conversion during infliximab treatment in patients with negative PPD and booster tests before infliximab therapy was started.

Method: All patients treated with infliximab in our Infusion Center during 5 months were included in the study. PPD test: five PPD-S units in one ml were injected intracutaneously into the volar forearm. Reaction was read measuring the transverse diameter of induration 48 hours later. Reactions ≥ 10 mm were considered positive. When tuberculine test is negative, it is repeated one week after (booster). Patients with positive PPD or booster test are considered to have latent TB and treated accordingly.

Results: 185 patients being treated with infliximab were included in the study: 60/185 rheumatoid arthritis, 81/185 ankylosing spondylitis, 33/185 other spondyloarthritis, 11/185 other connective tissue diseases. 120/180 (64.9%) had negative PPD/booster test before infliximab therapy started and a new tuberculin/booster test was performed during infliximab treatment. In 96/120 (80%) patients PPD/booster remained negative, 4/120 (3.3%) had a positive PPD test and 10/120 (8.3%) a positive booster. Nine patients were not available to perform the test. One patient developed miliary TB (previous PPD/booster test negative), typically associated with primary infection, before the second tuberculin/booster test was performed.

Conclusion: 14/120 (11.7%) patients previously negative showed positive PPD/booster test after infliximab treatment started. Positive booster was more frequent than PPD positive test. New primary TB infection may happen in patients treated with infliximab and may cause clinical disease. PPD/booster tests should be routinely included in the follow-up of patients treated with anti-TNF and prophylactic treatment started when appropriated.

Disclosure: M. Montoro, None; **C. Gonzalez**, Roche Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5 ; **F. J. López-Longo**, Roche Pharmaceuticals, 5, Schering-Plough, 5 ; **E. Calvo**, None; **E. Becerra**, None; **C. Martinez**, None; **D. Gerona**, None; **F. Aramburu**, None; **C. Marín**, None; **I. Monteagudo**, None; **L. Carreño**, None.

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Ocular Syphilis (Os): An Increasing and Confusing Cause of Uveitis. Mario Agudo Sr.[1], David de la Hera Sr.[1], Ricardo Blanco Sr.[1], Joaquin Cañal[1], Juan Ventosa[1], Fernando Martinez-Sanz Sr.[1], Victor M. Martinez-Taboada Sr.[1], Marien Peiro[1], Jose Luis Peña Sr.[1], Ignacio Villa Sr.[2], Lorena Alvarez-Rodriguez[1], Manuel Gutierrez-Cuadra[1], Maria del Carmen Fariñas[1] and Cristina Martinez-Dubois[1], [1]Hospital Universitario Marques de Valdecilla, Santander, Spain, [2]Hospital de Sierrallana, Torrelavega, Spain

Purpose: The ocular involvement may be the first manifestation of syphilis presenting as uveitis, indistinguishable morphologically from inflammatory uveitis.

Method: We describe 6 patients that presented with OS, diagnosed at the Multidisciplinary Uveitis Unit of our Hospital. The diagnosis of syphilis was performed by the following tests: RPR, TPHA, Western Blot and detection of specific anti-*Treponema pallidum* antibodies (QL). The ophthalmological exploration besides the routine tests included: slit lamp examination, retinography and ocular coherence tomography. For neurosyphilis a study of the cerebrospinal fluid (VDRL, cells and proteins) was performed.

Results: Six patients (3 women and 3 men, median age 47 years, range 20 to 70 years) were diagnosed with OS as the first manifestation of syphilis. Five patients had panuveitis with more severe involvement of the posterior pole; the remaining case had isolated posterior uveitis. In 4 cases the OS was bilateral. The median diagnostic delay was 1.5 months (range 0-15). Prior to their diagnosis 3 patients were treated as non-infectious uveitis with high doses of prednisone, combined with methotrexate in 1 of them.Once the diagnosis of OS was made, five patients received penicillin G 2 million Units /4h i.v. for 2 weeks with marked improvement and no relapses. The only patient treated with penicillin G benzathine 2.4 million Units weekly during 3 weeks had a relapse; she was then treated with penicillin G 2million Units /4h i.v. for 2 weeks, but the inflammation persisted, suffering a detachment of the retina; he required laser therapy and ceftriaxone. In the whole group the median visual acuity at diagnosis was 0.1 (range 0.05-0.8) improving after treatment to 0.7 (range 0.05-1). One patient had positive serology for HIV infection and another had neurosyphilis.

Conclusion: We conclude that in order to avoid diagnostic delays and potentially harmful treatments with prednisone and immunosuppressive agents, OS should be considered early in the differential diagnosis of panuveitis or isolated posterior uveitis. The best therapeutic results were obtained with high dosages of i.v. penicillin.

Disclosure: M. Agudo, None; **D. de la Hera**, None; **R. Blanco**, None; **J. Cañal**, None; **J. Ventosa**, None; **F. Martinez-Sanz**, None; **V. M. Martinez-Taboada**, None; **M. Peiro**, None; **J. L. Peña**, None; **I. Villa**, None; **L. Alvarez-Rodriguez**, None; **M. Gutierrez-Cuadra**, None; **M. D. C. Fariñas**, None; **C. Martinez-Dubois**, None.

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Reliability of Tuberculosis Screening Tests in Patients Receiving Tumor Necrosis Factor Antagonist Therapy in a United States Rheumatology Clinic. Himabindu Borra[1], Michelle Sit[2], Michael J. Morris[1], Kirk H. Waibel[1], Ramon A. Arroyo[1], Gerald A. Merrill[1] and Daniel F. Battafarano[1], [1]San Antonio Military Medical Center (SAMMC), San Antonio, TX, [2]David Grant Medical Ctr, Travis AFB, CA

Purpose: To assess the reliability of latent tuberculosis infection (LTBI) screening in patients treated with tumor necrosis factor (TNF) antagonist therapy in an outpatient rheumatology clinic.

Methods: Rheumatology clinic patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) being treated with TNF antagonist therapy were recruited in an ongoing IRB approved study. Patients with prior Bacillus calmette-Guerin (BCG) vaccination, previous positive tuberculin skin test (TST) or no documentation of TST prior to anti-TNF initiation were excluded. Enrolled patients consented to yearly TST, anergy screening, and chest x-ray (CXR). Quantiferon-TB Gold (QTB-G) blood testing became available 18 months after study initiation and was performed yearly thereafter. CXRs were interpreted by a pulmonologist. PPD induration of ≥ 5 mm at 48-72 hours was considered positive and anergy testing was correlated. Seroconverted patients and those with CXR findings concerning for LTBI were referred to Infectious Disease for evaluation.

Results: One-hundred and twenty-six patients were screened and 104 met inclusion criteria and consented to participate. Of these, 66 (63%) were female and 65 (63%) were Caucasians with a mean age of 54 (range 19-79). Seventy-five patients had RA, 17 had PsA, and 12 had AS. Forty- eight (46%) were on other immunosuppressive agents including prednisone (<10mg), methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Duration of TNF antagonist therapy ranged from 2 weeks to over 10 years. Number of patients enrolled and their results to date are as follows:

Year	Participant number	Abnormal CXRs/total* (%)	+TSTs/total (%)	Anergic pts/Total (%)	+QTB-G/total (%)
0	104	12/98 (12)	1/104 (1)	37/68 (54)	0/12 (0)
1	47	13/43 (30)	1/47 (2)	28/39 (72)	0/32 (0)

2	4	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)

*Abnormal CXR findings were not consistent with TB

The 2 patients with positive TSTs had indurations measuring 11 mm and 15 mm.

Conclusion: In this ongoing study of TNF antagonist treated patients in a typical US rheumatology clinic, 2 patients had TST seroconversion with negative QTB-G. In addition, 61% of our patients were anergic and at risk for LTBI. The implications of the current results are uncertain during this limited observation period. Further data collection from our patient population will better clarify the incidence of LTBI versus false positive or false negative TSTs. We recommend continued vigilance and screening for pulmonary and extra-pulmonary TB in patients treated with TNF antagonist therapy.

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ACR Poster Session A

Insights From Innate Immunity

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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The "Alarmin" S100A8 Causes Severe Cartilage Damage in Antigen-Induced Arthritis through TLR4 Activation and Upregulation of FcgRI and FcgRIV. Peter van Lent[1], Arjen Blom[1], Annet Sloetjes[1], Thomas Vogl[2], Johannes Roth[2] and Wim B. van den Berg[1], [1]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [2]University of Muenster, Muenster, Germany

Purpose: The "alarmins" S100 A8 and A9 have been described not only as markers for inflammation but may also be involved in induction of erosive cartilage destruction (1). S100A8 represents the active form whereas S100A9 binds to S100A8 protecting the protein from degradation. The aim of the study is to identify the mechanisms of S100 involvement in severe cartilage destruction during antigen-induced arthritis.

Methods: Antigen-induced arthritis (AIA) was induced in knee joints of S100A8/A9-/- mice (myeloid cells also lack S100A8) and their WT controls and severe cartilage destruction was measured using immunolocalisation of VDIPEN neoepitopes and chondrocyte death. rS100A8 was injected into mouse knee joints, synovium was isolated and mRNA levels were measured using RT-PCR. M-CSF stimulated bone marrow macrophages were stimulated by rS100A8 ,rS100A9 and S100A8/S100A9 complexes and mRNA and protein levels of FcγR were measured using RT-PCR and FACS analysis.

Results: AIA was induced in control and S100A9 deficient mice. Cartilage proteoglycan loss at day 2 was not different in the knockouts, but VDIPEN expression and severe surface erosion was markedly suppressed at day 7. To identify the mechanism of S100 involvement, we injected rS100A8 (5 µg) into the knee joint of normal mice. This caused only mild joint inflammation, but pronounced upregulation of activating FcγRI and IV (mRNA levels 64 and 256 fold respectively). We know from earlier studies that FcγRI and IV are crucial factors in immune complex mediated cartilage damage in this model. In vitro analysis with bone marrow derived macrophages confirmed this upregulation by S100A8 and showed profound increases of type I and IV protein expression with FACS analysis. S100A9 or S100A8/S100A9 complex were less potent in stimulating activating FcγRI and FcγRIV. Similar studies with a granulocyte cell line did not show any upregulation of Fc receptors, underlining the specificity for macrophages. Of great interest when bone marrow cells were taken from TLR4-/- mice, S100A8 mediated upregulation of FcγRI and IV was virtually absent, identifying that S100A8 caused this effect through TLR4. TLR4 and activating FcγR were highly expressed in inflamed synovium taken at day 7 AIA whereas in S100A9-/- knockout activating FcγR were strongly diminished underlining that S100A8/S100A9 regulates FcγR expression during AIA.

Conclusion: S100A8 is a strong inducer of activating FcγRI and IV through activation of TLR4 and drives FcγR expression and severe cartilage destruction in antigen-induced arthritis.

[1] van Lent PL et al. Stimulation of chondrocyte-mediated cartilage destruction by S100A8 in experimental murine arthritis. Arthritis Rheum. 2008 Dec;58(12):3776-87.

Disclosure: P. van Lent, None; **A. Blom**, None; **A. Sloetjes**, None; **T. Vogl**, None; **J. Roth**, None; **W. B. van den Berg**, None.

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Vitamin D Limits TLR9/IFN-Alpha Induced Antigen Presenting Cell Maturation. Melissa A. Lerman, Homaira Rahimi, Edward M. Behrens and Jon M. Burnham, Children's Hospital of Philadelphia, Philadelphia, PA

Purpose: Overactivation of antigen presenting cells (APC) plays an integral role in systemic lupus erythematosus (SLE) pathogenesis. Increased expression of interferon-a (IFNa) results in clinical and laboratory features of SLE, and IFNa drives *in vitro* monocyte maturation in SLE sera. Stimulation through toll-like receptor-9 (TLR9) has also been shown to be important in APC activation in SLE via IFNa dependent and independent mechanisms. 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$) can limit IFN-induced maturation of monocytes. The ability of $1,25(OH)_2D$ to limit monocyte maturation in SLE has not been examined. We explored whether $1,25(OH)_2D$ treatment could affect APC maturation via TLR9 and IFNa mediated pathways in mice and humans, respectively.

Methods: C57/BL6 bone marrow-derived murine cells were harvested and matured in culture for one week with cytokines to differentiate distinct APC populations. Cells were stimulated through TLR9 via CpG-DNA in the presence or absence of $1,25(OH)_2D$. CD11c+ dendritic cells and CD11b+ macrophages were analyzed for surface activation markers. Human monocytes were elutriated from whole human blood and incubated with sera from 15 patients with SLE and 5 control patients in the presence or absence of $1,25(OH)_2D$. These cells were also stimulated with IFNa +/- 1,25(OH)2D and cell surface activation markers were assessed using flow cytometry.

Results: In murine dendritic cells, incubation with $1,25(OH)_2D$ inhibited direct TLR9-induced activation, as evidenced by lower levels of MHC Class II, CD40, and CD86. We next explored whether $1,25(OH)_2D$ would maintain its inhibitory potential on human monocytes grown in the TLR9 induced, interferongenic environment of SLE sera. In human monocytes, stimulation with exogenous IFNa increased expression of MHC Class II, CD40, and CD86. However, when $1,25(OH)_2D$ was added to human monocytes cultured in the 5 control or 15 SLE sera, expression as measured by median florescence intensity (MdFI) of MHC Class II (median MdFI of 6587 vs 3631), CD40 (1010 vs 733), and CD86 (2481 vs 1961) was significantly reduced (all $P < 0.05$, Mann-Whitney test).

Conclusion: We demonstrated that $1,25(OH)_2D$ limits APC activation via direct TLR9 activation in murine bone marrow-derived APCs, and via IFNa-induced activation of human APCs. We also show that 1,25(OH)2D inhibits APC activation by SLE sera, suggesting that it may be possible for 1,25(OH)2D to reduce the immunostimulatory effects of the SLE cytokine milieu. Together, these results suggest that 1,25(OH)2D could inhibit APC activation in SLE by preventing both direct TLR9 activation via the putative TLR9 ligands present in SLE patients as well as by the soluble cytokine mediators in the sera of SLE patients. Further clinical trials are warranted to test this hypothesis.

Disclosure: M. A. Lerman, None; **H. Rahimi**, None; **E. M. Behrens**, None; **J. M. Burnham**, None.

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Role of Interferon Regulatory Factors in the Synoviocyte Type I IFN Response. Susan E. Sweeney, Trevor B. Kimbler and Gary S. Firestein, UCSD School of Medicine, La Jolla, CA

Purpose: Activation of innate sensors likely contributes to synovial inflammation in rheumatoid arthritis (RA). Of the receptors implicated in RA, TLR3 expressed by synoviocytes binds to ligands such as dsRNA and necrotic debris in the joint. TLR3 ligation activates NF-κB, MAP kinases, as well as interferon regulatory factors 3 and 7 (IRF), resulting in production of type I IFNs (IFNα and β), RANTES, IP-10, MCP-1 and other viral-stress inducible genes. Previous studies indicate that IRF3, rather than IRF7, plays a key role in production of the type I IFN response in primary human synoviocytes. The present study was designed to investigate the mechanism of this regulation in cultured synoviocytes and to determine the role of IRF3 and IRF7 in the expression of other cytokines, chemokines, and degradative enzymes implicated in RA.

Method: Fibroblast-like synoviocytes (FLS) were stimulated with poly (I-C) and transfected with IRF3 or IRF7 siRNA or control scrambled siRNA to knockdown transcription factor expression. Western blots, luciferase assay after transfection with an IFN-stimulated response

element (ISRE) reporter construct, AP-1 DNA binding assays, and Q-PCR were performed to evaluate the role of IRF3 and IRF7 in poly (I-C)-induced gene expression.

Results: IRF3 siRNA markedly decreased poly (I-C)-induced IFNβ, IRF5, IRF7, RANTES, IP-10, MCP-1, and MIP1α gene expression (90-100% inhibition; $p<0.01$). IRF3 deficiency also decreased ISRE promoter activity by 57%, suggesting that this transcription factor acts by modulating IFN-responsive gene transcription (n=3, $p<0.03$). IRF7 knockdown had minimal effect on most genes but did decrease MIP1α by 70%. ISRE activity was not significantly decreased by IRF7 deficiency (21% inhibition, n=3, $p>0.1$). Surprisingly, IRF3 knockdown almost completely blocked expression of other genes involved in RA, such as MMP3, MMP9, IL-6 and IL-8. IRF7 siRNA had little or no effect on these genes. We then investigated a possible role for IRF3 in AP-1 activation because this promoter is present in all four of these genes and is the dominant promoter element in MMP gene expression. IRF3 deficiency decreased AP-1 binding by 52% compared with control (n=3, $p <002$).

Conclusion: In contrast to immune cells, IRF3 rather than IRF7 is the dominant IRF transcription factor that regulates TLR3-mediated type I IFN responses in human synoviocytes. IRF3 activates synoviocyte IFN-response gene expression by increasing ISRE promoter activity. In addition, IRF3 can regulate other cytokines, chemokines, and MMPs through a novel mechanism that involves the AP-1 promoter site. Because the signaling pathway modulated by IRF3 plays a crucial role in synoviocytes, targeting IRF3 represents a potential approach to suppress diverse mediators while limiting suppression of IRF7-mediated adaptive immune responses.

Disclosure: S. E. Sweeney, None; **T. B. Kimbler**, None; **G. S. Firestein**, None.

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Modulation of TLR7 and TLR8 Activation in Human Macrophages. Elena V. Komissarova[1], Ekambar R. Kandimalla[2], Sudhir Agrawal[3], Robert M. Clancy[4] and Jill P. Buyon[1], [1]NYU School of Medicine, New York, NY, [2]Idera Pharmaceuticals, Cambridge, MA, [3]D. Phil, CEO, CSO, and President, Idera Pharmaceuticals, Cambridge, MA, [4]Tisch Hospital 4-407, New York, NY

Purpose: Two percent of neonates born to mothers with SSA/Ro autoantibodies have congenital heart block (CHB). It has been hypothesized that macrophage engagement of Toll-like receptors (TLR) via binding to the ssRNA moiety of the target autoantigen exposed on the surface of the fetal cardiocytes is involved in the pathogenesis. Using a RNA-based TLR agonist and an antagonist of TLR7 and TLR9, activation of TLR was studied by TNFα release.

Method: Macrophages were derived from CD14+ monocytes of healthy donors cultured in suspension with growth medium RPMI1640/10% FBS and 10ng/ml GM-CSF for at least 7 days. Cells were plated at $4x10^5$ per well into 12-well plates and adhered macrophages were treated with TLR7 or TLR8 agonists in the absence or presence of antagonist for 24 hours. The levels of TNFα in culture supernatants were measured by ELISA. Cytotoxicity of compounds for macrophages was assessed in MTS assay. Expression of TLR7 and TLR8 mRNA was determined in RT-PCR.

Results: Macrophages from different donors showed variability in the levels of TLR7 and TLR8 mRNA expression and corresponding variability in response to TLR agonists.TLR7 agonist R837 (imiquimod, InvivoGen) at 5μg/ml induced statistically significant TNFα release from 31.6 to 457.7±85.9pg/ml ($p=0.0033$, N=7). RNA-based TLR8 agonist at 20μg/ml induced statistically significant TNFα release from 31.6 to 621± 124.6pg/ml ($p=0.0029$, N=7). The novel TLR antagonist at 80μg/ml (nontoxic for macrophages) reduced the induced TNFα release by TLR8 agonist (20μg/ml) from 621±124.6 to 11.4±5.9pg/ml (N=3). Endosomal acidification neutralizing agent, chloroquine at a nontoxic concentration of 5μg/ml inhibited the induced TNFα secretion by R837 (5μg/ml) from 457.7±85.9 to 184.6±31.07 ($p=0.0086$, N=6) and by TLR8 agonist (20μg/ml) from 621±124.6 to 4.4 pg/ml (N=2). No toxicity was seen in macrophages exposed for 24 hours to TLR antagonist at concentrations up to 100 μg/ml (MTS assay). In contrast, after a 24-hour exposure to 21μg/ml chloroquine only 75% of the macrophages were viable in MTS assay. The LC_{50} value for chloroquine was 40μg/ml.

Conclusion: Variability of TLR7 and TLR8 expression in isolated human macrophages from different donors may be relevant to the inflammatory cascade to CHB and discordant disease in fetuses exposed to anti-Ro antibodies. Given the profound TLR inhibition, antimalarial compounds, already in use during human pregnancy, and TLR antagonist studied herein may be relevant candidates for study in the prevention of disease.

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Functional Role of the Intracellular Pattern-Recognition Receptor Nucleotide-Binding Oligomerization Domain 1 (NOD1) in Rheumatoid Arthritis Synovial Fibroblasts. Kazuhiro Yokota[1], Astrid Jungel[1], Christoph Kolling[2], Toshihide Mimura[3], Renate E. Gay[1], Beat A. Michel[1], Steffen Gay[1] and Caroline Ospelt[1], [1]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland, [3]Dept. Rheum. & Appl. Immunol. Fac. Med. SMU, Saitama, Japan

Purpose: Previously, we have reported that synovial fibroblasts (SF) express functional pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain 2 (NOD2). Activation of these innate immune receptors on SF plays a key role in the pathogenesis of rheumatoid arthritis (RA) by induction of proinflammatory cytokines, chemokines, and matrix degrading enzymes. Since cytoplasmic PRR NOD1 was shown to have proinflammatory functions in different cell types, we analyzed here the function and expression of this receptor in RASF and a possible crosstalk with TLR pathways.

Method: RASF were stimulated with the NOD1 ligand L-Ala-γ-D-Glu-mDAP (Tri-DAP), the TLR2 ligand bLP, the TLR3 ligand poly I:C, the TLR4 ligand LPS or with TNF-α or IL-1β. Real-time PCR was employed to quantitate the levels of mRNA for IL-6, CCL5/RANTES, matrix metalloproteinases (MMPs), and TLRs. ELISA was used to quantitate protein levels of IL-6.

Results: Stimulation of RASF (n=6) with Tri-DAP for 24 h significantly up-regulated the expression of the proinflammatory cytokine IL-6 (3.7±1.6-fold, $p<0.05$), and the chemokine CCL5 (86.2±47.0-fold, $p<0.05$). Also the matrix degrading enzymes MMP-1 (25.0±11.6-fold, $p<0.05$), MMP-3 (6.6±1.9-fold, $p<0.05$), MMP-9 (3.8±1.2-fold, $p<0.05$), and MMP-13 (2.3±0.6-fold, $p<0.05$) were significantly up-regulated by stimulation of NOD1. Whereas the expression of TLR4 was not changed by Tri-DAP, mRNA levels of TLR2 and TLR3 increased 3.6±0.7-fold ($p<0.05$) and 2.5±0.8-fold ($p<0.05$) respectively. To elucidate a possible crosstalk between NOD1 and TLR pathways, RASF were cultured with Tri-DAP in the presence or absence of TLR ligands (bLP, poly I:C, LPS) (n=6). NOD1 as well as TLR stimulation significantly increased the levels of IL-6. However, there was no synergistic or antagonistic effect by simultaneous stimulation of the two types of receptors. To gain further knowledge about how the expression of NOD1 is regulated in RASF, we stimulated RASF with Tri-DAP, TLR ligands, TNF-α or IL-1β. RASF expressed high levels of NOD1 mRNA which was up-regulated by poly I:C after 8 h (n=3, 2.5±0.3-fold, $p<0.05$) and after 24 h (n=5, 2.9±0.3-fold, $p<0.05$), and by LPS after 8 h (n=3, 2.2±0.3-fold, $p<0.01$). In contrast, the expression of NOD1 was not changed by Tri-DAP, bLP, TNF-α or IL-1β at any time-point.

Conclusion: NOD1 is a newly described innate immune receptor expressed on SF and induces the expression of proinflammatory and matrix degrading molecules.

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Adrenomedullin Induces Semi-Matured Tolerogenic Dendritic Cells: Implication of a Neuropeptide in Peripheral Tolerance. Sandrine Rullé[1], Marie-Dominique Ah Kioon[2], Carine Asensio[2], Hang-Korng Ea[2], Marie-Christophe Boissier[1], Frederic Lioté[2] and Geraldine Falgarone[1], [1]Paris 13 University; AP-HP, Bobigny, France, [2]Rheumatology Department; Inserm UMR-S606; Paris-Diderot University, hôpital Lariboisiere, Paris, France

Purpose: Dendritic cells (DC) are antigen presenting cells and are also important for tolerance. They can stimulate or expand regulatory T cells (Treg) to favor the immune response control. Among molecules expressed by tolerogenic DC, indoleamine dioxygenase (IDO) can promote Treg development and suppress T cell activation (1). Adrenomedullin (AM) is a neuropeptide with anti-apoptotic and anti-inflammatory effects and can reduce arthritis in collagen-induced arthritis. AM could decrease TH1 effector cells and favor Treg expansion (2). AM and its receptors are expressed by several immune cells but its role in immune homeostasis is unknown. The aim of this study is to evaluate AM effects on DC maturation and functions.

Methods: Bone marrow-derived DC were cultured in Gm-CSF during 6 days, stimulated or not with CpG motifs, lipopolysaccharide (LPS), AM alone or in combination during 24 hours. DC maturation was evaluated by flow cytometry, cytokine titration, allogeneic T cell

proliferation and endocytosis analysis. The expression of IDO, AM, AM receptors CLR/RAMP (Calcitonin receptor Like Receptor/ Receptor Activating Modifying Protein) and orphan receptors RDC-1 and L1 were studied by q-RT-PCR and western blot.

Results: In comparison with LPS- or CpG-stimulated DC, AM-stimulated DC expressed lower MHC class II, CD40, CD80 and CD86 molecules, and secreted less pro-inflammatory cytokines (IL-12p70, IL-1α, IL-1β) than mature DC; surprisingly, AM seemed to reduce LPS induced-TNF secretion and induces high levels of IFN gamma but not of IL-10.

However, allogeneic and endocytosis capacities were comparable to that of semi-mature and mature DC. Moreover, although DC expressed at basal level the AM receptor CLR, the co-factor RAMP-2, and RDC-1, DC maturation was accompanied with an increase of all these molecules. DC expressed also low level of secreted AM and exogenous AM increases this level. Finally IDO mRNA was expressed after AM stimulation.

Conclusion: For the first time, we have demonstrated that AM and its receptors are expressed in DC and that exogenous AM is able to modify DC phenotype and functions. AM-stimulated DC are characterized by a semi-mature phenotype with reduced endocytic capacities. This action seems to be specific of its receptors CLR and RAMP. Through IDO expression and others yet unknown mechanisms, this effect could be involve in peripheral tolerance and could be a promising strategy to favor Treg expansion.

1. Jaen O et al. Dendritic cells modulated by innate immunity improve collagen-induced arthritis and induce regulatory T cells in vivo. Immunology 2009;126:35-44.

2. Gonzalez-Rey E, et al. Adrenomedullin protects from experimental arthritis by down-regulating inflammation and Th1 response and inducing regulatory T cells. Am J Pathol 2007;170:263-71.

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Expression of Sirtuins in Rheumatoid Arthritis Synovial Fibroblasts. Fabienne Niederer[1], Fabia Brentano[1], Caroline Ospelt[1], Beat A. Michel[1], Christoph Kolling[2], Renate E. Gay[1], Steffen Gay[1] and Diego Kyburz[1], [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland

Purpose: Sirtuins are a conserved family of NAD+ dependent histone deacetylases (HDAC) and mono-ADP-ribosyltransferases. The seven human sirtuins, SIRT1-7, are critical regulators of many cellular processes, including cell survival. Sirtuins are also mediators of inflammation in a variety of diseases. Since it is not known whether sirtuins contribute to the development of rheumatoid arthritis (RA), we analyzed the expression and regulation of SIRTs in synovial fibroblasts (SF) of RA and osteoarthritis (OA) patients.

Methods: RASF and OASF were obtained from patients undergoing joint replacement surgery. Cells were lysed and RNA was extracted using the RNeasy Mini Kit. Expression of SIRT1-4, 6 and 7 mRNA in RASF (n=8) and OASF (n=4) was measured with SYBR green Real-time PCR. RASF (n=4,8) were stimulated with the TLR2 ligand Pam3 (300 ng/ml), the TLR3 ligand poly(I-C) (10 µg/ml) and the TLR4 ligand LPS (10 ng/ml) for 24 hours.

Results: We show that both RASF and OASF express all analyzed SIRTs. However, basal mRNA levels of SIRT1 and SIRT4 were 3.9 fold (ΔCT RASF 8.6 ± 1.4; OASF 10.6 ± 0.9; p=0.03) and 3.8 fold (ΔCT RASF 14.4 ± 1.2; OASF 16.3 ± 0.9; p=0.02) higher in RASF as compared to OASF. Stimulation with the TLR2 ligand Pam3 reduced the expression of SIRT2 (p=0.04), SIRT3 (p<0.01) and SIRT7 mRNA (p<0.01) by 30 % each. Poly(I-C) significantly lowered the expression levels of SIRT1 mRNA by 40 % (p<0.01), SIRT2 mRNA by 70 % (p<0.01) and SIRT3 mRNA by 50 % (p<0.05), whereas stimulation with LPS decreased the levels of SIRT2 (p<0.01) and SIRT7 (p<0.01) mRNA in RASF by 50 and 25 %, respectively.

Conclusion: Based on the fact that the expression of TLRs has been observed already in early arthritis, our findings suggest that stimulation of TLR effector pathways may result in a decreased expression of sirtuins in RASF and thereby contributes to the activation of RASF by inhibiting the cell protective effects of specific sirtuins.

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Anti-TNF Therapy Leads to Decreased TNF Expression and NF-Kappa-B Signalling in RA Neutrophils. Helen L. Wright[1], Batsi Chikura[2], Roger C. Bucknall[2], Robert J. Moots[1] and Steven W. Edwards[1], [1]University of Liverpool, Liverpool, United Kingdom, [2]Royal Liverpool Hospital, Liverpool, United Kingdom

Purpose: Neutrophils are the major cell infiltrate in RA synovial fluid and are a source of TNFα, expressing the membrane-bound TNFα precursor protein (mTNF) that becomes active extracellularly upon cleavage. mTNF may also induce signalling via cell-cell contact with TNF receptors on neighbouring cells, and may also reverse-signal via engagement of soluble- or cell-expressed TNF receptors, or anti-TNF drugs. The purpose of this investigation was to investigate the effect of anti-TNF therapy on neutrophils from RA patients.

Method: 20 patients with RA were prescribed Etanercept, Adalimumab or Infliximab. Blood was collected before commencement of anti-TNF therapy, and at 4 and 12 weeks after first infusion. Neutrophils were isolated by one-step centrifugation through Polymorphprep, and expression of mTNF was measured by flow cytometry. Protein levels were analysed by Western blot, and mRNA was quantified by real-time PCR. Neutrophils from age-matched controls were also analysed.

Results: 80% (16/20) of patients achieved a response to therapy in accordance with EULAR guidelines. Baseline mTNF was significantly higher in RA patients compared to controls, and decreased significantly after 12 weeks therapy ($p<0.05$). mTNF levels at 4 weeks significantly correlated with 12-week DAS28 ($p<0.05$, $r_s=.560$). PCR analysis of TNFα mRNA levels showed a significant correlation between the decrease in TNFα mRNA and the decrease in disease activity (DAS28) from baseline to 12 weeks ($p<0.05$, $r_s=0.582$). Patients achieving low disease activity (DAS28 $\leq$3.2) after 12 weeks showed a significantly greater decrease in TNFα mRNA levels compared to other patients ($p<0.05$). Patient neutrophils showed significantly increased phosphorylation of NFκB (p65), elevated levels of the anti-apoptotic protein Mcl-1 and lower activation of caspase-9 compared to controls. Expression of caspases-8 and -3 was unchanged by anti-TNF therapy. Neutrophils from patients who achieved low disease activity after 12-weeks showed a significant decrease in NFκB phosphorylation compared to other patients ($p<0.05$).

Conclusion: Neutrophils from RA patients had an activated phenotype characterised by enhanced NFκB signalling, and levels of proteins which may induce slower rates of constitutive apoptosis. RA neutrophils expressed significantly higher membrane TNFα levels than controls, and mTNF expression following 4-weeks anti-TNF therapy was indicative of 12-week DAS28. Intracellular signalling via NFκB was reduced by anti-TNF therapy in those patients who went on to achieve low disease activity, and these patients also showed a significant decrease in TNFα mRNA production.

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Active Involvement of "Alarmins"S100A8 and S100A9 in Synovial Activation and Joint Destruction During Osteoarthritis. Peter van Lent[1], Arjen Blom[1], Johannes Roth[2] and Wim B. van den Berg[1], [1]Radboud University Medical Center, Nijmegen, Netherlands, [2]University of Muenster, Muenster, Germany

Purpose: Prominent proteins released by activated macrophages are the "alarmins" S100 A8 and A9. Both proteins accumulate in inflammatory synovial fluids and have been postulated to be involved in the pathogenesis of RA. S100A8 is assumed to be the active component whereas S100A9 functions as the regulatory subunit preventing S100A8 from degradation. The aim is to study the active involvement of S100A8/A9 in synovial activation and cartilage destruction in osteoarthritis.

Methods: Experimental OA was either induced by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM) or by injection of collagenase into murine knee joints, which causes local instability. OA phenotypes were studied within 8 weeks after induction. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 during the course of osteoarthritis was measured using immunolocalisation. Both models were induced in $S100A9^{-/-}$ deficient mice (myeloid cells also lack S100A8 at the protein level). Synovial activation and cartilage destruction was measured by histology. MMP-mediated cartilage destruction was measured with immunolocalisation using anti-VDIPEN antibodies.

Results: Kinetic studies show that in the surgically induced DMM model, S100A8 and A9 was marginally expressed within the synovium, only evident at day 7 after induction and consistent with limited synovial thickening. In addition, cartilage destruction was measured in various cartilage surfaces (medial and lateral tibia and femur) of the knee joint. No differences in cartilage destruction were observed in S100A9$^{-/-}$ and WT mice at day 42 after induction of DMM.

In contrast, during the course of collagenase-induced osteoarthritis, S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at day 14 ,28 and 42. Expression of these proteins nicely correlated with thickening of the synovial lining layer comprising activated macrophages. When collagenase-induced-osteoarthritis was elicited in S100A9$^{-/-}$ mice, significantly lower synovial activation was observed when compared to WT mice. Synovial activation was 62% lower at day 42. Cartilage destruction was strongly and significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. In line with this, MMP-mediated cartilage destruction (VDIPEN) was clearly present in cartilage of osteoarthritic controls but markedly decreased in medial cartilage layers of day 42 osteoarthritic S100A9$^{-/-}$ mice, suggesting that S100A8/A9 are involved in activating MMPs.

Conclusion: Alarmins S100A8/A9 play a crucial role in synovial activation and cartilage destruction in an osteoarthritis model that shows clear synovial involvement. S100A8/A9 expression in the synovium causes pathology probably by stimulating MMP-mediated damage in the cartilage matrix.

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Inhibition of Jak3-Stat6 Pathway Leading to An Anti-Inflammatory Process in Rheumatoid Arthritis. Kunihiro Yamaoka, Keisuke Maeshima, Koichi Oshita, Kazuyoshi Saito and Yoshiya Tanaka, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Purpose: Janus kinase 3 (Jak3) is a tyrosine kinase necessary for lymphocyte differentiation and proliferation, causing severe combined immunodeficiency. Because of its necessity for lymphocyte function, it is also known to be expressed at the inflammation site such as synovium from rheumatoid arthritis (RA) patients. Recently, a transcription factor Stat6, which is activated by Jak3 was reported to be specifically expressed on dendritic cells in the synovium from RA patient. Recent clinical trials of a Jak inhibitor CP-690,550 for RA has been conducted showing dramatic effects. Herein we have analyzed the function of dendritic cells (DCs) from Jak3 and Stat6 deficient mice to elucidate the involvement of Jak3-Stat6 in inflammatory process.

Objective: To elucidate the role of Jak3-Stat6 in dendritic cell function and inflammatory process.

Method: Jak3 and Stat6 deficient mouse was used to obtain splenic DCs or bone marrow derived DCs. Mouse bone marrow and purified human monocyte was cultured with GM-CSF and IL-4 or GM-CSF only to derive DC in vitro. Human monocyte and bone marrow derived DCs was positively purified with CD14 or CD11c microbeads respectively. Jak3 and Stat6 expression was analyzed by western blotting and cytokine concentration was measured by enzyme-linked immunosorbent assay (ELISA) or cytokine beads array.

Results: Jak3 and Stat6 deficient mice showed normal DC development in vivo and in vitro. Further evaluation with DC cell surface marker and antigen uptake was comparable with wild-type mice. Surprisingly, both Jak3 and Stat6 deficient DCs showed increased IL-10 production in response to toll-like receptor ligand stimulation while other inflammatory cytokine (TNF-a, IL-6) was at comparable level with wild type DCs. We further evaluated the cytokine profile with different genetic background and found that overproduction of IL-10 by Stat6-/- DCs was a consistent phenomenon.

Conclusion: We have evaluated DCs from Jak3 deficient and Stat6 deficient mice and found normal development with high production of IL-10 which was not affected by genetic background of the mice. Recently, a Jak inhibitor possessing high potency to Jak3 has been shown to have anti-rheumatic activity. It has shown potent anti-inflammatory effect with minimum side effect on haematopoietic cells leading to a question on its mechanism of action. Our results suggests that Jak3-Stat6 not only plays an important role in lymphocyte function but also has essential roles in regulating DC function and its inhibition leads to suppression of RA by enhancing IL-10 production by DC.

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BAFF Induction by Viral Infection Is a General Phenomenon but Types of Viruses as Well as Mechanisms Involved in This Process Are Cell Type-Dependent. Marc Ittah[1], Corinne Miceli-Richard[2], Nicolas Gestermann[1] and Xavier Mariette[3], [1]Bicêtre hospital, INSERM U802, Le Kremlin Bicêtre, France, [2]Bicêtre hospital, INSERM U 802, Le Kremlin Bicêtre, France, [3]Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France

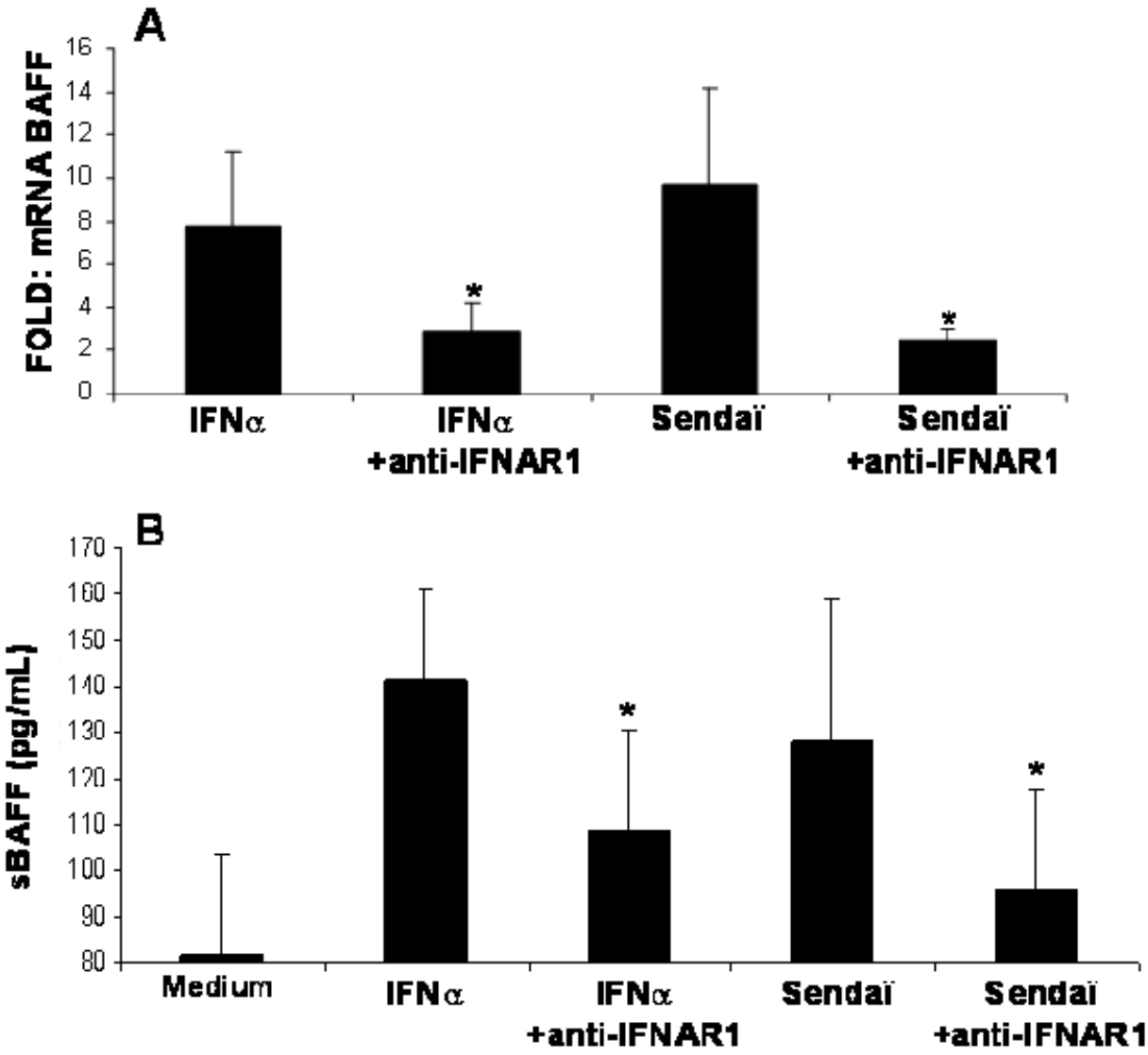
Purpose: B-cell activating factor (BAFF) plays a key role for promoting B-lymphocyte activation and survival. In primary Sjögren's syndrome (pSS), we have previously shown that salivary gland epithelial cells (SGECs), the resident targeted cells of autoimmunity in this disease, are able to produce BAFF after infection with a double stranded RNA virus through a Protein Kinase RNA-dependent (PKR) mechanism. In this study, we wanted to assess the effect of different viruses or agonists on different cell types, SGECS but also dendritic cells (DCs) and monocytes,on BAFF induction.

Method: Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood by Ficoll-density gradient centrifugation. Monocytes were separated from PBMCs by immunomagnetic anti-CD14-beads. DCs were differentiated from monocytes with GM-CSF and IL-4 during 7 days. Cultures of SGECs were established from minor salivary glands. Cells were stimulated with poly (I:C), reovirus-1 (a double-stranded RNA virus), or Sendaï virus (a single-stranded RNA virus). To prevent PKR activation or type 1 IFN pathway induction, 2-Aminopuirine or anti-IFNAR1 was used, respectively before in vitro treatment. Expression of BAFF mRNA was investigated by Q-PCR and BAFF protein was assessed in the supernatant by ELISA.

Results: Poly(I :C) increased BAFF expression by DC but 2-Aminopurine failed to reduce this expression. Poly(I:C) and reovirus-1 had no effect on BAFF expression by monocytes. However Sendaï virus induced BAFF expression both by SEGCs and monocytes. The 2-aminopurine also failed to reduce BAFF expression on Sendaï infected monocytes. However, blocking type 1 IFN receptor by the anti-IFNAR1 antibody, on Sendaï infected monocytes, induced a strong inhibition of BAFF expression (Figure 1-A, -B).

Conclusion: Double stranded RNA viruses may induce BAFF in SGECs and DC but through a PKR-dependant mechanism only in the latter. Single stranded RNA viruses may induce BAFF in SGECs and in monocytes through a PKR-independent and a Type 1 IFN-dependant mechanism. Thus, BAFF induction by viral infection is a general phenomenon but types of viruses as well as mechanisms involved in this process are cell type-dependent.

Figure 1: Induction of BAFF mRNA and protein in blood monocytes stimulated with type 1 IFN or infected with sendai virus. *: $p<0.05$



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Double Role of Mannose-Binding Lectin in Relation to Carotid Intima-Media Thickness in Patients with Rheumatoid Arthritis. Lone N. Troelsen[1], Peter Garred[2], Buris Christiansen[3], Chr. Torp-Pedersen[3], Ib J. Christensen[4], Eva Narvestad[5] and Soren Jacobsen[6], [1]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Denmark, 2100-DK Copenhagen, Denmark, [2]2Laboratory of Molecular Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Denmark, 2100-DK Copenhagen, Denmark, [3]3Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark, 2900-DK Hellerup, Denmark, [4]4Finsen Laboratory, Copenhagen Biocenter, Copenhagen, Denmark, 2200-DK Copenhagen, Denmark, [5]5Department of Radiology, Rigshospitalet, Copenhagen University Hospital, Denmark, Denmark, [6]Copenhagen University Hospital, Copenhagen, Denmark

Purpose: Patients with rheumatoid arthritis (RA) have increased risk of atherosclerosis and cardiovascular disease (CVD) that cannot be explained by excess of traditional risk factors. Several studies indicate that mannose-binding lectin (MBL) may modify development of atherosclerosis; both high and low serum levels of MBL are reported to be associated with CVD. In a recent follow-up study we experienced that genetically determined high serum levels of MBL increased the risk of myocardial infarction and ischemic heart disease in patients with RA. Intima-media thickness of the common carotid artery (ccIMT) is a validated non-invasive anatomic measure of subclinical CVD. We examined the relation between ccIMT and MBL in 114 RA patients.

Methods: In a cross-sectional study *MBL2* extended genotypes (YA/YA, YA/XA, XA/XA, YA/YO, XA/YO and YO/YO) and serum concentrations of MBL were assessed. ccIMT was determined by means of ultrasonography. The following traditional and RA related cardiovascular risk modifiers were assessed: male sex, age, blood pressure, smoking, body mass index, story of diabetes, lipid profile, insulin resistance, duration of RA, joint destruction calculated by Total Sharp Score, functional disability assessed by the Health Assessment Questionnaire score, serum anti-cyclic citrullinated peptide antibodies, C-reactive protein, serum IL-6, serum TNF-a, serum non-galactosylated IgG and present treatment with antirheumatic drugs.

Results: The median ccIMT was 0.67 mm (range: 0.37-1.1 mm). In one-way analysis of variance we found no significant difference in ccIMT and the investigated *MBL2* genotypes (P-value = 0.625). Using a general linear model, ccIMT was not linearly associated with serum MBL (P-value = 0.284) but was highly associated with the quadratic term of serum MBL (MBL^2) (P=0.002) reflecting a U-shaped relation. MBL^2 was also significantly associated with ccIMT in a multivariate analysis adjusting for traditional and RA related risk factors for CVD (p=0.025).

Conclusion: In RA patients, a quadratic U-shaped relation between serum MBL and ccIMT was observed independent of the effects of traditional and RA related risk factors for CVD. These results provide further support to the notion that both high and low levels of MBL may be associated with CVD. Future studies should focus on the differentiated mechanisms by which MBL may influence development of atherosclerosis in RA and if our findings may be applicable beyond RA.

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Accelerated Glomerular Injury in Mer Deficient Mice with Anti-GBM Nephritis. Wen-Hai Shao[1], Yuxuan Zhen[1], Joshua Rosenbaum[2], Robert A. Eisenberg[3], Tracy L. McGaha[4], Mark Birkenbach[1] and Philip L. Cohen[1], [1]Temple University, Philadelphia, PA, [2]University of Miami, Miami, FL, [3]University of Pennsylvania, Philadelphia, PA, [4]Medical College of Georgia, Augusta, GA

Purpose: The Mer receptor tyrosine kinase plays an important role in clearance of apoptotic cells and in modulation of both innate and adaptive immunity. Mice with the Mer kinase domain deletion (Mer-KO) develop progressive lupus-like autoimmunity. In kidney, Mer expression was shown in the glomeruli with immunofluorescence staining. We thus compared the susceptibility of WT and Mer-KO mice to nephrotoxic anti-glomerular basement membrane-induced murine nephritis.

Method: We induced nephritis in our experimental mice by iv injection of 7.5 ml of nephrotoxic serum per kg mouse body weight. The nephrotoxic serum was raised in sheep against mouse glomerular basement membrane.

Results: Mer-KO but not WT B6 recipients showed increased proteinuria by day 3. Glomeruli from Mer-KO mice were hyperplastic and later became necrotic. PAS-positive staining was evident in Mer-KO capillary spaces as well within tubules, consistent with massive protein leakage. Apoptotic bodies were detectable in the Mer-KO kidney. This early pathological change was associated with a lower survival rate in Mer-KO mice compared to WT. We observed early deposition of mouse anti-sheep IgM antibody on glomeruli from Mer-KO mice but not WT mice. Cytokine profile changes are undergoing investigation.

Conclusion: We discovered a novel protective role of Mer in the development of anti-GBM nephritis. Our data suggest that Mer acts to preserve the kidney from immune-related inflammation.

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The C-Terminus of the Cyclin Dependent Kinase Inhibitor p21$^{(WAF1/CIP1)}$ Suppresses Cytokine Production and Inflammatory Arthritis. Melissa Mavers[1], Hemant Agrawal[2], Dimitrios Balomenos[3] and Harris R. Perlman[4], [1]Saint Louis University School of Medicine, St. Louis, MO, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Centro Nacional de Biotecnología, Madrid, Spain, [4]Northwestern University, Chicago, IL

Purpose: Rheumatoid arthritis (RA) is a destructive autoimmune disease of unknown etiology. Previous studies demonstrated reduced expression of cyclin dependent kinase (CDK) inhibitors, which suppress cell cycle progression, in RA joints. We have shown that the CDK inhibitor p21 also suppresses inflammatory cytokine production by macrophages (MΦ), including IL-1β, IL-6, and TNFα. Furthermore, deficiency for p21 results in increased severity of lipopolysaccharide (LPS)-induced endotoxic shock. Herein, we further elucidate the role of p21 in suppression of inflammatory disease and determine the domain of p21 important for this function.

Methods: Wild-type (Wt) or p21-/- mice (C57BL/6) were injected intraperitoneally (i.p.) with 300 μL K/BxN serum and ankle circumference was measured over 7-25 days. Ankles were then harvested and embedded in paraffin for sections, which were stained for histochemical or immunohistochemical analysis and scored by a pathologist blinded to the study. For peptide studies, a polycationic peptide derived from HIV-1 Tat was fused to p21-mimetic peptides. Thioglycollate-elicited peritoneal MΦ were incubated with peptide (10 μM) for 2 hr, followed by 6 hr of 10 ng/ml LPS stimulation (in the presence of peptide). Supernatants were then collected and analyzed for various cytokines by multiplexed bead array. For *in vivo* studies, Wt B6;129 mice were injected i.p. with 10 mg/kg peptide 30 minutes prior to K/BxN serum and daily throughout.

Results: Mice deficient for p21 developed more severe arthritis, with enhanced ankle swelling, joint destruction, and inflammatory infiltrate, as compared to Wt mice. Furthermore, the disease failed to fully resolve in p21-/- mice. To determine the domain of p21 important in suppression of cytokine production, MΦ were treated with Tat-conjugated peptides corresponding to several domains of p21 prior to, and during, incubation with LPS. Peptides corresponding to amino acids (aa) 46-65 and aa 141-160 reduced the production of inflammatory cytokines as compared to a control peptide. *In vivo* treatment with these peptides demonstrated that the aa 141-160 peptide was superior in suppressing inflammatory arthritis, with 36.1-, 6.4-, and 3.6-fold reductions in ankle swelling at days 2, 4, and 7 post-K/BxN serum injection, respectively, as compared to control peptide.

Conclusion: These data demonstrate a pivotal role for the CDK inhibitor p21 in the suppression of inflammation. A peptide corresponding to aa 141-160, which significantly reduces cytokine production and the severity of inflammatory arthritis, contains the proliferating cell nuclear antigen binding domain and a putative cyclin-binding domain. Therefore, therapies using mimics to this p21 domain may have potential in the treatment of inflammatory disease.

Disclosure: M. Mavers, None; **H. Agrawal**, None; **D. Balomenos**, None; **H. R. Perlman**, None.

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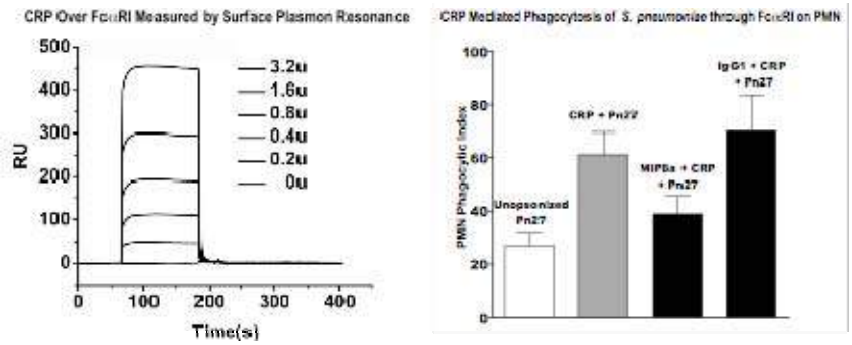
C-Reactive Protein Binds and Induces Phagocytosis through FcαRI. Kristopher D. Marjon[1], Jinghua Lu[2], Lorraine L. Marnell[1], Kye S. Park[1], Carolyn Mold[1], Peter D. Sun[2] and Terry W. Du Clos[3], [1]University of New Mexico, Albuquerque, NM, [2]National Institute of Allergy and Infectious Disease, Rockville, MD, [3]VA Medical Center, Albuquerque, NM

Purpose: C-reactive protein (CRP) is an acute phase serum pentraxin and its serum concentration can increase up to a thousand fold due to inflammatory stimuli. Pentraxins such as serum amyloid P component (SAP) and CRP have been shown to interact with the FcγR family. FcαRI is a receptor for IgA that is functionally related to FcgR, but has a higher sequence homology and structural similarity to members of the leukocyte receptor complex. FcαRI plays a role in IgA-mediated host defense and immunoregulation. FcαRI is expressed on neutrophils, eosinophils, monocytes, and dendritic cells. The purpose of this study was to determine if CRP functionally interacts with an additional immunoglobulin receptor such as FcαRI.

Methods: CRP or IgA binding affinity to FcαRI was quantitatively measured by surface plasmon resonance (SPR). CRP and IgA binding to rat basophilic leukemia (RBL) cells and FcαRI-transfected RBL (G248) cells was measured by flow cytometry. FcαRI mediated degranulation of RBL and G248 cells was measured using a colorimetric assay for β-hexosaminidase release. CRP-mediated phagocytosis was measured using human neutrophils and CRP-opsonized FITC labeled *Streptococcus pneumoniae* type 27 (*Pn*27). Phagocytosis was measured by flow cytometry using intracellular fluorescence of neutrophils after quenching

extracellular bacterial fluorescence with trypan blue. Specificity of CRP mediated phagocytosis though FcaRI was established by inhibition with anti-FcαRI mAb MIP8a.



Results: We report that CRP interacts with FcαRI with micromolar affinity and induces cellular responses. CRP bound to G248 cells and was inhibited by MIP8a, a well characterized mAb that blocks IgA binding to FcαRI, to the level of background binding to untransfected RBL cells. CRP also induced degranulation in G248 cells comparable to IgA induced degranulation. SPR studies confirmed the binding interaction between CRP and FcαRI and also demonstrated that C1q inhibited CRP binding to both FcαRI and FcγRIIa. IgA and CRP do not compete for FcαRI but are both inhibited by MIP8a. To investigate the role of this interaction further we used human neutrophils to determine if CRP could induce phagocytosis of heat-killed *S. pneumoniae* type 27. We found that CRP increased the phagocytic index above background and that CRP-mediated phagocytosis was inhibited by MIP8a.

Conclusion: These findings shed light on a novel interaction for CRP and FcαRI and give insight into a functional role between the two. This study broadens the functional role for CRP in innate immunity and identifies FcαRI as an additional CRP receptor on neutrophils.

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Suppressor of Cytokine Signaling 3 Dampens Invariant NKT Cell Responses by Inhibiting the Immunostimulatory Function of Antigen-Presenting Cells. Sharon Veenbergen[1], Miranda B. Bennink[1], Jerome Biton[2], Natacha Bessis[2], Onno J. Arntz[1], Wim B. van den Berg[1] and Fons A. van de Loo[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]EA 4222 Paris 13 University, Bobigny, France

Purpose: Invariant NKT (iNKT) cells are a remarkably plastic population that orchestrate innate and adaptive immune responses, but their exact role in rheumatoid arthritis remains to be elucidated. Invariant NKT cells are activated by costimulatory cytokines such as IL-12 and IL-18 as well as glycolipids presented by antigen-presenting cells (APCs) in a CD1d-dependent manner. Recent studies have shown that APCs with enhanced suppressor of cytokine signaling (SOCS)3 expression exhibit a tolerogenic phenotype and are able to steer the outcome of T helper immunity. The aim of the present study was to determine the effect of enhanced SOCS3 expression in APCs on iNKT cell immune responses under normal and arthritic conditions.

Methods and Results: We injected 3x10e8 infectious particles of adenovirus encoding SOCS3 intravenously in DBA1/J mice which resulted in enhanced SOCS3 transgene expression in especially macrophage-like cells of both liver and spleen. These splenic APCs isolated from SOCS3-treated and control mice showed no differences in surface expression of CD1d. Interestingly, enhanced SOCS3 expression in splenic APCs led to decreased production of IL-18 and IL-12 by these cells upon TLR2 and 4 stimulation. A co-culture of SOCS3-transduced APCs with the iNKT cell hybridoma DN32.D3 led to a significant inhibition of IL-2 and IFNgamma production by the iNKT cell clone upon stimulation with alpha-galactosylceramide (aGC). A combination of aGC and TLR agonists led to a more pronounced IL-2 and IFNgamma production by the iNKT cells in the presence of APCs from control mice, however, this cytokine production was completely inhibited using APCs from SOCS3-treated mice. This suggests that the cytokine-dependent activation of iNKT cells induced by TLR

engagement on APCs can be modulated by SOCS3. Next, we injected adenoviruses encoding SOCS3 intravenously just before clinical manifestation of collagen-induced arthritis (CIA). As described previously by us, applying this strategy leads to a clear protection against arthritis development. Here, we show that the induction of CIA caused an increase in liver and spleen iNKT cell percentages in control mice, which was markedly reduced in SOCS3-treated mice. In addition, SOCS3 gene transfer reduced the expression of the CD69 early activation marker on the iNKT cell population from both the liver and spleen. Furthermore, primary liver iNKT cells from SOCS3-treated mice also produced less IFNgamma and IL-4 upon aGC stimulation.

Conclusion: This study clearly showed that ectopic expression of SOCS3 in APCs dampens the iNKT cell immune response. This result suggests that modulation of APC function could be a feasible approach to fine-tune the iNKT cell immune response in autoimmune diseases e.g. rheumatoid arthritis.

Disclosure: S. Veenbergen, None; **M. B. Bennink**, None; **J. Biton**, None; **N. Bessis**, None; **O. J. Arntz**, None; **W. B. van den Berg**, None; **F. A. van de Loo**, None.

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Over-IFNg-Production by NK Cells During SLE Flares. Baptiste Hervier[1], Vivien Beziat[2], Julien Haroche[3], Pierre Lebon[4], Pascale Ghillani[5], Patrice Debré[6], Vincent Vieillard[2] and Zahir Amoura[3], [1]Hôpital Pitié-Salpétrière, Paris, France, [2]INSERM 543, Paris, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [4]Department of Virology, Saint-Vincent de Paul Hospital, Paris, France, [5]Hôpital Pitié-Salpetrière, Paris, France, [6]INSERM U543, Paris, France

Purpose: To determine the phenotype and the functionality of natural killer cells (NK) in systemic lupus erythematosus (SLE).

Method: Sixty-three patients with SLE were included (61 females, 2 males, median age 33 years) and compared to 20 healthy controls. SLE flares were defined by a SLEDAI ≥ 4.

All the immunologic tests were done on freshly isolated PBMCs. NK cell phenotype was determined by flow cytometry. NK cell natural cytotoxicity and antibody mediated cytotoxicity (ADCC) were determined both by 51Cr release assay and CD107a mobilization assay. IFNg production by NK cells was evaluated by flow cytometry after an overnight in vitro stimulation by IL12 and IL18. IFNa levels in SLE patient sera were calculated using an antiviral cytopathic bioassay.

Results: During SLE flares, lymphocyte count was decreased but percentage of CD3- CD56+ NK cells and CD3- CD56dim NK cells were not modified. The NK cell phenotype during SLE flares was significantly altered: expressions of CD69 & NKG2A were increased, whereas expressions of CD16, CD8 and KIR 2DL1 were decreased. The natural cytotoxicity and ADCC of NK cells were not modified in SLE patients. The in vitro production of IFNg by NK cells during SLE flares was dramatically increased, as attested by a higher percentage of IFNg positive NK cells (50.2% for active patients vs 31.7% for inactive patients, $p<0,007$). Whereas serum levels of IL12 and IL18 were equivalent in active compared to inactive SLE patients, IFNa serum levels were positively correlated with the disease activity score. Moreover, these levels were positively correlated with the percentage of IFNg positive NK cells ($p<0,04$).

Conclusion: During SLE flares, NK cells disclose a phenotype in agreement with an impaired maturation. In vitro, these particular NK cells are able to produce larger amount of IFNg in response to IL12 and IL18. This over-production of IFNg is correlated with IFNa serum levels, suggesting that the link between innate and adaptative immunity in SLE is assumed by NK cells through these cytokines.

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Regulatory Natural Antibodies to Apoptotic Cell Membrane Determinants Inhibit TLR Mediated Activating MAPK Signal Transduction in Dendritic Cells. Gregg J. Silverman and Yifang Chen, UC San Diego, La Jolla, CA

Purpose: Naturally arising antibodies (NAbs) to apoptotic cell membrane (ACM) determinants, such as phosphorylcholine (PC), can distinguish cells undergoing cell death from healthy cells, and form complexes that have potent properties to downregulate inflammatory responses. By recruitment of early complement factors, C1q and MBL, these NAbs amplify the immunomodulatory properties of ACMs and can inhibit MyD88- and TRIF-dependent TLR signaling in macrophages and dendritic cells (DCs), as well as prevent collagen-induced arthritis. To better understand the signal transduction pathways responsible for these immunosuppressive properties, we have investigated for effects on the Mitogen Activated Protein Kinase (MAPK) system that plays central roles in TLR responses.

Method: Cytokine production and MAPK signaling responses were studied in LPS stimulated murine bone-marrow derived conventional DCs, using standard approaches that include ELISA, Luminex assays, immunoblotting, intracellular flow cytometry and quantitative PCR of transcripts.

Result: We found that a monoclonal IgM anti-PC Mab, but not isotype control, only when co-incubated in serum-free media with purified early complement factors, MBL and C1q, significantly inhibited LPS-induced DC secretion of IL-6, TNFa, IL-12p70, IL-10, IP-10, MCP-1, while there was no induction of TGFb. This anti-ACM NAb also significantly inhibited LPS-mediated phosphorylation of cytoplasmic P38 MAPK, while there was no effect on JNK or ERK1/2. The regulatory NAb also inhibited LPS-mediated phosphorylation of the downstream nuclear transcription factor, ELK. The inhibitory activity of the regulatory NAb on P38 MAPK was comparable to that of dexamethasone, a potent glucocorticoid, which acts in part via transactivation of the dual specificity phosphatase, MKP-1 (also known as DUSP-1 and CL100). Moreover, co-incubation of the anti-ACM NAb with LPS, but not LPS alone, anti-ACM NAb alone, or LPS with isotype control, induced the early (i.e., 10 minute) induction of MKP-1 at a protein and transcript level, while the related MKP-5 was not induced. Intracellular flow cytometric studies confirmed that the NAb, when added to LPS-stimulated DC cultures, rapidly induced MKP-1 levels and suppressed P38 kinase phosphorylation. Studies in MKP-1 deficient cells are currently in progress.

Conclusion: Our studies demonstrate that an IgM regulatory NAb, which forms complexes with ACM and early complement factors to inhibit a broad range of pro-inflammatory TLR responses, can suppress activating P38 MAP kinase responses known to play central roles in inflammatory signal transduction pathways. These studies also provide the first evidence of potentially overlapping pathways responsible for the anti-inflammatory properties of glucocorticoids and regulatory NAbs.

Disclosure: G. J. Silverman, None; **Y. Chen**, None.

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Mannose Binding Lectin Gene-2 Haplotype Analysis in Korean Patients with Ankylosing Spondylitis. Churl Hyun Im[1], Eun Ha Kang[2], Joonwan Kim[1], Ran Song[1], Jin Hyun Kim[1], Yun Jong Lee[2], Kyung Sook Park[3], Eun Young Lee[1], Eun Bong Lee[1] and Yeong Wook Song[1], [1]Seoul National University Hospital, Seoul, South Korea, [2]Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Sungshin Women's University, Seoul, South Korea

Purpose: Mannose binding lectin (MBL) is a component of innate immune system, and it's serum levels or genetic polymorphisms are associated with autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. It was reported that MBL deficiency showed more severe radiographic progression in ankylosing spondylitis (AS) patients. We investigated MBL2 genetic polymorphisms and haplotype analysis in AS patients and healthy controls.

Methods: 95 AS patients, diagnosed by modified New York classification criteria, and 252 healthy controls were enrolled and their clinical data were evaluated. MBL2 gene promoter polymorphisms at -550 (H/L), -221 (Y/X), +4 UTR (P/Q) and exon polymorphisms at codon 52 (Arg/Cys), 54 (Gly/Asp, or A/B), 57 (Gly/Glu) were investigated using polymerase chain reaction and restriction fragment length polymorphism. Genetic polymorphisms and their associations were analyzed by SPSS program (ver 12.0). Haplotype associations were analyzed by Unphased program (ver 3.1.2).

Results: MBL 52 and MBL 57 genetic polymorphisms were not found in this population. Other MBL2 genetic polymorphisms were not significantly different between AS patients and healthy controls. In haplotype analysis, haplotype frequency of HYPB (4.40 % vs 0.52 %, OR 9.14, 95 % CI: 1.80 - 46.49, p value=0.0040), LYPA (16.78 % vs 8.95 %, OR 2.02, 95 % CI: 1.17 - 3.47, p value = 0.015) were significantly increased in AS patients than healthy controls. In contrary, LYPB haplotype frequency was significantly decreased in AS patients than healthy controls (9.26 % vs 21.64 %, OR 0.46, 95 % CI 0.25 - 0.85, p value = 0.0009). Clinical characteristics including family history for AS, HLA-B27 positivity, uveitis, or peripheral joint involvements were not associated with any MBL2 genetic polymorphisms or haplotypes.

Conclusion: Haplotypes of MBL2 genetic polymorphisms are associated with AS patients, suggesting that MBL2 genetic polymorphisms may have a role in development of AS.

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SLP-76 Is Required for Optimal NK Cell Activation and Shaping of the Ly49 Receptor Repertoire. Rebecca May and Taku Kambayashi, University of Pennsylvania, Philadelphia,, PA

Purpose: Natural killer (NK) cells are innate immune cells that provide a critical line of defense against intracellular pathogens and tumors by displaying cytotoxicity and producing immune-activating cytokines. The activation of NK cells is regulated by the expression of activating receptors that are finely counterbalanced by inhibitory receptors. Although mechanisms by which activating signals are blocked by inhibitory receptors are well defined, the proximal signaling pathways that lead to NK effector function are incompletely understood. The adaptor molecule SLP-76 is important in mediating signals downstream of ITAM-containing activating receptors in a variety of hematopoietic cell types. Thus, we examined whether SLP-76 is important also in NK cell signaling downstream of the Ly49D activating receptor.

Methods: To investigate the involvement of SLP-76 in Ly49D signal transduction, SLP-76 phosphorylation and clustering at the plasma membrane was examined in Ly49D-activated NK cells. Furthermore, the role of SLP-76 in NK cell signal transduction, activation, and development was assessed in SLP-76-deficient compared to wildtype (WT) NK cells.

Results: SLP-76 was phosphorylated and clustered at the plasma membrane following Ly49D stimulation, suggesting that SLP-76 is activated downstream of the Ly49D receptor. SLP-76 was required for optimal signal transduction through Ly49D as NK cells from SLP-76-deficient mice exhibited diminished ERK and Akt phosphorylation compared to WT mice. This correlated with decreased IFNγ production and cytotoxicity by SLP-76-deficient NK cells. NK cells from SLP-76-deficient mice appeared developmentally mature as expression of late maturation markers DX5 and CD11b were expressed normally. However, Ly49 family member inhibitory and activating receptors were expressed on a significantly lower proportion of NK cells from SLP-76-deficient compared to WT mice. Moreover, this selective developmental defect was NK cell-autonomous as WT/SLP-76 mixed bone marrow chimeras failed to correct the defect. However, this defect was not observed when SLP-76 was inducibly deleted in NK cells after full maturation. Despite normal development, these SLP-76-deficient NK cells still displayed defective IFNγ production and cytotoxicity.

Conclusion: SLP-76 is vital for Ly49D-mediated NK cell signaling and in shaping of the NK cell Ly49 repertoire during development. These results demonstrate a critical role of SLP-76 in NK cell tolerance and activation.

Disclosure: R. May, None; **T. Kambayashi**, None.

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Mutation of Y145 of SLP-76 Reduces FcγR- and Integrin-Dependent Neutrophil Functions and Protects Mice From Dermal Inflammation and Serum-Induced Arthritis. Laurie E. Lenox[1], Christopher Prieto[1], Martha S. Jordan[2], Ralph M. Bunte[3], Karsten Sauer[4], Gary A. Koretzky[5] and Kim E. Nichols[6], [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Abramson Family Cancer Research Institute, Univeristy School of Medicine, Philadelphia, PA, [3]University Laboratory Animal Resources, Philadlephia, PA, [4]The Scripps Research Institute, La Jolla, CA, [5]Univ Pennsylvania 415 BRB 2/3, Philadelphia, PA, [6]Children's Hospital of Philadelphia, Philadelphia

Purpose: SLP-76 is an essential adaptor molecule in neutrophils, where it is required for FcγR- and integrin-induced functions. SLP-76 contains three N-terminal tyrosines at residues 112, 128 and 145 that together are critical for its function. We sought to explore the relative importance of these tyrosines during neutrophil activation.

Methods: We examined in vitro functions using bone marrow isolated neutrophils isolated from knock-in mice harboring phenylalanine substitution mutations at tyrosines 112 and 128 (Y112/128F) or 145 (Y145F). We also examined the effects of these mutations on in vivo neutrophil activation using models of dermal inflammation and serum-induced arthritis.

Results: Mutations at Y112/Y128 and Y145 both interfered with SLP-76 activity; however, the Y145F mutation had a greater impact than Y112/128F on many in vitro FcγR-induced functions such as calcium mobilization and reactive oxygen intermediates (ROI) production. These tyrosine units (Y112/128 and Y145) are both key motif within SLP-76 that are similarly required for integrin-dependent functions such as spreading, degranulation and ROI production. In vitro functional defects were recapitulated in vivo, where mice expressing the Y→F mutations exhibited greater attenuation of neutrophil-mediated inflammatory responses. Most notably, the Y145F mutation protected against the development of joint inflammation in the neutrophil-dependent K/BxN model of serum-induced arthritis.

Conclusion: These data indicate Y145 is the most critical tyrosine supporting SLP-76 function in neutrophils. Future efforts to dissect how Y145 mediates SLP-76-dependent signaling in neutrophils will increase our understanding of this lineage and provide insights into the treatment of inflammatory conditions.

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The NF-Kb Essential Modulator Zinc Finger Domain Regulates NF-Kb Activation by Innate Immune Receptors in T Cells and Links to Inflammatory Disease. Eric P. Hanson[1], Linda Shawver[1], Lisa A. Madge[2], Michael J. May[2] and Jordan S. Orange[1], [1]Joseph Stokes Jr Research Institute, Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA

Purpose: NEMO-ID is a rare X-linked congenital immunodeficiency which results from mutations in IKBKG, the gene coding for the NF-κB essential modulator, a transcription factor with an important role in immunity, development and programmed cell death. A recently published database of naturally occurring NEMO hypomorphic mutations has revealed novel genotype-phenotype correlations that link protein regions to defects in innate and adaptive immunity, in addition to unexpected links to inflammatory disease. Eight of 32 (25%) of the mutations described in this database are associated with inflammatory or autoimmune disease. These mutations cluster in the 1st coiled coil/alpha helix domain or result in partial or complete truncation of the C-terminal zinc finger domain. Individuals with NEMO-ID, due to the E391X mutation that results in loss of the C-terminal Zinc finger domain, have recently been described; these patients exhibit prolonged systemic inflammation following infection and inflammatory colitis.

Method: A NEMO-deficient T cell line was stably reconstituted with E391X or with the naturally occurring Q403X partial zinc finger truncation mutation and the effects of TNF Receptor, Toll-like receptor and T Cell receptor activation were measured by standard biochemical assays and microscopy.

Results: Activation of E391X-reconstituted cells with the TLR5 ligand, flagellin, or with TNF-α led to increased and sustained IKK complex activation. This was accompanied by increased IkBα degradation, and nuclear translocation and DNA binding of the p65 subunit of NF-κB. However, the nuclear translocation of zinc finger truncated NEMO was impaired.

Conclusion: These results indicate that the zinc finger has an important role in regulating IKK complex kinase activity and nuclear translocation of NEMO following TNF-α activation. In conclusion, these results provide insight into the phenotype of inflammatory disease in individuals with NEMO-ID, suggest broader implications for understanding the regulatory role of NEMO in NF-κB activation, and may help direct the rational development of immunomodulatory therapy.

Disclosure: E. P. Hanson, None; **L. Shawver**, None; **L. A. Madge**, None; **M. J. May**, None; **J. S. Orange**, None.

ACR Poster Session A

Large Vessel Vasculitides

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Incidence of Herpes Zoster in Patients with Giant Cell Arteritis: A Population-Based Cohort Study. Valentin S. Schäfer, Tanaz A. Kermani, Cynthia S. Crowson, Gene G. Hunder, Sherine E. Gabriel, Eric L. Matteson and Kenneth J. Warrington, Mayo Clinic, Rochester, MN

Purpose: The incidence of herpes zoster (HZ) in patients with giant cell arteritis (GCA) is unknown. The aim of this study was to determine whether GCA is associated with an increased risk of HZ.

Methods: All incident cases of GCA diagnosed between January 1, 1950 and December 31, 2004 were identified for this population-based study. For each GCA patient, 2 subjects without GCA of the same sex and similar age and length of medical history were selected from the same population. Each non-GCA subject was assigned an index date corresponding to the date of diagnosis of GCA of the corresponding GCA patient. Cases of HZ were identified in both groups using diagnostic codes. Medical records of all patients with a code of HZ were reviewed to confirm the diagnosis. Patients in both cohorts were followed until death, last contact, or December 31, 2006. The proportions of patients with a history of HZ in the GCA and non-GCA cohorts were compared by Chi-square test. The cumulative incidence of HZ during follow-up was estimated using Kaplan-Meier methods. Cox proportional hazard models were used to examine the influence of GCA on the development of HZ after adjusting for age, sex and calendar year of GCA diagnosis index date.

Results: The study population consisted of 204 GCA patients and 407 non-GCA subjects. The GCA cohort consisted of 163 (79%) women and 41 (21%) men, mean age 76.0 (± 8.2) years with median follow-up 7.7 years (total 1856 person-years). The non-GCA cohort consisted of 325 (80%) women and 82 (20%) men, mean age 75.6 (± 8.4) years with median follow-up 8.1 years (total 3890 person-years). At index date, 26 (13%) GCA patients and 48 (12%) non-GCA patients had a history of HZ (p=0.73). During follow-up, 21 GCA patients and 38 non-GCA subjects developed HZ. The 2, 10 and 20 year cumulative incidences (± standard error) of HZ were 2.5% (± 1.2%), 14.5% (± 3.5%) and 26.7% (± 7.0%) among GCA patients and 2.0% (± 0.8%) 12.4% (± 2.3%) and 22.2% (± 4.2%) among non-GCA patients. There was no difference in the development of HZ in GCA patients compared to non-GCA patients (HR: 1.22; 95% CI: 0.71, 2.08; adjusted for age, sex and calendar year). There were no differences in the short-term occurrence of HZ following index date. No GCA patients and 1 non-GCA subject developed HZ within 6 months of index date. One GCA patient and 5 non-GCA subjects developed HZ within 1 year of index date. Four (19%) GCA and 9 (24%) non-GCA subjects were diagnosed with post-herpetic neuralgia (PHN) (p=0.64). The median duration of pain from PHN was similar; 4 months in GCA patients (range 2-36 months) and 2 months in non-GCA subjects (range 1-16 months, rank-sum p=0.50).

Conclusion: Patients with GCA do not appear to be at increased risk of HZ compared to age and gender-matched referent subjects, even during the first six months of therapy when glucocorticoid doses are usually highest. The occurrence of postherpetic neuralgia was similar in patients with, and without GCA.

Disclosure: V. S. Schäfer, None; **T. A. Kermani**, None; **C. S. Crowson**, None; **G. G. Hunder**, None; **S. E. Gabriel**, None; **E. L. Matteson**, None; **K. J. Warrington**, None.

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Evaluation of 18F-FDG PET as a Diagnostic Procedure in Giant Cell and Takayasu Arteriitis by Investigator Dependant Assessment and Standard Uptake Value. Petra Lehmann[1], Sarah Buchtala[2], Nelli Achajew[1], Peter Haerle[1], Boris Ehrenstein[1], Hamid Lighvani[1], Martin Fleck[1] and Joerg Marienhagen[1], [1]University Hospital Regensburg, Regensburg, Germany, [2]University Hospital Regensburg, Germany

Purpose: Large vessel vasculitis can be visualized by positron emission tomography (PET) due to an enhanced uptake of radioactive labeled fluoro-18-deoxyglucose (18F-FDG). Previous studies have demonstrated a high sensitivity of this method compared to MRI or conventional angiography. However, the significance and diagnostic value of FDG-PET is yet undetermined. We therefore performed a study to evaluate the reliabilitiy and validity of FDG-PET for the diagnosis of giant cell arteriitis (GCA) and Takaysu arteriitis (TA) and calculated a cut-off value for the maximum standardized uptake value (SUVmax).

Method: We selected patients with established diagnosis of GCA or TA (according to ACR criteria or positive arterial biopsy) and a pathologic ^{18}F-FDG PET in clinical routine. These PET scans and PET scans obtained from age- and sex-matched oncologic control patients were independently re-evaluated by two experienced nuclear specialists. As an observer independent approach, SUVmax was separately assessed for vessels of the upper (carotid/axillar region) and lower (iliacal region) extremities and a ROC analysis performed to establish a cut-off value for vasculitis.

Results: PET scans of 20 patients and 24 controls were evaluated. In 86% of the examinations, both observers agreed on the diagnosis or exclusion of vasculitis. The inter-rater agreement measured by Cohens kappa was 0.72($CI_{95\%}$: 0,52- 0,93). Specificity was calculated with 79% ($CI_{95\%}$: 58%- 93%) Sensitivity with 65 % ($CI_{95\%}$:41% – 85%), yielding an overall diagnostic accuracy of 73 % ($CI_{95\%}$: 57%- 85 %). The mean SUVmax of the carotid and subclavian region was significantly higher in vasculitis than in control patients (2.78 ± 1.02 vs. 2.04 ± 0.62; difference 0.7375; $CI_{95\%}$: 0.2023-1.2727, p=0.0085). SUVmax of the iliacal regions did not differ significantly between vasculitis and control patients. ROC analysis revealed the highest sensitivity of 60% and specifity of 75% for a SUVmax cut-off point of 2.24 (AUC 0.72).

Conclusion: 18F-FDG PET findings are reproducible and independent of the investigator. Calculation of SUV of the upper extremities has the potential to improve the clinical utility of this method. However, the low sensitivity and specifity indicate that enhanced vascular uptake might be overrated if clinical details are suggestive for vasculitis. Therefore, the diagnosis of large vessel vasculitis should not be based on PET only.

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Malignancy Risk in Giant Cell Arteritis: A Population-Based Cohort Study. Tanaz A. Kermani, Valentin S. Schäfer, Cynthia S. Crowson, Gene G. Hunder, Sherine E. Gabriel, S.R. Ytterberg, Eric L. Matteson and Kenneth J. Warrington, Mayo Clinic, Rochester, MN

Purpose: To determine the incidence of malignancy in a population-based cohort of patients with giant cell arteritis (GCA).

Methods: All incident cases of GCA diagnosed between January 1, 1950 and December 31, 2004 were identified for this population-based study. For each GCA patient, 2 subjects without GCA of the same sex and similar age and length of medical history were selected from the same population. Each non-GCA subject was assigned an index date corresponding to the date of diagnosis of GCA of the corresponding GCA patient. Diagnostic codes for malignancy were used for case ascertainment in both groups. Medical records of all subjects with a malignancy code were reviewed, and the diagnosis confirmed based on histopathology. Patients in both cohorts were followed until death, last contact, or December 31, 2006. The cumulative incidence of malignancy during follow-up was estimated using Kaplan-Meier methods. Cox proportional hazard models were used to examine the influence of GCA on the development of cancer.

Results: Our study included 204 GCA patients and 407 non-GCA subjects. The GCA cohort consisted of 163 (79%) women and 41 (21%) men, mean age 76.0 years (± 8.2 years) with median follow-up 7.7 years (total 1856 person-years). The non-GCA cohort consisted of 325 (80%) women and 82 (20%) men, mean age 75.6 years (± 8.4 years) with median follow-up 8.1 years (total 3890 person-years). Eighty-four (41%) GCA patients and 154 (38%) non-GCA subjects were ever-smokers (p=0.32). During follow-up, 52 GCA patients and 107 non-GCA subjects developed malignancy (HR: 1.07; 95% CI: 0.77, 1.50). Excluding patients with prevalent cancer at index date, 46 GCA patients and 76 non-GCA subjects developed a cancer during follow-up (HR: 1.26; 95% CI: 0.87, 1.83). Adjustment for smoking did not alter the results. The 1, 10 and 20 year cumulative incidences (± standard errors) of any malignancy (excluding patients with prevalent cancer) were 5.9%, 33.6% and 50.0% among GCA patients and 2.6%, 27.0% and 47.0% among non-GCA patients. GCA patients appeared more likely to be diagnosed with malignancy in the first year following index date (HR: 2.35; 95% CI: 0.87, 6.31; p=0.09), but this finding was statistically non-significant. There were no differences between the two groups with respect to frequency of hematologic (p=0.27) or solid (p=0.88) malignancies. Non-melanoma skin cancers were the most commonly observed cancers in both cohorts. While similar types of cancers were noted in both groups, colon cancer appeared more commonly in the GCA group (HR: 2.71; 95% CI: 0.94, 7.83; p=0.07). There was no difference in mortality between GCA and non-GCA patients following any incident malignancy (HR: 0.80; 95% CI: 0.52, 1.24; p=0.32).

Conclusion: GCA patients are not at increased risk of first cancer after diagnosis. The occurrence of colon cancer may be higher in GCA patients. Mortality following cancer is similar in GCA and non-GCA subjects.

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Cancer Preceding Giant Cell Arteritis: A Case-Control Study. Tanaz A. Kermani, Valentin S. Schäfer, Cynthia S. Crowson, Gene G. Hunder, S.R. Ytterberg, Eric L. Matteson, Sherine E. Gabriel and Kenneth J. Warrington, Mayo Clinic, Rochester, MN

Purpose: To study the association between previous cancer and giant cell arteritis (GCA).

Methods: All incident cases of GCA diagnosed between January 1, 1950 and December 31, 2004 were identified for this population-based study. For each GCA patient, 2 subjects without GCA of the same gender, similar age and length of medical history were selected from the same population. Each non-GCA subject was assigned an index date corresponding to the date of diagnosis of GCA of the corresponding GCA patient. Diagnostic codes for malignancy were used for case ascertainment in both groups. Medical records of all subjects with a malignancy code were reviewed, and the diagnosis confirmed based on histopathology. Both groups were followed until diagnosis of GCA/index date. Logistic regression models were used to examine the association between previous malignancy and GCA status.

Results: Our study included 204 GCA patients and 407 non-GCA subjects. The GCA group consisted of 163 (79%) women and 41 (21%) men, mean age 76.0 years (± 8.2 years). The non-GCA group consisted of 325 (80%) women and 82 (20%) men, mean age 75.6 years (± 8.4 years). Median length of medical history prior to index date was 44.5 years (total 9288 person-years) in the GCA group and 45.8 years (total 16,965 person-years) in the control group. Eighty-four (41%) GCA patients and 154 (38%) non-GCA subjects were ever-smokers (p=0.32).

At index date, 45 (22%) GCA patients and 125 (31%) non-GCA patients had a previous cancer (age, sex and calendar year adjusted OR: 0.63; 95% CI: 0.42, 0.94; p=0.022). Further adjustment for smoking did not alter these results. Mean age at diagnosis of first cancer before index date was similar in cases (67.5 ±11.9 years) and controls (64.9 ±13.2 years), p =0.32. Mean duration from first cancer to index date was 9.8 years (±9.9) in GCA patients and 11.7 years (±10.8) for non-GCA patients (p=0.31). In the year prior to index date, 7 (3.4%) GCA patients and 11 (2.7%) controls had a malignancy (age, sex and calendar year adjusted OR: 1.25; 95% CI: 0.47, 3.30; p=0.65). Excluding non-melanoma skin cancers, fewer women with GCA had cancer before index date than women controls (10% vs. 22%, p=0.003) while similar number of GCA and non-GCA men experienced malignancy before index date (15% vs. 18%, p=0.59). This apparent gender difference did not reach statistical significance (p=0.34). GCA patients had fewer solid tumors compared to controls (22% vs. 29%, p=0.038). Cancer types were similar in both groups but fewer gynecological malignancies were noted in GCA patients (OR: 0.39; 95% CI 0.13, 1.15; p=0.09). Colon cancer also appeared less commonly in cases compared to controls (OR: 0.22; 95% CI 0.03, 1.74; p=0.15).

Conclusion: In this population-based case-control study, GCA patients had significantly fewer malignancies prior to index date compared to age-and gender-matched population controls. While we adjusted for smoking, the effect of other confounders cannot be eliminated. Alternatively, immunologic phenotypes that predispose GCA in some people may have a protective role in the development of cancer.

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Clinical Impact and Management of the Pathologic Diagnosis of "Healed Arteritis". Yvonne C. Lee, Erika H. Noss, Anne H. Fossel, Robert F. Padera, Don C. Bienfang, Matthew H. Liang and William P. Docken, Brigham and Women's Hospital, Boston, MA

Purpose: Healed arteritis is a pathologic diagnosis associated with clinical uncertainty. Although histologic characteristics of healed arteritis have been described, no standardized diagnostic criteria are available. Some have questioned whether healed arteritis exists or whether it simply reflects changes due to aging and atherosclerosis. We describe the clinical implications and management of a pathologic diagnosis of healed arteritis.

Method: Pathology reports with the diagnosis of “healed arteritis” were identified from 418 temporal artery biopsies performed between 1994 and 2003 at an academic medical institution. Two rheumatologists reviewed the medical record for clinical symptoms (unexplained headache, visual changes, jaw claudication, fever) preceding biopsy, corticosteroid treatment at the time of biopsy, corticosteroid treatment following the diagnosis of healed arteritis, and long-term outcomes. Corticosteroid dosing at the time of biopsy was categorized as: 1) no corticosteroids, 2) low/moderate dose steroids (< prednisone 40 mg daily) and 3) high dose steroids (≥ prednisone 40 mg daily). Corticosteroid dosing post-biopsy was categorized as: 1) no corticosteroids, 2) low/moderate dose steroids (< prednisone 40 mg daily for a month) and 3) high dose steroids (≥ prednisone 40 mg daily for a month).

Results: 43 (10.5%) patients with healed arteritis were identified. Thirty-six (83.7%) were women. Mean age was 73.2 years, and mean erythrocyte sedimentation rate was 76.7 mm/hr. Twelve (27.9%) had a documented history of polymyalgia rheumatica/giant cell arteritis

(GCA) in the medical record. The most common reason for biopsy was unexplained headache (60.5%). Data on corticosteroid dosing was available for 38 out of 43 patients at the time of biopsy and 36 out of 43 patients post-biopsy. At the time of biopsy, 17 (44.7%) were not treated with corticosteroids, 7 (18.4%) were treated with low/moderate dose corticosteroids, and 14 (36.8%) were treated with high dose corticosteroids. Among those on corticosteroids, median dose was prednisone 40 mg daily. Median treatment duration was 7 days. After a pathologic diagnosis of healed arteritis was reported, 11 (30.6%) received no additional corticosteroid treatment, 15 (41.7%) were treated with a low/moderate corticosteroid regimen, and 10 (27.8%) received high dose corticosteroids for at least a month, consistent with treatment for active GCA. Among the 43 patients with healed arteritis, 1 developed visual loss, and 1 developed aortic/large vessel disease, unexplained by another diagnosis.

Conclusion: In this cohort, over 10% of temporal artery biopsies received a pathologic diagnosis of "healed arteritis." Given a pathology report indicating healed arteritis, clinicians frequently changed treatment, favoring low/moderate corticosteroid regimens over no corticosteroids or high dose regimens. On follow-up, only 1 case of visual loss and 1 case of aortic/large vessel disease were noted.

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Correlation of Clinical Features and Outcomes of Temporal Artery Biopsy in Giant Cell Arteritis. Anisha Sodha[1] and Antoni Chan[2], [1]Royal Berkshire Hospital, NHS Foundation Trust, Reading, England, [2]Royal Berkshire Hospital, NHS Foundation Trust, Reading RG1 5AN, United Kingdom

Purpose: Giant cell arteritis (GCA) is the commonest form of primary vasculitis in adults. Features at presentation can be variable making diagnosis difficult. Despite the advent of new investigations such as ultrasound, temporal artery (TA) biopsy remains the gold standard for diagnosis. The aims of this study were threefold; to investigate correlation of clinical features at presentation and outcome of biopsy; to analyse histological specimens; and to determine if biopsy results affect management of patients with suspected GCA.

Method: Our retrospective study identified all patients referred for TA biopsy in our hospital between the years 2003 to 2008. Of these 113 patients, 106 sets of notes were analysed, giving us a 99% confidence interval. Specifically designed proformas identified presenting clinical features, ESR and CRP, treatment commenced, temporal artery biopsy specimen length and result. We compared positive and negative biopsy patients, and obtained final diagnoses from medical records.

Results: Of the presenting features, 78.3% of all patients had temporal headaches, 51.8% had visual symptoms and 28.3% had jaw claudication. 30.2% of all biopsies were positive. Jaw claudication was the most predictive clinical feature of a positive biopsy, being present in 50% with a positive biopsy compared to 18% with a negative biopsy ($p=0.001$). An abnormal artery on clinical examination also had predictive value (59.4% compared to 39.4% in positive and negative biopsy groups respectively). Mean CRP and ESR were higher (101.6 mg/L and 77.9 mm/hr respectively), in biopsy positive compared to (61.06 mg/L and 62.1 mm/hr respectively) in biopsy negative patients. Patients with positive biopsies also had more systemic features (fever and weight loss). The mean specimen length was 8.43mm. Biopsies of length greater than 10mm yielded significantly more positive results. Considering the ACR classification for GCA, 86.7% with a positive biopsy had at least 3 criteria before biopsy compared to 59% with a negative biopsy. Management plans were altered for 79.5% after biopsy results. In biopsy negative patients, 62% had steroids reduced, while 69% had diagnosis changed.

Conclusion: The four most predictive features were jaw claudication, abnormal temporal artery on examination, elevated CRP/ESR, and the presence of systemic features. Specimens longer than 10mm allowed for better histological analysis and had a higher positive yield rate. Biopsy results affected management in a large proportion (80%) of patients. A negative biopsy, along with observing a poor response to steroids, may be useful as it prompts clinicians to look for other diagnoses. We conclude that temporal artery biopsy should remain gold standard for diagnosis of GCA until other investigative modalities are validated and committing patients to long term corticosteroids is justified with histology.

Disclosure: A. Sodha, None; **A. Chan**, None.

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Long-Term Prognosis and Causes of Death in PMR: The Prospective, Double-Cohort GRACG Study. Jean Schmidt[1], Pierre Duhaut[1], Valery Salle[1], Amar Smail[1], Denis Chatelain[1], Sylvie Bosshard[2], Jean -Charles Piette[3], Hélène Pellet[2] and Jean-Pierre Ducroix[1], [1]Amiens University Hospital, Amiens, France, [2]Claude Bernard University, Lyon, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France

Purpose: Survival in Giant Cell Arteritis has been shown to be similar as in the general population, with a slight increase of cardiovascular mortality at least during the first two years of the disease. However, data on survival and causes of death in pure polymyalgia rheumatica (PMR) not associated with GCA are scarce. Our goals were 1- to assess survival on a large, prospective cohort of PMR patients, and 2- to assess the causes of death.

Method: Patients with pure PMR were included in a multicenter study at the onset of the disease, before any steroid therapy or at the latest within 48 hours after steroid onset. Patients with signs or symptoms of temporal arteritis, or with a positive temporal artery biopsy, are excluded from this analysis. All patients fulfilled the Hunder criteria. Inclusion was performed on a pre-formatted questionnaire collecting initial clinical and biological data, and final inclusion was declared after an independent, centralized review of the questionnaire. Age- and sex-matched, population based, randomly selected controls were included at the time of inclusion of the cases. Current (diagnosed within the year before inclusion) or active cancers were exclusion criteria for both cases and controls. Patients and controls were then followed up with a pre-established questionnaire every 6 months during a five-year period. Survival was estimated by Kaplan-Meir methods, log-rank tests were performed for univariate analysis, and lifetest procedure (SAS) for multivariate analysis.

Results: One hundred and ninety five cases (117 females, 78 males, mean age 74 ± 8 years) were included from 1991 to 2007 and compared to 724 controls. Loss of follow-up was less than 2 % in cases and controls. Mains causes of death (% of total death in each group) are given in the table below:

	Cerebral Infarction	Cancers	Septic shock	Dementia	Myocardial Infarction	Cardiac failure	Respiratory Failure
Patients	13.6	25	11.4	0	0	6.8	0
Controls	5.3	12.6	4.5	2.7	7.2	15.3	3.6

Unknown causes accounted for 40.9% of total deaths in cases, and 38.7 in controls (NS). Pulmonary embolism, mesenteric infarction, occlusion, sigmoiditis, post-operative complications accounted for less than 2 death causes each. Survival was superior in controls than in cases ($p = 0.005$, log rank test). Over the whole period of follow-up, infection-related or cerebral infarction-related death rates were not statistically different between cases and controls ($p = 0.11$ and 0.44, respectively), whereas cancer-related death causes were more frequent in cases ($p = 0.05$), and cardiac-related causes more frequent in controls ($p = 0.022$).

Conclusion: Unlike in GCA, overall mortality seems higher in PMR patients than in population based, age- and sex-matched controls, and the mortality increase is associated with cancers undiagnosed, unknown, or non-existent at the time of PMR diagnosis.

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Elevations in Central Pulse Pressure Are Associated with An Increased Risk of Critical Ischemia Requiring Revascularization in Takayasu Arteritis. Stuart M. Levine and Allan C. Gelber, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Takayasu arteritis (TA) is a large vessel vasculitis which can lead to critical ischemia and significant morbidity. Recent data suggest that an elevated central pulse pressure (PP) is a valid and important predictor of major cardiovascular morbidity in the general population. The predictive value of central PP monitoring has not been previously examined in TA. Given both the frequent difficulty and

limitation in measuring peripheral blood pressures in patients with TA, we examined whether central PP measurement can identify those patients at greatest risk for major vascular compromise.

Method: Invasive arteriography with central hemodynamic monitoring was performed on consecutive patients with TA. Pulse pressure was defined as the difference between systolic and diastolic BPs. Peripheral PP was obtained at the time of angiography at a site where a BP was measurable; central PP was determined centrally during angiography, and the aortic site with the highest BP reading was selected for analysis. All revascularization procedures (angioplasty/stenting or surgical bypass grafting) were ascertained by history during routine clinical follow-up. Student's t-test was used to compare mean PP values between those patients with TA who did, versus those who did not, undergo a revascularization procedure; Fisher's exact test was used to compare categorical variables between these two groups.

Results: A total of 27 patients meeting ACR classification criteria for TA were evaluated. Mean age was 39 +/-13 years; all but 1 was female. In total, 49 arteriograms were performed, with an average of 1.7 arteriograms per patient (range 1-4). Overall, 11 of the 27 (41%) patients underwent a revascularization procedure. Importantly, elevations in central PP were significantly associated with undergoing a revascularization procedure. As such, mean central PP was greater in those requiring revascularization compared to those who did not (97 +/- 20 mmHg vs.75 +/-24; p=0.02), whereas peripheral PP did not differ between the two groups (68 +/- 36mmHg vs. 60 +/-39, p=0.57). In addition, the median central PP in the cohort as a whole was 93 mmHg. It is noteworthy that 73% of those undergoing revascularization, and only 31% of those who did not, had a central PP value above this level (p=0.05). In contrast, no significant difference between the two groups was observed in the proportion of patients exceeding the median peripheral PP value of 65mmHg, accordingly to their vascular procedure status (55 vs. 44%, p=0.7).

Conclusion: Central pulse pressure determination may offer a predictive benefit in terms of identifying which patients with TA are at greatest risk for requiring revascularization. This might be particularly important in patients with non-detectable peripheral BPs, in whom accurate pulse pressure determination is not possible.

Disclosure: S. M. Levine, None; **A. C. Gelber**, None.

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Metabolic Steroid Side Effects in GCA and PMR: The GRACG, Prospective Double Cohort Study. Jean Schmidt[1], Pierre Duhaut[1], Amar Smail[1], Valery Salle[1], Denis Chatelain[1], Sylvie Bosshard[2], Jean -Charles Piette[3], Hélène Pellet[2], Jean-Pierre Ducroix[1] and GRACG study members[4], [1]Amiens University Hospital, Amiens, France, [2]Claude Bernard University, Lyon, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [4]France

Purpose: Steroids remain the only validated treatment of Giant Cell arteritis (GCA) and Polymyalgia Rheumatica (PMR). Incentives to test biotherapies or DMARTS are high, based on the notion that steroid side effects impose a heavy burden in the elderly. However, data on side effects incidence are scarce, and relative risks as compared to the general population of same age range, unknown. Our goal was to assess the relative risks of metabolic complications, i.e. incident diabetes, bone or vertebra fractures, and osteonecrosis of the hip in GCA and PMR patients.

Method: We designed a prospective, multicentric, double cohort study. Patients with GCA and/or PMR were included at the onset of the disease, before any steroid therapy or at the latest within 48 hours after steroid onset. All GCA patients fulfilled the ACR criteria, and all PMR patients, the Hunder criteria. Inclusion was performed on a pre-formatted questionnaire collecting initial clinical and biological data, and final inclusion was declared after an independent, centralized review of the questionnaire. Age- and sex-matched, population based, randomly selected controls were included at the time of inclusion of the cases. Patients and controls were then followed up with a pre-established questionnaire every 6 months during a five-year period. Semestrial density incidences for metabolic side effects, and 5-year cumulative incidences, were computed.

Results: Seven hundred and forty four cases (517 females, 227 males, mean age 74 ± 8 years; 606 GCA, 138 PMR) were included from 1991 to 2007 and compared to 711 controls. Results are given in the table below.

	5-year cumulative incidence (%)				
	Cases	Controls	RR	95% CI	p
Diabetes	7.11	2.21	3.22	1.86-5.58	6.10^{-6}

Bone fractures	9.40	4.97	1.89	1.28-2.79	0.001
Vertebral fractures	11.28	4.00	2.82	1.87-4.24	1.10^{-7}
Hip Osteonecrosis	2.01	0	NA	NA	5.10^{-5}

Diabetes was present at diagnosis in 10.50 % of cases and 14.1 of controls (p = 0.037). Incident diabetes mainly occurred during the first year of treatment, without further increased incidence afterwards. Bone fracture incidence was similar in cases and in controls during the first two years, and increased afterwards. Vertebra fractures were constantly more frequent in cases than in controls over time, with a proportion of attributable risk to steroid assessed at 64%.

Conclusion: Steroid-attributable cumulative incidence of metabolic side effects did not exceed 7.3 % of patients (for vertebral fractures) and was lower for diabetes, bone fractures or osteonecrosis. These incidences should be taken into account when designing trials on steroid-sparing agents and measuring their potential benefits or risks in GCA and/or PMR patients.

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Quality of Life in GCA/PMR Patients Under Steroid Therapy: The GRACG Study. Pierre Duhaut[1], Jean Schmidt[1], Laurence Le Page[1], Julien Desblache[1], Sylvie Bosshard[2], Jean -Charles Piette[3], Hélène Pellet[2], Jean-Pierre Ducroix[1] and GRACG study members[4], [1]Amiens University Hospital, Amiens, France, [2]Claude Bernard University, Lyon, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [4]Amiens, France

Purpose: Corticosteroids remain the only validated treatment of GCA and PMR, with remarquable efficacy on disease symptoms at the expense of long term side effects. Recent trials on biotherapies or DMARTs have failed to show any sparing effect on steroid dose or duration. Side effects are supposed to be a burden in the elderly. However, treatment duration of GCA or PMR is shorter than in most other inflammatory diseases, and personal tolerance may be different in the elderly than in younger, more active patients. Our goal was to assess the feelings and perceptions about steroid treatment –efficacy, inconveniences, daily burden- in GCA and PMR patients, independently of physicians perceptions.

Method: Living patients included in the prospective, multicentric GRACG study constituted the target population. First, a letter was sent to sample of 100 patients randomly selected from the database, and they were asked to write freely on a blank sheet all their feelings about the action, whether positive or negative, of steroids, and the course of the disease in relation with treatment. From the answers, a pre-formatted questionnaire including all remarks classified by topics was build, and send to all living patients of the cohort. Main topics defined by the patients covered weight and appetite, diet, quality of sleep and mood, physical signs or symptoms, associated treatments, duration of treatment, pain and fatigue.

Results: Three hundred and thirty patients answered to the preformatted questionnaire (224 women and 106 men, mean age 72 ± 7 years), including 115 with pure GCA, 91 with pure PMR, and 124 with GCA-PMR. Perception on duration of treatment did not differ between the 3 groups, and was considered as no or little constraining by 61%, 76% and 65 % of patients, respectively. 73 % were ‘less tired’ than before the disease, and only 1% declared being ‘more tired’. Pain completely disappeared in 73 % of patients, whereas 7% considered having more pain than before. 84 % were globally satisfied or very satisfied by the treatment, 1% were not satisfied at all, 2 % ‘little satisfied’. 86 % gained no weight or ‘a little’, 63 % declared that food preparation under diet rules was ‘easy or very easy’, and half of them that diet did not affect their social relations. For all items analyzed, there was no significant difference between the 3 subgroups or between men or women.

Conclusion: Overall, steroid treatment and its constraints (mainly sugar and salt-poor diet) was better tolerated in GCA/PMR patients than usually estimated. The majority of patients emphasized their well-being by comparison to the pain of the disease. In this age range, some constraints may be better accepted than in young patients, more particularly when diet and food preparation is concerned: avoiding visible side effects such as cushingoid face or weight gain may have contributed to the good acceptance of treatment.

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Experience of Performing Temporal Artery Ultrasound Scanning in the Diagnosis of Temporal Arteritis in a Large Teaching Hospital. Alice Lorenzi[1], Ismael Atchia[2] and Philip Platt[1], [1]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [2]Northumbria-Healthcare NHS Foundation Trust, Northumbria, United Kingdom

Purpose: Accurate diagnosis of temporal arteritis (TA) is vital. A missed diagnosis may result in blindness and other vascular complications. However, a false positive diagnosis results in significant associated morbidity as a consequence of prolonged exposure to high dose corticosteroid (CS) – including steroid induced diabetes, weight gain, osteoporosis and increased risk of infection. We have introduced temporal artery ultrasound scanning (as described by Schmidt et al 1997 – New Eng. Journal Med.) to our diagnostic TA work up. We report the results of our first 100 scans and correlate these with biopsy results.

Method: 94 patients with suspected TA consecutively referred patients from primary and secondary care were scanned. All patients were assessed according to our normal clinical assessment procedure. In addition, all patients were scanned using a Toshiba Aplio scanner with power Doppler and 6 patients were subsequently re-scanned on symptomatic recurrence. Of these, 34 met routine clinical criteria for TA biopsy, did not have contraindications, consented to the procedure and were biopsied.

Results: In 3 of 34 patients biopsy failed to provide an arterial sample (all had positive scans). In 31 successfully biopsied patients, 27 had scan and biopsy results that were concurrent (14 positive, 13 negative). The 4 cases in which a negative scan was associated with a positive biopsy were in patients in whom steroids had been prescribed for more than 2 weeks at a therapeutic dose (>60mg oral prednisolone). The scan was quick to perform and well tolerated by patients. Four patients with negative scans and no biopsy have been treated for TA on clinical suspicion alone. In 1 patient with a movement disorder we failed to get an adequate scan because of movement artefact.

Conclusion: Doppler USS scanning is a useful adjunct to the diagnostic work up of patients with suspected TA. It is acceptable to patients, quick to perform and provides reassurance to those in whom clinical suspicion is low.

Further validation is required before this technique can be considered diagnostic. However, in our hands TA USS is currently very useful as a test with high negative predictive value – allowing us to prevent unnecessary CS exposure. Scans are only useful if performed less than two weeks after starting high dose CS.

Disclosure: A. Lorenzi, None; **I. Atchia**, None; **P. Platt**, None.

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Consistency of DEI.Tak and Kerr Criteria for Disease Activity Assessment in Takayasu's Arteritis. Sibel Zehra Aydin, Neslihan Yilmaz, Servet Akar, Kenan Aksu, Sevil Kamali, Omer Karadag, Muge Bicakcigil, Huseyin T. Ozer, Sedat Kiraz, Fatos Onen, Murat Inanc, Gokhan Keser, Nurullah Akkoc and Haner Direskeneli, Turkish Takayasu's Arteritis Study Group, Istanbul, Turkey

Purpose: DEI.Tak (Disease Extent Index-Takayasu)(Sivakumar MR, Misra R and Bacon PA, 2005) is a new index developed for the follow-up of Takayasu's Arteritis (TA), assessing only clinical findings without the requirement of imaging techniques. We aimed to compare the effectiveness of DEI.Tak with active disease definition defined by Kerr et al. which includes imaging methods in a large cohort of TA patients in Turkey.

Method: The initial DEI.Tak forms were filled cross-sectionally for 105 TA patients in 7 centers to detect the baseline damage. Follow-up was performed in 144 visits only by including the new or worsening symptoms within the last 6 months, reflecting current activity. Scores were compared with physician's global opinion (PGO) (inactive, persistent and active disease), activity according to Kerr criteria and treatment changes.

Results: TA patients were mostly female (90%) with a mean (SD) age of 39.5 (12.1) years. Mean (SD) disease duration was 11.2 (8.9) years. The mean time period between the first and final evaluation was 27.8±29.5 months. At follow-up, most of the evaluations (69.4%, 100/144) showed no difference according to DEI.Tak (score=0). However, 14% of these patients (n=14) were accepted to be active and 17% (n=17) persistent disease according to PGO. Eighteen percent of patients (8/44) with a DEI.Tak ≥ 1 were inactive according to PGO. According to

Kerr criteria, 44 of 112 patients were active (39.3%). The total agreement between DEI.Tak and Kerr criteria was 93% (kappa value: 0.78). Compared to PGO, Kerr criteria had a total agreement of 76% (85/112) and DEI.Tak 68% (97/144). Patients requiring an increase in drug doses or new therapies had higher DEI.Tak scores compared to patients without modification (1.3±1.9, 1±1.3 vs 0.2±0.6 respectively, p<0.001).

Conclusion: In over 2 years of follow-up, most patients with TA of long disease duration showed no clinical activity with DEI-Tak. The agreement between Kerr criteria and DEI.Tak is excellent. However using Kerr criteria instead of DEI.Tak increased the consistency with PGO, which can be explained by the influence of imaging methods or acute phase-reactants to physician's decisions.

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Side Effects of Long-Term Use of Glucocorticoids in Giant Cell Arteritis. Rosaria Talarico, Chiara Stagnaro, Anna d'Ascanio and Stefano Bombardieri, University of Pisa, Pisa, Italy

Purpose: Giant cell arteritis (GCA) represents the most common vasculitis in the elderly, and it usually involves large and medium sized arteries. Glucocorticoids (GC) are commonly used for the treatment or GCA, although their long-term use is limited by concomitant appearance of side effects. The aim of this study was to retrospectively evaluate the prevalence GC-related long-term side effects in a cohort of patients with GCA, followed in the last twenty years in a single centre.

Method: Two hundred and ten GCA patients (176 females, mean ± SD age 77±8 years) were retrospectively studied. The diagnosis was made according to the ACR criteria in 196 patients and on the basis of the clinical decision in the others. The main GC related side effects evaluated were: diabetes arterial hypertension, cataract, gastropathy, osteoporosis (T score £ 2.5 SD), morphometric vertebral fractures, arisen after starting GC therapy. In those cases in which diabetes and arterial hypertension were pre-existing, any further worsening that required higher doses of antidiabetic or anti-hypertensive therapy were evaluated as side effects. Bone mineral density was examined by dual-energy X-ray absorptiometry (DXA). On the basis of the GC treatment duration (months), we have conventionally subdivided our cohort into 4 groups: I) from 6 to 12, II) from 12 to 24, III) from 24 to 60, IV) >60; moreover, on the basis of the total GC doses (grams), we have further subdivided the patients into 3 groups: A) <3, B) between 3 and 6, C) >6 g.

Results: GC alone were administered to 45% of patients, while 55% received GC plus immunosuppressant agents (methotrexate 91 patients, cyclophosphamide 13, azathioprine 7 and infliximab 4); 51% received calcium/vitamin D supplements and bisphosphonates, 30% calcium/vitamin D alone, while 19 % of patients, mainly due to a poor compliance, did not assume any osteoporosis treatment. Prevalence of diabetes was 5% (9/196), of which 2 new onsets and 7 worsened; arterial hypertension was reported in53% (103/196), all of which worsened. Prevalence of the other side effects was: cataract 42% (82/196), osteoporosis 37% (72/196), gastropathy 17% (34/196), vertebral fractures 10% (19/196). No significant differences in the prevalence of side effects was noted among sub-groups of GC duration and total dose, with the exception of vertebral fractures, that were reported as follows: I) 2%, II) 6%, III) 22%, IV) 38% (*p* 0,0002) and A) 2%, B) 15%,C) 21% (*p* 0,0033). Additionally, significant differences were observed in the prevalence of arterial hypertension (64% vs 46%, *p* 0,003) and osteoporosis (64% vs 31% p 0,04) between the groups of patients who received only GC and GC plus immunosuppressant therapy, respectively.

Conclusion: The most frequent side effect reported was arterial hypertension, which was pre-existing in all cases. Vertebral fractures correlated with duration and total doses of GC; the use of immunosuppressant agents seems to be useful to reduce the side effects of GC in GCA, sparing steroid doses.

Disclosure: R. Talarico, None; **C. Stagnaro**, None; **A. d'Ascanio**, None; **S. Bombardieri**, None.

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Clinical Profile and Long-Term Outcome in a Monocentric Cohort of 210 Patients with Giant Cell Arteritis. Rosaria Talarico, Chiara Stagnaro, Anna d'Ascanio and Stefano Bombardieri, University of Pisa, Pisa, Italy

Purpose: Glucocorticoids (GC) are commonly used for the treatment or GCA; however, tapering or withdrawing GC therapy can be associated with disease flares. The aims of this study were to retrospectively evaluate the prevalence of clinical findings and the long-term outcome in a cohort of patients with GCA, followed in the last twenty years in a single centre.

Method: Two hundred and ten GCA patients (176 females, mean ± SD age 77±8 years) were retrospectively studied. The diagnosis was made according to ACR criteria in 196 patients and on the basis of the clinical decision in the others. Clinical features at the onset, therapeutic approach in all cases and long-term outcomes in patients with a minimum follow-up of 5 years were retrospectively analysed. We have defined as disease flare any further clinical manifestations compatible with the clinical spectrum of GCA and/or an increase of ESR ≥ 40 mm/hour, not otherwise justifiable, that required higher doses or new introduction of GC therapy.

Results: The most frequent clinical manifestations included: new onset headache and/or scalp pain 77%, constitutional symptoms 46%, jaw claudicatio 36%, vision loss 34%, abnormal temporal artery on examination 32%, dizziness 29%, neuropsychiatric symptoms 29%, cough 10%, cerebrovascular accidents 6% and hearing loss 5%. Irreversible blindness was reported in 7% of patients, mainly due to a latency period between onset and treatment of ≥ 2 months. Temporal artery biopsy was performed in 160/210 of patients, resulting positive in 58%. High-medium doses of pulse intravenous GC were administered at the onset (250-500mg for 3 consecutive days in those cases characterized by severe visual or neurological involvement and 40 mg in the others), followed by a rapid tapering scheme to low GC oral regimen; specifically, all our patients received a single morning mean dose of 4 mg of methyl-prednisolone. GC alone were administered to 45% of patients, while 55% received GC plus immunosuppressant agents, which in the majority of cases (91) consisted of methotrexate (MTX) at a mean dose of 10 mg/week; 13 patients were treated with cyclophosphamide, 7 patients with azathioprine, and 4 with infliximab. A total of 137 patients were followed for a minimum period of 5 years. At least one disease flare was observed in 13% of patients treated with GC plus immunosuppressant agents and in 35% of cases treated with only GC ($p < 0.0005$). Additionally, 53% and 36% stopped GC within 2 years from the onset in the group of GC plus immunosuppressant agents and in the group who received GC alone respectively ($p < 0.02$)

Conclusion: According to the literature data, new onset headache represents the most frequent clinical finding in GCA. GC still remain the therapy of choice, being essential in inducing remission and improving the visual prognosis in GCA; nevertheless the use of steroid sparing drugs seems to be useful in order to reduce the frequency of disease flares.

Disclosure: R. Talarico, None; **C. Stagnaro**, None; **A. d'Ascanio**, None; **S. Bombardieri**, None.

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Definition of Remission and Relapse in Polymyalgia Rheumatica – Data From a Literature Search and a Delphi Based Expert Consensus. Christian Dejaco[1], Christina Duftner[1], Marco A. Cimmino[2], Bhaskar Dasgupta[3], Carlo Salvarani[4], Cynthia S. Crowson[5], Hildal Maradit-Kremers[5], Andrew Hutchings[6], Eric L. Matteson[5], Michael Schirmer[7] and ACR group for Development of Classification Criteria for PMR, [1]General Hospital of the Elisabethinen, Klagenfurt, Austria, [2]University, Genova, Italy, [3]Southend University Hospital, Essex, United Kingdom, [4]Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [5]Mayo Clinic, Rochester, MN, [6]London School of Hygiene and Tropical, London, United Kingdom, [7]Medical University, Innsbruck, Austria

Purpose: To compare definitions of remission (REM) and relapse (REL) in PMR in current studies, and definitions based on an expert consensus using a Delphi survey.

Methods: A literature search was conducted in PubMed, key items “polymyalgia rheumatica”, “remission” and “relapse”. Relevant studies published through 11/03 (update 06/09) were screened for definitions on REM and REL and parameters relevant for monitoring PMR disease activity. For the Delphi survey 25 rheumatologists (R) and 25 general practitioners (GP) were invited. The questionnaire included clinical (n=33), laboratory (n=54) and imaging (n=7) parameters from literature research. The importance (“essential”, “less important”, “not important”) and availability (“routinely available”, “not always available”, “not available”) were assessed. A consensus was defined by agreement of >80%. Parameters considered “not important” or “not available” by >50% were excluded.

Results: Of the 6025 articles screened, definitions on REM and REL were available in 22 and 26 studies, respectively. Definitions on REM included improvement of pain (n=6), morning stiffness (MS, n=5), absence of PMR clinical symptoms (PCS, n=16), normal ESR (n=19), CRP (n=9), blood count (n=2) and fibrinogen (n=1) and low/no therapy (n=5). REL was defined by a flare of PCS (n=26), elevation of ESR (n=18), CRP (n=10) and response to corticosteroids (n=14).

In Delphi exercise 34/50 responded to the 1st and 22/34 experts to the 2nd questionnaire rounds. In the 1st round 63/94 items were excluded. After the 2nd round a consensus was obtained on the following parameters to be essential for the definition of REM and REL (limits of metric parameters with highest agreement rate in parentheses):

REM: MS (a limit of <15min had a 94.7% agreement), patients`assessment of pain [<10mm on a VAS (range 0-100mm), 58.8%], limitation of upper limb elevation (LULE, qualitative item), shoulder-pain worsened by mobilization (qualitative), clinical sign of coxo-femoral synovitis (qualitative), ESR (<20mm/1sth, 57.9%), CRP (<0.8mg/dL, 68.4%).

REL: MS (>30min, 94.7%), patients assessment of pain (>20mm, 93.8%), corticosteroid dose required to control symptoms (any dose increment, 62.4%), LULE, shoulder-pain worsened by mobilization, clinical sign of coxo-femoral synovitis, ESR (>40mm/1sth, 57.9%), CRP (>1.0mg/dL, 52.6%).

Conclusion: In a literature search and a consensus based Delphi survey the absence of typical clinical symptoms, normal ESR- and CRP-levels were considered to be important for the definition of REM and REL in PMR.

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Increased Interferon Gamma Response to M. Tuberculosis Is Present in Patients with Active Takayasu's Arteritis. Omer Karadag[1], Kenan Aksu[2], Abdurrahman Sahin[1], Figen yargucu Zihni[2], Burcin Sener[1], Nevsun Inanc[3], Umut Kalyoncu[1], Sibel Zehra Aydin[3], Sibel Ascioglu[1], Pinar Talu Ocakci[2], Sule Apras Bilgen[1], Vedat Inal[2], Haner Direskeneli[3], Meral Calguneri[1], Ihsan Ertenli[1] and Sedat Kiraz[1], [1]Hacettepe University, Ankara, Turkey, [2]Ege University, Izmir, Turkey, [3]Marmara University, Istanbul, Turkey

Purpose: A possible relationship between Takayasu arteritis (TA) and Tuberculosis (TB) has been suggested. An increased frequency of tuberculin skin test (TST) was observed in TA patients. Quantiferon-TB Gold (QFT-G) is a new in vitro assay measuring interferon-gamma responses of PBMNc after stimulation by M. tuberculosis antigens and helpful in diagnosing latent TB infection. The aim of this study was to evaluate the frequency of latent TB infection among TA patients using both TST and QFT-G test and investigate its relationship with disease activity

Method: Ninety four (male/female:7/87) TA patients fullfilling ACR 1990 TA criterias from three different University Hospitals in Turkey and 97 control subjects without inflammatory diseases were included in the study. Data about medical history, TB exposure (previous TB infection or family history of TB), socioeconomic indicators (education status, income and job), smoking and demographics were collected for both TA and control groups. TST and QFT-G test (ELISA) were performed in both groups. Disease activity previous and current treatments were recorded. TST values ≥5 mm for TA patients and ≥15 mm for controls was accepted as TST positivity.

Results: Eventhough TA group was older (40 ±12 vs. 32± 8, p<0.001) there was no difference between TA patients and controls regarding smoking, socioeconomic indicators and medical history except previous TB infection. 6 TA patients and one control had a history of TB infection (p=0.05). Although TST positivity was higher in TA group [55 patients (62.5%) vs 24 controls (41.4%), p=0.008] , QFT positivity was similar between two groups [21 patients (22.3%) vs 24 controls (22.4%), p>0.05] . Thirty-four (36.1%) TST(+) TA patients were QFT(-), 2 of QFT(+) TA patients were TST(-). Thirty five (40%) TA patients had active disease whereas 53 (60%) were in remission. Active and remission groups were similar in previous TB infection history, TB exposure and TST(+), but active TA patients had higher QFT positivity than patients in remission [13 (37.1%) vs. 8 (15.1%), p=0.018]. No significiant difference was found between active and remission groups regarding previous/current treatments except for cyclophosphamide Twenty two (42.9 %) patients on cyclophosphamide treatment had QFT positive, but 9 of other TA patients had QFT positive (p=0.003).]

Conclusion: Despite similarity of QFT positivity between TA and control group, active TA patients had higher latent TB infection demonstrated by QFT. This result may suggest that In TA patients with latent TB infection, an infection-induced autoimmunity possibly induced by chronic antigenic stimulus, molecular mimicry and/or other tissue specific antigens may increase disease activity in TA.

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Study of Vascular Endothelial Growth Factor (VEGF) and Hypoxia Inducible Factor 1 Alpha (HIF-1α) Gene Polymorphisms in Patients with Polymyalgia Rheumatica. Esther F. Vicente[1], María E. Fernández-Contreras[2], Santos Castañeda[1], Ana M. Ortiz[1], Amparo Casado[1] and Carlos Gamallo[3], [1]Rheumatology. Hospital de la Princesa, Madrid, Spain, [2]CIBERED. Hospital Universitario de la Princesa, Madrid, Spain, [3]CIBERED. Pathology Department. Hospital Universitario de la Princesa, Madrid, Spain

Purpose: The role that angiogenesis might play in the pathogenesis of polymyalgia rheumatica (PMR) is controversial. The purpose of our study was to determine the genotype frequencies of some vascular endothelial growth factor (VEGF) and hypoxia inducible factor (HIF)-1α single nucleotide polymorphisms (SNPs) in PMR patients, and to evaluate their possible divergence from a group of healthy volunteers. A secondary objective was to analyze the association of VEGF and/or HIF-1α genotype with some of the most frequent clinical manifestations of PMR, as well as with concurrent risk factors for cardiovascular disease (CVDRF).

Method: A cross-sectional study including 80 patients with clinical diagnosis of isolated PMR (67.5% females) and a group of 154 healthy volunteers (60% females) was performed. Samples consisted of genomic DNA extracted from whole peripheral blood mononuclear cells. Identification of -G634C VEGF and HIF-1α (C1772T and G1790A) SNPs was performed by polymerase chain reaction (PCR) and subsequent RFLP using Bsc4I, Aci I and BsmFI endonucleases. Mutation refractory PCR was used to determine -A2578A and -G1154A VEGF SNPs. Demographic, clinical and analytical variables, as well as the typical CVDRF (smoking, hypercholesterolemia, diabetes mellitus and hypertension) were collected. Immunossupressive treatments and glucocorticoid dose were compiled. Anemia (Hb<11g/dl), increased erythrocyte sedimentation rate (>40 mm/h) and biochemistry were also analyzed. Genotype differences between patients and healthy volunteers and associations of HIF-1α and VEGF genotype with the variables included, were estimated using the Fischer exact test or the Pearson's χ^2 test. Statistical significance was assumed for $p<0.05$ two-tail tests (SPSS software, v 15.0).

Results: Comparisons of genotype frequencies between patients and healthy volunteers yielded the following **results:** The frequencies of carriers of the variant VEGF -1154A and -2578C alleles in PMR patients were 91.3% and 97.8% ($p<0.0001$ and $p=0.03$, respectively). The genotype distribution of -G634C SNP did not differed from that of healthy donors. Variant HIF-1α 1772TT homozygous were predominant within the PMR group (23.9 vs. 5.4%; $p=0.001$). None of the studied polymorphisms showed any relationship with the clinical manifestations studied nor with the classical CVDRF.

Conclusion: The genotype distributions of -G1154A, -A2578C (VEGF) and C1772T (HIF-1α) genotypes observed in PMR patients strikingly diverged from those of healthy volunteers, the variant alleles being more frequent among the former. However, the studied polymorphisms do not seem to be related with the PMR clinical manifestations, or with the analyzed CVDRF.

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Giant Cell Arteritis: A Negative Association with Cancer? Eamonn S. Molloy, Gary S. Hoffman and Carol A. Langford, Cleveland Clinic, Cleveland, OH

Purpose: To ascertain the odds of cancer associated with giant cell arteritis (GCA) as compared with non-GCA controls.

Methods: Data was obtained from the 2004 US Nationwide Inpatient Sample, a national hospital discharge database. Diagnoses were identified by ICD9 coding. Records coded for GCA (n=4,566) were matched with 18,264 controls (1:4); matching variables were age, sex, race and admission status (elective/non-elective). Conditional logistic regression was used to calculate odds ratios (OR) for GCA compared to controls, for cancer outcomes (all cancers, hematologic cancer, non-hematologic cancer, metastatic cancer) and non-malignant neoplasms. Demographic and clinical covariates were considered for inclusion in multivariate models, including age, sex, race, income, insurance payer, length of stay, AHRQ comorbidity measures.

Results: Based on both upon univariate (table 1) and multivariate analyses (table 2), GCA was associated with significantly reduced odds for all cancers compared to controls but.the odds of non-malignant neoplasms did not differ between GCA and controls.

Conclusion: GCA was associated with reduced odds of all measured cancer outcomes compared with non-GCA controls. There was however, no difference in the odds of non-malignant neoplasms between GCA and non-GCA controls, suggesting that the observed reduced

odds of cancer associated with GCA was not related to under coding of GCA where that was not the primary diagnosis. Potential, but not evaluable, explanations for these observations include [1] detection and management of pre-cancerous lesions may have occurred during initial evaluation for GCA, [2] more frequent physician visits and thus adherence to malignancy screening guidelines may have occurred in the GCA group [3] an effect of medications for GCA such as prednisone, aspirin and non-steroidal anti-inflammatory drugs could have influenced malignancy outcomes and [4] patients with a predisposition to GCA may be inherently less vulnerable to cancer. Further study will be required to explore these hypotheses.

Outcome	Odds Ratio	95% Confidence Interval	P Value
All cancer	0.47	0.41 – 0.54	<0.0001
Hematologic cancer	0.54	0.39 – 0.75	0.0002
Non-hematologic cancer	0.50	0.42 – 0.59	<0.0001
Metastatic cancer	0.39	0.30 – 0.50	<0.0001
Non-malignant neoplasms	0.97	0.79 – 1.21	0.81

Table 1. Results of univariate analyses for GCA versus controls.

Outcome	Odds Ratio	95% Confidence Interval	P Value
All cancer	0.48	0.41 – 0.56	<0.0001
Hematologic cancer	0.49	0.35 – 0.68	<0.0001
Non-hematologic cancer	0.53	0.45 - 0.64	<0.0001
Metastatic cancer	0.38	0.29 – 0.50	<0.0001
Non-malignant neoplasms	0.86	0.69 – 1.06	0.15

Table 2. Results of multivariate analyses for GCA versus controls.

Disclosure: E. S. Molloy, None; **G. S. Hoffman**, None; **C. A. Langford**, None.

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Toll-Like Receptor 2 Is a Receptor for beta2-Glycoprotein I On Endothelial Cells. Christophe Jamin[1], Jean-Eric Alard[1], Capucine Daridon[2] and Pierre Youinou[1], [1]Brest University Medical School Hospital, Brest, France, [2]Charite - Universitätsmedizin Berlin, , and Deutsches Rheumaforschungszentrum Berlin, 10117 Berlin, Germany, Berlin, Germany

Purpose: Toll-like receptors (TLRs) have long been suspected to bind to β2 glycoprotein I (β2GPI) on endothelial cells (ECs), yet interactions between TLRs and β2GPI have never been unequivocally proven. We elaborated the present study to identify the TLR directly involved in the binding of β2GPI on EC surface.

Method: ECs from human umbilical vein and EAhy926 cell line were cultured in vitro. Human and bovine β2GPI-specific antibodies were used to determine endogenous and exogenous expression of β2GPI in ECs. β2GPI-linked affinity column, confocal microscopy and western blotting analyses of purified lipid rafts were used to identify and localize the TLRs potentially associated with β2GPI. Co-immunoprecipitation with anti-β2GPI followed by mass-spectrometry identification of peptides were performed to identify which of the TLR2 or TLR4 interacted with β2GPI. Plasmon resonance-based approach was carried out to demonstrate the specific interaction. ECs deficient in TLR2 expression were obtained using short hairpin RNA interferences. Phosporylation status of IRAK following β2GPI stimulation of TLR2-deficient ECs was then evaluated.

Results: β2GPI is not synthesized and secreted by ECs in vitro, but rather taken up by ECs from fetal calf serum. β2GPI was localized within lipid rafts fraction of EC membrane together with TLR2 and TLR4. Mass-spectrometry analyses of anti-β2GPI co-immunoprecipitated protein indicated that TLR2, and not TLR4, interacted with β2GPI. Plasmon resonance experiments further confirmed that only TLR2 could bind β2GPI. Short hairpin RNA interferences generated TLR2-deficient ECs which loose their ability to bind biotinylated β2GPI and to trigger downstream phosphorylation of IRAK.

Conclusion: Though TLR4 may up-regulates TLR2 expression, thereby contributing to β2GPI uptake, our data demonstrate that direct binding of β2GPI on EC surface occurs through direct interaction with TLR2. Furthermore, signalling for anti-β2GPI may be envisioned as a multiprotein complex concentrated in lipid rafts on the EC membrane.

Disclosure: C. Jamin, None; **J. E. Alard**, None; **C. Daridon**, None; **P. Youinou**, None.

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CC Chemokine Receptor 5 Ppolymorphism in Chronic Periaortitis. Luigi Boiardi[1], Augusto Vaglio[2], Carlo Buzio[2], Davide Nicoli[3], Enrico Farnetti[3], Bruno Casali[3], Nicolò Pipitone[1], Luca Magnani[4] and Carlo Salvarani[1], [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Università di Parma, Parma, Italy, [3]Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [4]Arcispedale S.Maria Nuova, Reggio Emilia, Italy

Purpose: Chronic periaortitis (CP) is a rare condition, characterized by a fibroinflammatory tissue surrounding the abdominal aorta and the common iliac arteries. Three main entities are included: idiopathic retroperitoneal fibrosis (IRF), inflammatory abdominal aortic aneurysms (IAAAs), and perianeurysmal retroperitoneal fibrosis (PRF). A systemic inflammatory nature of this condition is suspected by the presence of elevated acute phase reactants, constitutional symptoms and prominent adventitial inflammation. Chemokines may contribute to the inflammatory CP process through their binding to CC chemokine receptor 5 (CCR5). The aim of this study was to examine if the 32 base pair deletion allele in CCR5 (CCR5 delta 32 allele) might be associated with CP susceptibility.

Method: We enrolled 100 consecutive Italian patients with CP. As a control group we used 180 healthy blood donors from the same geographic areas. The CCR5 genotype of all CP patients and controls was studied by polymerase chain reaction amplification of the region which includes the 32 deletion (CCR5 delta 32).

Results: Homozygosity for CCR5 delta 32 allele was not detected in CP patients and controls. Carriers of the CCR5 delta 32 allele were significantly more frequent among the CP patients than among the controls (15% versus 5.6%; P corr = 0.018; odds ratio [OR] 3.0 [95% confidence interval (95% CI) 1.3-7.0]). No significant associations were found for comparisons of CP patients with and those without specific manifestations.

Conclusion: The presence of CCR5 delta 32 significantly influences disease susceptibility of CP in an Italian study population. Further studies are required to replicate our findings in other populations.

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Disease Activity, Adverse Events and Quality of Life in the Second Year of Polymyalgia Rheumatica. Bhaskar Dasgupta[1], Andrew Hutchings[2] and UK PMR Study Group, [1]Southend University Hospital, Essex, United Kingdom, [2]London School of Hygiene and Tropical, London, United Kingdom

Purpose: PMR is a chronic inflammatory rheumatic disease of the elderly which can run a prolonged relapsing course of 2-3 years with adverse effects associated with long term steroid therapy. We have previously reported on the first year of an inception cohort study of 129 patients on the initial steroid response, quality of life, disability, course, adverse events and diagnostic uncertainty. The study showed severe impact on QOL, disability, frequent relapses and adverse events. We now report the 24 month follow up for this cohort study.

Method: A cohort of newly diagnosed PMR patients were studied from 8 centres meeting a modified version of the Jones & Hazleman criteria. 129 participants were recruited. Participants followed a tapered steroid schedule starting at 15mg daily oral prednisolone. Data on

disease activity, adverse events, and quality of life at 8 assessments were collected over 2 years. The impact of disease activity and adverse events on quality of life (physical and mental component of SF-36) on follow up was measured using general estimating equations and multivariable analysis adjusted for baseline covariates, comorbidity and socio-demographic variables.

Results: Relapse-free survival in the cohort at one and two years was 68.8% (95% CI 58..8 - 75.3) and 42.4% (95% CI 33.1 -51.4) respectively. The median (inter-quartile range) of mean daily steroid dosage and cumulative steroid dose at 24 months was 0.5 mg (0- 2.8) and 3310 mg (3300 – 3800) respectively. Adverse events over 24 months are as in the table.

	W3	W6	M3	M6	M12	M18	M24	Overall
% weight gain from baseline (mean)	0.1	1.0	2.5	3.6	4.4	2.6	2.0	-
Bruising (%)	2.3	3.9	8.7	9.8	13.1	12.8	6.7	22.5
Moonface (%)	0.8	6.3	15.9	17.9	12.3	6.4	1.0	28.7
Ankle oedema (%)	3.9	9.4	11.9	10.6	11.5	14.7	10.6	26.4
Poor diabetic control (%)	8.5	8.7	9.5	9.8	12.3	11.0	10.6	14.0
Fractures (%)	0.0	0.8	1.6	0.8	2.5	0.0	0.0	4.7

Improvement in QOL and HAQ at 12 months was maintained in the second year. In terms of disease activity both ESR ($p< 0.01$) and shoulder pain ($p< 0.01$) had significant impact on physical and mental component of scores of the SF-36. Among adverse events only bruising had an impact on physical QOL ($p= 0.02$).

Conclusion: Our study suggests that there is good control of disease activity in the second year in PMR although relapses continue to be reported. Chronic complications such as diabetes and hypertension were seen although we recorded few fractures – perhaps reflecting correct disease assessment and use of steroids in minimum effective doses. This also explains the reduction in weight gain, bruising and moonface in the second year.

QOL improves with steroid therapy in the first year and there does not appear to be a long term impact of PMR. Disease activity rather than adverse events were associated with changes in physical and mental quality of life

Disclosure: B. Dasgupta, None; **A. Hutchings**, None.

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Interleukin 10 Promoter Polymorphisms in Patients with Elderly Onset Inflammatory Conditions. Lorena Alvarez-Rodriguez[1], Eugenio Carrasco-Marin[2], Marcos Lopez-Hoyos Sr.[2], Cristina Mata[3], Maria Jose Marin[2], Jaime Calvo Sr.[3], Ricardo Blanco Sr.[1], Lorena Fernandez-Prieto[2], Ignacio Villa Sr.[4], Cristina Martinez-Dubois[2], Vicente Rodriguez-Valverde[2] and Victor M. Martinez-Taboada Sr.[1], [1]Hospital Universitario Marques de Valdecilla, Santander, Spain, [2]Hospital Universitario Marques de Valdecilla-IFIMAV, Santander, Spain, [3]Hospital Sierrallana, Torrelavega, Spain, [4]Hospital de Sierrallana, Torrelavega, Spain

Purpose: Cytokines driving the inflammatory response seem to be disturbed in elderly-associated inflammatory conditions, such as polymyalgia rheumatica (PMR), giant cell arteritis (GCA) and elderly-onset rheumatoid arthritis (EORA). IL-10 is considered a suppressor cytokine that can counteract the effect of inflammatory cytokines. Genetic differences in the promoter of IL-10 have been studied in GCA with non-conclusive results. The aim of the present study was to assess the frequencies of two SNPs in the promoter region of the IL-10 gene in PMR, GCA and EORA patients and to investigate their association with clinical features and IL-10 production.

Method: Two SNPs (-1082 G/A and -592 C/A) in the IL-10 gene promoter were genotyped in 171 patients with PMR, 78 patients with GCA, 94 patients with EORA, 79 patients with young-onset rheumatoid arthritis (YORA) and 190 unrelated age-matched controls (HC). The genotype was determined using allele-specific PCR and restriction fragment length polymorphism analysis. Levels of serum IL-10 were measured by the cytometric beads array (CBA).

Results: Carriers of the A-1082 allele (A/A or A/G) were significantly more frequent in PMR (OR 3.0, 95% CI: 1.5-6.1, p=0.001), in GCA (OR 3.8, 95% CI: 1.7-8.5, p=0.001) and EORA (OR 3.0, 95% CI: 1.4-6.7, p=0.004) than in HC. Distribution of A-1082 allele in EORA was more similar to the other age-associated inflammatory conditions and differed from YORA where it was less frequent (OR 0.3, 95% CI: 0.1-0.9, p=0.03). The frequency of the A-592 allele (A/A or A/C) was similar between age-associated disorders and HC. Again, YORA and EORA patients differed marginally in the carriage rate for this allele (OR 0.5, 95% CI: 0.3-0.99, p=0.045). Haplotype analysis showed a similar frequency of haplotypes between PMR and EORA and diminished frequency of the ACC haplotype in GCA patients as compared with HC (; OR: 1.9, 95% CI: 1.3-2.8, p = 0.002). The ATA haplotype was more frequent in YORA than in EORA (OR 1.7, 95% CI: 1.1-2.8, p= 0.029) or HC (OR 1.87, 95% CI: 1.25-2.8, p= 0.005). In our study we did not find an association between any of the haplotypes and IL-10 serum levels or in vitro production of IL-10.

Conclusion: Our results suggest that the IL-10 A-1082 allele confers genetic susceptibility to elderly onset inflammatory conditions. YORA differs from EORA and the other age-related inflammatory conditions, and is associated with a lower IL-10 producing phenotype.

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IgG4-Related Systemic Disease Accounts for a Significant Proportion of Thoracic Lymphoplasmacytic Aortitis Cases. John H. Stone[1], Arezou Khosroshahi[1], Vikram Deshpande[2] and James R. Stone[2], [1]Massachusetts General Hospital, Boston, MA, [2]Boston, MA

Purpose: IgG4-related systemic disease, a disorder recognized only recently, can cause lymphoplasmacytic inflammation in the thoracic aorta. The percentage of aortitis cases caused by IgG4-related systemic disease is not known. We hypothesized that IgG4-related systemic disease accounts for a subset of cases of thoracic aortitis and for a significant fraction lymphoplasmacytic thoracic aortitis cases. To test this hypothesis, we reviewed the experience at our institution with thoracic aortitis over a five-year period and evaluated the existing literature in light of this experience. We also sought to establish pathologic criteria for identifying involvement of the thoracic aorta by this disorder.

Methods: We searched our Pathology Service database to identify all patients with non-infectious thoracic aortitis who underwent resection over a 5-year time span. The essential inclusion criterion for the designation of non-infectious aortitis was the presence of chronic inflammation that was not characteristic of either atherosclerosis or aortic dissection. The exclusion criteria were a history of previous aortic surgery or evidence of an infectious aortitis. We subclassified the non-infectious aortitis cases into two categories based on the nature of the inflammatory component. Those cases with granulomatous inflammation with or without a significant plasma cell component were classified broadly as "granulomatous". Granulomatous inflammation was defined as an inflammatory infiltrate that was rich in activated (epithelioid) macrophages, with or without giant cells. In contrast, cases with lymphoplasmacytic infiltrates in which granulomatous inflammation was absent were classified as lymphoplasmacytic aortitis. All cases of lymphoplasmacytic aortitis along with representative cases of giant cell aortitis and atherosclerosis were stained by immunohistochemistry for IgG4 and for CD138, a plasma cell marker CD138. We thereby determined the fraction of plasma cells that stained for IgG4.

Results: Of 638 resected thoracic aortas, 33 (5.2%) contained non-infectious aortitis. Four of these cases (12% of all patients with non-infectious aortitis) had histologic features of lymphoplasmacytic aortitis. Three of those four cases (9% of non-infectious aortitis cases) demonstrated pathologic involvement by IgG4-related systemic disease. Among those three cases, an elevated proportion of plasma cells (0.82±0.08) stained for IgG4, compared with cases of giant cell aortitis (0.18±0.13) and atherosclerosis (0.19±0.08)($P < 0.00001$).

Conclusion: IgG4-related systemic disease accounted for 75% of lymphoplasmacytic aortitis cases and approximately 9% of all cases of non-infectious thoracic aortitis in our institution during a five-year period. Immunohistochemical assessment of the percentage of plasma cells that stain for IgG4 in resected aortas is helpful in identifying patients who have IgG4-related systemic disease. The knowledge that IgG4-related systemic disease can be associated with thoracic aortitis signals the need for a re-classification of non-infectious aortitis.

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Changes in Gene Expression Induced by Blocking Interferon Gamma (IFNg) IN EX-Vivo Cultured Arteries from Patients with Giant-CELL Arteritis (GCA). Marc Corbera-Bellalta, Ester Lozano, Ana García-Martínez, Georgina Espígol-Frigolé, Sergio Prieto, Montserrat Butjosa, Ester Planas-Rigol, José Hernández-Rodríguez and Maria C. Cid, Hospital Clínic. IDIBAPS. University of Barcelona, Barcelona, Spain

Background: IFNg is barely detectable in normal arteries but strongly expressed in GCA lesions. Based on its crucial role in macrophage activation and granuloma formation, IFNg has been considered a potential therapeutic target in GCA. However blocking IFNg has not consistently demonstrated efficacy in animal models of other chronic inflammatory diseases, indicating the need for a better understanding of the role of IFNg in GCA.

Purpose: To investigate changes in gene expression induced by a neutralizing monoclonal antibody against IFNg as compared to glucocorticoids in *ex-vivo* cultured temporal artery biopsies from patients with GCA

Methods: Temporal artery sections from 2 patients with biopsy-proven GCA and 2 controls with normal temporal artery biopsies were cultured *ex-vivo*, on the reconstituted basement membrane Matrigel^{TM}. Sections were treated with medium, an anti-human monoclonal antibody (A6) (kindly provided by W Ferlin and MH Kosko-Vilbois, Novimmune SA) generated with high potency to block IFNg-induced responses *in vitro* (10 mg/ml), control IgG1 (same concentration), or dexamethasone (0,5mg/ml). After 5-day incubation, RNA was extracted, reverse- transcribed and a screening of gene expression (90 genes) was performed using real-time PCR-based micro fluidic expression cards (Taqman^{R} Human Immune Array) from Applied Biosystems. Data was analyzed with the SDS 2.3 software.

Results: GCA arteries had increased expression of macrophage (CD68), T cell (CD3, CD4, CD8) and B cell (CD19) markers, co-stimulatory molecules (CD28, CD40, ICAM-1), proinflammatory cytokines (IL-2, IL-1b, TNFa, IL-6), chemokines (CCL3, CCL19, CCL2, CCL5, CXC10, CXCL11), chemokine receptors (CCR2, CCR5, CCR7, CXCR3), and colony –stimulating factors (particularly CSF 3) compared to control arteries. Conversely, Th2 cytokines (IL-4, IL-10 and IL-13) were decreased. Treatment of GCA arteries with dexamethasone or A6 led to a dramatic decrease in all the above cell markers, co-stimulatory molecules, proinflamatory cytokines, chemokines and receptors and CSF3. Th2 cytokines slightly increased. Overall, the effect was more prominent for dexamethasone than for IFNg inhibition. Quantitative assessment of these markers by real-time PCR in a larger series of cultured arteries is ongoing with the aim of better discriminating potential relevant differences between dexamethasone effect and IFNg neutralization on cultured GCA arteries.

Conclusion: With the limitation of the reduced number of cases studied, these preliminary results indicate that IFNg neutralization, down-regulates a number of inflammatory markers which are thought to contribute to disease pathogenesis in GCA. SAF 05/06250 and MTV3 06/0710.

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Utility of FDG-PET CT Scanning in a Rheumatology Service: Indications, Results and Influence On Management Decisions. Imran Riaz[1], Parasar Ghosh[1], Frances Borg[1] and Bhaskar Dasgupta[2], [1]Southend University Hospital NHS Foundation Trust, Westcliff on Sea, United Kingdom, [2]Southend University Hospital, Essex, United Kingdom

Purpose: ^{18}F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) with Computed Tomography (CT) is mainly used in the evaluation of malignancy, but is known to identify inflammatory conditions, including large vessel vasculitis and infiltrative diseases.The current data on utility of FDG-PET in rheumatology are sparse and the reiumbursement of such scans for non-oncology use is difficult. There are no existing rheumatology guidelines regarding its utility or indications**.**

Method: We report a retrospective case series of 31 rheumatology patients who had PET-CT from 2004-2008. Case notes were reviewed for the underlying diagnosis, indication for the scan and its effect on therapy decisions. The PET scans were reviewed, and FDG uptake was graded on a 4-point scale: none (grade 0), lower than liver uptake (grade 1), similar to liver (grade 2) and higher than liver (grade 3). Grade 2 or more was accepted as PET positivity.

Results: 31 patients were identified (16 male, median age 62, range 10-82, all caucasian).

PMR and GCA

11 patients had PMR and 7 had cranial GCA. All had systemic features and poor response to treatment. 5 patients had positive scans. In 4 of these, strong FDG uptake was seen in subclavian, aortic, and axillary arteries, suggesting the development of associated large vessel arteritis. All these patients had subsequent successful response to treatment with methotrexate or leflunomide. The remaining patient proved to have Erdheim Chester histiocytosis and was treated with infliximab. However, PET-CT was negative in all 7 patients with cranial GCA.

Large vessel ischaemia

Of 6 younger patients with symptoms of aortic, large vessel or peripheral ischaemia with inflammatory response, 2 were found to have inflammatory aortitis on PET-CT. Both had excellent response to therapy with methotrexate and high dose steroids.

Miscellaneous

Three patients with multisystem sarcoidosis and one with granulomatous mastitis underwent PET-CT to establish the burden of active disease, and guide the choice of therapy. PET was positive in all 4 patients. One was treated with steroids, two with infliximab and one with methotrexate and steroids.

In 3 patients with connective tissue disease and severe constitutional symptoms (1 Sjogrens, 1 RA and 1 post-thymectomy SLE) ; FDG-PET study was negative.

Conclusion: Our results suggest that PET-CT may be useful in ruling in or out large vessel arteritis in PMR and GCA patients with persistent systemic features; unresponsive to corticosteroid therapy and where other investigations (e.g. CT, MRI) have been non-contributory. It can also distinguish between inflammatory and atherosclerotic peripheral vascular disease. It may have a role in assessing active disease burden and planning immunosuppression in infiltrative diseases like sarcoidosis and histiocytosis.

We suggest the development of international guidelines for the indications for FDG-PET scanning in rheumatology.

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Study of Vascular Endothelial Growth Factor (VEGF) and Hypoxia Inducible Factor 1 Alpha (HIF-1α) DNA Polymorphisms in Patients of with Giant Cell Arteritis. Santos Castañeda[1], María E. Fernández-Contreras[2], Esther F. Vicente[1], Isidoro González-Álvaro[1], Inmaculada Carvajal[1], Txaro García-Vicuña[1] and Carlos Gamallo[3], [1]Rheumatology Department. Hospital de la Princesa, Madrid, Spain, [2]CIBERED. Hospital de la Princesa, Madrid, Spain, [3]CIBERED. Pathology Department. Hospital Universitario de la Princesa, Madrid, Spain

Purpose: To determine the genotype distribution of 3 single nucleotide polymorphisms (SNPs) within vascular endothelial growth factor (VEGF) gene and two within hypoxia inducible factor (HIF)-1α in a group of giant cell arteritis (GCA) patients and to analyse the association of these VEGF and/or HIF-1α genotypic variants with the occurrence of the most representative clinical manifestations of GCA.

Method: A cross-sectional study including 60 patients (51 females) with biopsy-proven GCA and 154 healthy volunteers (60% females). Genomic DNA was extracted from whole peripheral blood mononuclear cells. Determination of C1772T and G1790A HIF-1α and -G634C VEGF SNPs was performed by PCR-RFLP using specific restriction endonucleases. A specific PCR was used for -A2578C and -G1154A VEGF identification. Demographic, clinical, analytical (haemoglobin, ESR and RF), arterial ischaemic manifestations (jaw claudication, visual impairment, stroke, ischaemic heart disease and peripheral arteriopathy), and classical risk factors for cardiovascular disease (CVDRF) as smoking, hypercholesterolemia, diabetes and hypertension were collected. Genotype differences between patients and controls, and the association of SNPs with demographic, analytical, and clinical variables were estimated using the Fischer exact test or the Pearson's $\chi 2$ test. Statistical significance was assumed for $p< 0.05$ two-tail tests (SPSS software, v 15.0).

Results: Comparisons of both overall and sex adjusted genotype frequencies showed: VEGF: The variant -634CC was infrequent in GCA patients, compared to healthy donors (5.4% vs. 33.7%; $p<0.001$), -634GG homozygous wild type prevailing (51.4% vs. 20.7%; $p<0.001$). The vast majority of GCA patients (86.8%) were carriers of the variant -1154A allele ($p< 0.0001$). HIF-1α: The variant homozygous 1772TT genotype was more frequent within the GCA group (12.8% vs. 4.4%; $p=0.03$). VEGF -2578CC genotype was related to the occurrence of severe ischaemic manifestations (22.2% vs. 0% in patients without ischaemia; $p=0.02$); meanwhile, the -2578A wild type allele was

associated to hypertension (p=0.007). Wild type homozygous 1772CC (HIF-1α) prevailing among patients with hypercholesterolemia (95% vs. 66.7% of patients with normal cholesterol; p=0.04).

Conclusion: The present study reveals differences in the genotype distribution of a number of VEGF and HIF-1α SNPs between GCA patients and healthy volunteers. Concerning clinico-pathological variables, VEGF -2578CC resulted to be associated to the occurrence of severe ischaemic manifestations of the disease, but none of the studied genotypes was related to the analysed CVDRF.

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Identification of Target Antigens of Anti-Endothelial-Cell and Anti-Vascular-Smooth-Muscle-Cell Antibodies in Patients with Giant Cell Arteritis : a Proteomic Approach. Alexis Régent[1], Hanadi Dib[1], Christian Agard[2], Luc Camoin[3], Babette Weksler[4], Cedric Broussard[3], Loïc Guillevin[5] and Luc Mouthon[6], [1]Paris Descartes University, UPRES-EA 4058, Paris, France, [2]Internal medicine, Hotel Dieu hospital, Nantes, France, [3]Inserm U 567, CNRS UMR 8104, Cochin Institute, Paris, France, [4]Cochin Institute, Paris, France, [5]Hospital Cochin, Paris, France, [6]Paris Descartes University, UPRES-EA 4058, Department of Internal Medicine, Cochin Hospital, Paris, France

Purpose: In giant cell arteritis (GCA), immunological studies suggest the existence of a triggering antigen of unknown nature activating T-cell in the arterial wall. In experiments performed in animal models, a proliferation of T-cells from the xenotransplant suggests a possible recognition of a locally expressed antigen. We thus decided to use a proteomic approach in order to identify the target antigens of auto-antibodies directed against endothelial cells (EC) and vascular smooth muscle cells (VSMC).

Method: Sera from 15 GCA patients were tested in pools of 3 sera and compared to a sera pool from 12 healthy controls (HC). Serum IgG reactivity was analyzed by use of a 2-D electrophoresis and immunoblotting technique with antigens from normal human umbilical vein endothelial cells (HUVEC) and mammary-artery-VSMC. Targets antigens were identified by mass spectrometry (MALDI-TOF-TOF).

Results: Serum IgG recognized 162±3 and 158±61 protein spots from HUVEC and VSMC respectively, whereas serum IgG antibodies from HC recognized 79 and 228 protein spots respectively. Twenty-eight spots from HUVEC were recognized by at least 2/3 pools and not by HC. Twelve spots from VSMC were recognized by at least 3/5 pools and not by HC. Among identified proteins we found lamin A/C, voltage dependent anion selective channel protein 2, annexin V and other protein involved in cell energy metabolism and key cellular pathways.

Conclusion: IgG anti-EC antibodies and anti-VSMC antibodies are present in the serum of patients with GCA. These antibodies recognize cellular targets playing key roles in cell biology and maintenance of homeostasis. The function of these antibodies and their possible role in pathology have to be further explored.

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ACR Poster Session A

Osteoarthritis Epidemiology & Imaging

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Clinical Burden of Erosive Hand Osteoarthritis. J. Bijsterbosch, I. Watt, I. Meulenbelt, FR Rosendaal, Twj Huizinga and M. Kloppenburg, LUMC, Leiden, Netherlands

Purpose: To investigate the clinical burden of erosive hand osteoarthritis (EHOA) in terms of pain, functioning, and quality of life.

Method: In this analysis 42 patients with EHOA and 194 patients with non-EHOA, participating in the Genetics ARthrosis and Progression (GARP) study, were included (83% women, mean age 65 yrs). EHOA was defined as the presence of erosive radiographic features in at least

2 interphalangeal joints. Self-reported pain was measured with the Australian/Canadian Osteoarthritis Hand Index (AUSCAN). The number of self-reported painful joints and pain intensity upon joint palpation were assessed. Functioning was evaluated with the AUSCAN, the Michigan Hand Outcome Questionnaire (MHQ), grip strength, pinch grip, finger-palm distance upon finger flexion, and the Hand Mobility in Scleroderma test (HAMIS). The HAMIS assesses all movements in the range of motion of the hand, higher scores reflecting worse mobility. Quality of life was assessed with the physical and mental component scales (PCS and MCS) of the Short Form-36 (SF-36). Additionally, patient satisfaction with hand function and aesthetics were evaluated. Measures were compared between patient groups using t-test and Mann-Whitney U test. To determine whether differences can be attributed to erosive disease or disease severity in general, corrections were made for the number of nodes using linear regression.

Results: Demographic characteristics did not differ between the groups. Patients with EHOA experienced more pain and reported more functional limitations, less satisfaction with hand function, and more aesthetic complaints than patients with non-EHOA (table). Grip strength and pinch grip did not differ. Finger mobility was worse in EHOA, while thumb mobility was comparable. The SF-36 was similar for the groups. After correction for the number of nodes, being higher in EHOA, only finger mobility, satisfaction with hand function and aesthetics remained significantly different between the groups.

	EHOA *n=42*	*Non-EHOA* *n=194*	*P-value*
Pain			
AUSCAN pain (0-20)	9.0 (5.0)	7.1 (4.8)	0.02
Number of painful joints (0-30)*	10 (6-17)	6 (2-12)	<0.01
Pain intensity (0-90)*	6.5 (3-13)	4 (1-10)	0.03
Function			
AUSCAN function (0-36)	17.3 (8.7)	13.3 (8.6)	<0.01
MHQ ADL (0-100)*	77 (64-88)	83 (70-94)	0.03
Grip strength, kg	19.7 (8.4)	21.2 (10.1)	0.37
Pinch grip, kg	3.2 (1.8)	3.1 (1.5)	0.79
HAMIS thumb (0-3)	1.5 (1.0)	1.3 (0.9)	0.19
HAMIS fingers (0-9)	1.8 (1.6)	0.6 (1.0)	<0.01
Finger-palm distance, mm*	45 (9-83)	0 (0-16)	<0.01
Quality of life			
SF-36 PCS	44.1 (9.0)	45.0 (9.1)	0.53
SF-36 MCS	50.2 (9.4)	50.6 (10.2)	0.82
MHQ function satisfaction (0-100)*	48 (29-59)	63 (40-83)	<0.01
MHQ aesthetic satisfaction (0-100)*	81 (63-83)	89 (75-100)	<0.01
Number of nodes (0-30)	***17.0 (3.5)***	***12.3 (5.4)***	***<0.01***

Values are means (SD) unless stated otherwise

*Median (interquartile range)

Conclusion: Patients with EHOA experience more pain, more functional limitations of especially the fingers, and less satisfaction with hand function and aesthetics than patients with non-EHOA. Quality of life was similar. Because of the higher number of nodes in EHOA, and the association between the number of nodes and outcome measures, it is unclear whether the differences can be attributed to erosive disease in itself or disease severity in general.

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Long-Term Clinical and Radiographic Progression of Hand Osteoarthritis and Its Determinants. J. Bijsterbosch, I. Watt, I. Meulenbelt, F.R. Rosendaal, T.W.J. Huizinga and M. Kloppenburg, LUMC, Leiden, Netherlands

Purpose: Because of limited knowledge on the natural history of hand osteoarthritis (HOA), clinical and radiographic progression of HOA and their determinants were investigated over a 6-year period.

Method: Data of 242 HOA patients (mean age 60 yrs, 83% women) participating in the Genetics, ARthrosis and Progression (GARP) study were used. HOA was defined by the ACR criteria for clinical HOA or the presence of structural abnormalities in the hands (nodes/radiographic OA). Self-reported hand pain and function were assessed with the Australian/Canadian Osteoarthritis Hand Index (AUSCAN). The number of self-reported painful joints, number of nodes and pain intensity upon joint palpation were assessed. On standardized hand radiographs osteophytes (OP), joint space narrowing (JSN) and subchondral erosions were scored using the OARSI atlas. Baseline determinants of clinical progression, reflected by AUSCAN change, were evaluated using linear regression. Logistic regression was used to assess baseline determinants of radiographic progression, which was defined as a change in OP and/or JSN above the smallest detectable change. Adjustments were made for age, sex and BMI.

Results: There was a significant increase in OP and JSN with a mean change ± SD of 1.8 ± 2.3 and 1.1 ± 2.0, respectively. Radiographic progression was present in 53% of patients. A small but significant worsening in AUSCAN pain, AUSCAN function, and pain intensity was seen with mean changes ± SD of 0.5 ± 4.1, 2.0 ± 6.8, and 2.7 ± 7.0, respectively. The number of painful joints at baseline was positively associated with change on AUSCAN pain. No other determinants of clinical progression were found. Determinants of radiographic progression are shown in the table. Radiographic progression was not associated with AUSCAN change.

Table: Risk of radiographic progression related to tertiles of baseline features and HOA subtypes

	Tertiles	*Risk ratio (95% CI)*
Baseline features		
AUSCAN pain (0-20)	<4	1.0
	4-8	1.3 (0.8-1.7)
	>8	1.6 (1.2-2.0)
AUSCAN function (0-36)	<6	1.0
	6-15	1.2 (0.8-1.6)
	>15	1.4 (1.0-1.7)
Number of painful joints (0-30)	<4	1.0
	4-8	1.6 (1.2-2.0)
	>8	1.4 (1.0-1.8)
Pain intensity (0-90)	<1	1.0
	1-3	1.8 (1.3-2.2)

	>3	1.9 (1.4-2.3)
Number of nodes (0-30)	<6	1.0
	6-12	2.3 (1.7-2.8)
	>12	2.7 (2.1-3.1)
OP (0-90)	<6	1.0
	6-12	1.2 (0.8-1.7)
	>12	1.8 (1.4-2.2)
JSN (0-90)	<14	1.0
	14-21	0.7 (0.5-1.1)
	>21	1.4 (1.1-1.6)
HOA subtypes		
Erosive HOA[1]	-	1.8 (1.5 – 2.0)
Nodal HOA[2]	-	2.4 (1.8 – 2.9)
Thumb base involvement	-	1.6 (1.3 – 1.9)

[1]Presence of subchondral erosions in ≥ 2 interphalangeal joints

[2]Presence of nodes in ≥ 2 rays of either hand

Conclusion: Radiographic progression of HOA over 6 years was considerable and associated with higher baseline levels of pain and structural abnormalities. Erosive HOA, nodal HOA, and thumb base involvement were associated with a higher risk for radiographic progression. This suggests that it is severity rather than HOA subtype that determines the risk for progression. In contrast, clinical deterioration was small and difficult to predict. Radiographic and clinical progression were not associated. This has implications for the appreciation of clinical outcomes in OA research, including possible need for improvement of outcome measures.

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Evaluation of the AUSCAN Index in Hand Osteoarthritis (HOA) Using Rasch Analysis. Ida K. Haugen[1], B. Slatkowsky-Christensen[1], Désirée M.F.M. van der Heijde[2] and T.K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands

Purpose: Previous studies of the Australian/Canadian (AUSCAN) index have shown satisfactory performance with regard to validity, reliability, and responsiveness. Our aim was to examine whether AUSCAN fits the Rasch model in a HOA cohort.

Method: AUSCAN index was completed by 209 HOA patients (190 women, 19 men) aged 50-70 at baseline and by 126 patients (115 women, 11 men) at 5-year follow-up. AUSCAN is a patient-reported questionnaire with three subscales: pain (5 items), stiffness (1 item) and physical function (9 items) on a 0-4 Likert scale. The Rasch Rating Scale Model (Winsteps software) was used for evaluation of item difficulty and person ability estimates, unidimensionality (fit statistics) and reliability. The Rasch model places both item and person ability estimates on the same logit scale. Items at the lower end (negative values) are "easier" items (most likely to be endorsed), while items at the other end (positive values) are considered as "difficult" (only endorsed when higher disability/pain). Mean person estimate should be close to mean item estimate (arbitrarily set to 0.0) for the scale to be well-targeted. High fit statistics (mean square (MNSQ) INFIT) > 1.2 indicate

measurement of another construct, while low fit statistics (< 0.8) indicate overlapping items. The analyses were first done for each subscale separately, and then for all 15 items together at both time points.

Results: Adequate range of item difficulty (2.52, 3.62 logits), and well-ordered category thresholds were found for the AUSCAN pain scale. Negative mean person estimates (-1.93 and -2.11) indicated that most items were too "difficult" in this sample. The most "difficult" item, "pain at rest", showed high fit statistics (1.49, 1.32), indicating measurement of an alternative construct. "Pain when gripping" showed low fit statistics (0.64, 0.56), indicating redundancy. Person and item reliability was excellent (> 0.91).

The AUSCAN physical scale showed large range of item difficulty (3.85, 3.75) and well-ordered category thresholds. Mean person estimates were closer to zero (-0.87, -0.65) than the pain subscale, showing better targeting of the scale. No items showed misfit to the model, and the reliability was excellent (> 0.93).

The only item in the stiffness scale showed high fit statistics (1.42, 1.43) when analysing all items together, indicating that this domain represents another construct different from pain and function. The hypothesis that pain and function are closely related was further emphasized since 4 of 5 pain items (except "pain at rest") showed low fit statistics, indicating redundant items.

Conclusion: Our findings, applying the Rasch model, confirmed unidimensionality of the the AUSCAN pain and physical function subscales. Pain and function seemed to capture the same construct, with possible redundant items, while morning stiffness was measuring a different construct. However, these findings need to be further analysed by residual component analyses.

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Comparison of the Performance of AUSCAN Physical Function Subscale, AIMS2 and FIHOA in Hand Osteoarthritis (HOA) by Rasch Analysis. Ida K. Haugen[1], B. Slatkowsky-Christensen[1], Désirée M.F.M. van der Heijde[2], N. Bellamy[3] and T.K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Mayne Medical School, Herston, Australia

Purpose: Several indices exist for assessment of physical function in HOA. Our aim was to compare the performance of Australian/Canadian (AUSCAN) physical function scale, Arthritis Impact Measurement Scale 2 (AIMS2) hand/finger scale and Functional Index for Hand Osteoarthritis (FIHOA) using the Rasch model in a HOA cohort.

Method: 126 patients (115 women, 11 men) aged 55-75 years were examined using three self-reported questionnaires; AUSCAN, AIMS2 and FIHOA. AUSCAN and FIHOA are disease-specific indices with 9 and 10 items measuring physical function on a 0-4 and 0-3 Likert scale, respectively. AIMS2 hand/finger subscale consists of 5 items on a 0-4 Likert scale. Rasch Rating Scale Model (Winsteps software) was used for evaluation of item difficulty and person ability estimates, unidimensionality (fit statistics) and reliability. Fitting data to the Rasch model places both item and person ability estimates on the same logit scale. Items at the lower end (negative values) are "easier" items (most likely to be endorsed), while items at the other end (positive values) are considered as "difficult" (only endorsed when higher disability). Mean person estimate should be close to mean item estimate (arbitrarily set to 0.0) for the scale to be well-targeted. High item fit statistics (mean square (MNSQ) INFIT) > 1.2 indicate measurement of another construct, while low fit statistics (< 0.8) indicate overlapping items.

Results:

	AUSCAN	**AIMS2 hand**	**FIHOA**
Range of item difficulty (logits)	3.75	2.93	2.32
Mean (SD) item estimate	0.00 (1.10)	0.00 (1.04)	0.00 (0.65)
Mean (SD) person estimate	-0.65 (2.39)	-0.79 (1.32)	-1.16 (1.63)
Item reliability	0.98	0.99	0.93
Person reliability	0.93	0.70	0.85

High fit statistics **(MNSQ INFIT value)**		"Open a jar" (1.33)	"Accept handshake" (1.47) "Clench fist" (1.99)
Low fit statistics **(MNSQ INFIT value)**			"Cut meat" (0.67) "Fasten buttons" (0.67) "Sew/screwdriver" (0.69)
Well-ordered category thresholds	Yes	No	Yes

The comparison of the three questionnaires showed that AUSCAN had adequate range of item difficulty, best targeting of the scale (mean person estimate close to mean item estimate), and high person and item reliability. Negative person estimates indicate that the persons have less average disability than average of the scale, and few items were at the lower end of the scale for both AIMS2 and FIHOA. The FIHOA items also showed clustering with small spread of items along the disability scale (SD < 1). AUSCAN had no misfitting items, while the FIHOA had two items with high fit statistics (indicating measurement of another construct) and three items with low fit statistics (indicating redundancy). For AIMS2 we found disordered thresholds, and collapsing categories may be considered.

Conclusion: Our study confirmed that the AUSCAN physical function subscale is a unidimensional, well-targeted scale with high person and item reliability and well-ordered thresholds, and performs better compared to AIMS2 and FIHOA.

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The Association Between Ultrasound (US), Joint Counts and Symptoms in Hand Osteoarthritis (HOA). Ida K. Haugen, B. Slatkowsky-Christensen, A. Mathiessen, T.K. Kvien and H.B. Hammer, Diakonhjemmet Hospital, Oslo, Norway

Purpose: To evaluate the relationship between US, joint counts and symptoms in a HOA cohort.

Method: 126 patients (115 women, 11 men) with mean age 68.5 years completed self-reported questionnaires, joint examination and US. Australian/Canadian (AUSCAN) hand index is a self-reported questionnaire measuring pain (5 items), stiffness (1 item) and physical function (9 items) on a 0-4 Likert scale. The subscales were normalized to a 0-10 scale, while Visual Analogue Scale (VAS) pain and global was measured on a 0-100 mm scale. Joint examination and US were done by two different rheumatologists at the same day blinded for the results from the questionnaire and the colleague's examination. Clinical assessment included counts (absent/present) of joints (DIP, PIP, MCP, CMC bilateral) with soft tissue swelling (SJC), bony swelling (BSJC), tenderness (TJC) and limited motion (LMJC). Same joints were examined by US (dorsal view) with scoring of osteophytes (OP), synovitis and vascularisation (Power Doppler, PD) on a 0-3 scale. Sum scores of OP, synovitis and PD were computed, and the number of affected joints were analysed after dichotomisation (0=absent, 1-3=present). The number of joints with OP vs. BSJC and synovitis vs. SJC were compared with students t test. Associations between US findings and joint counts vs. symptoms were assessed by Spearman rank correlation.

Results: US detected more OP than BSJC, with mean (SD) 15.9 (5.5) and 11.2 (5.0), respectively ($p<0.001$). However, clinical examination detected more swollen joints compared to the number of joints with synovitis, with mean (SD) 7.7 (4.5) and 4.7 (3.3), respectively ($p< 0.001$). Table 1 shows the correlations between US findings (sum score) and joint counts vs. symptoms. Similar correlations were found between US findings (number of affected joints) and symptoms.

US vs. symptoms	**AUSCAN pain**	**AUSCAN physical**	**AUSCAN stiffness**	**VAS pain**	**VAS global**
OP (score)	0.16 (0.11)	0.22 (0.04)	0.01 (0.91)	0.07 (0.49)	0.12 (0.25=

Synovitis (score)	0.26 (0.01)	0.32 (0.003)	0.22 (0.03)	0.24 (0.02)	0.25 (0.01)
PD (score)	0.20 (0.04)	0.22 (0.02)	0.19 (0.04)	0.09 (0.33)	-0.01 (0.95)
Joint count vs symptoms					
BSJC	0.12 (0.25)	0.15 (0.13)	0.08 (0.40)	-0.02 (0.80)	0.10 (0.30)
SJC	0.09 (0.36)	0.17 (0.10)	0.03 (0.76)	-0.07 (0.47)	0.00 (1.00)
TJC	0.45 (< 0.001)	0.44 (< 0.001)	0.34 (< 0.001)	0.25 (0.01)	0.40 (< 0.001)
LMJC	0.06 (0.54)	0.06 (0.53)	0.11 (0.22)	-0.07 (0.43)	-0.05 (0.57)

Conclusion: US is more sensitive than clinical examination in detection of OP, while SJC was more frequent than US detected synovitis. However, distinction between bony and soft tissue swelling may be difficult to assess clinically. US synovitis and vascularisation were correlated with all symptom scales and AUSCAN scales, respectively. Among joint counts, TJC was the only joint feature with significant correlations with patient-reported symptoms. .

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Improvement of the Reproducibility of the Radiographic Kellgren-Lawrence (KL) Scoring System in Hand Osteoarthritis (HOA) Using A New KL Scoring System Aid. E. Maheu[1], P. Ravaud[2], G. Baron[2], F. Berenbaum[3], X. Chevalier[4], L. Gossec[5], D. Loeuille[6], J F. Maillefert[7], B. Mazières[8], F. Rannou[9], P. Richette[10] and C. Cadet[11], [1]St-Antoine Hospital, Paris, France, [2]Bichat Hospital, Paris, France, [3]St-Antoine hospital - APHP, Paris, France, [4]Hopital Henri Mondor, Créteil, France, [5]Cochin Hospital, Paris, France, [6]CHU de Nancy, Vandoeuvre les Nancy, France, [7]Chu Dijon Hopital General, Dijon, [8]CHU Larrey, Toulouse, France, [9]Cochin Hospital, AP-HP; INSERM (IFR 25), Paris, France, [10]Hopital Lariboisière, Paris, France, [11]Rheumatology, Paris, France

Purpose: KL radiographic scale is the most widely used tool altogether to define HOA, assess HOA severity and follow-up the radiographic progression, but its interobserver reliability is usually low.

Objective: To study the impact of a new KL Scoring System Aid (KLSSA) on the reliability of KL scoring.

Method: 20 posteroanterior radiographs of both hands of HOA patients (covering HOA radiographic spectrum) obtained from a trial were initially scored twice by 10 experienced readers, instructed to score the KL (0-4), using the score as detailed by Kallman [AR 1989;32:1585-91] and their view of the definition of KL grades at a 15-days interval. No preliminary training session. During the 1st session they also scored joint space narrowing (JSN) and osteophytes (0st) (0-4*).* The distal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), scaphotrapezial and trapeziometacarpal joints (16 joints) of one hand selected at random (right/left) were scored. 8 readers (CC-EM designers of the KLSSA excluded) were then randomized to score again twice the 20 radiographs using or not the KLSSA. The KLSSA combines various levels of JSN (0-4) and Ost (0-4) for defining KL grades, presented in a table, accompanied by hand images to illustrate the grading. Radiographs were numbered at random from 1 to 20 for each session. *Statistics:* Intra-class correlation coefficient [95% confidence interval (CI)] for inter- and intraobserver precision; Bland-Altman graphical method for intraobserver precision.

Results: For interobserver reproducibility appear in the table.

	4 readers randomized without the KLSSA	***4 readers randomized to use the KLSSA***
	ICC [CI 95%]	***ICC [CI 95%]***

Interobserver reproducibility (1st reading) 1st turn before KLSSA		
Ost score (0-64)	0.66 [0.41-0.84]	0.50 [0.25-0.68]
JSN score (0-64)	0.47 [0.27-0.68]	0.58 [0.34-0.78]
KL score (0-64)	0.51 [0.26-0.72]	0.41 [0.20-0.64]
Interobserver reproducibility (3rd reading) 2nd turn with/without the KLSSA		
KL score (0-64)	0.48 [0.25-0.68]	0.79 [0.59-0.89]

Interobserver reproducibility improved only in the group using the KLSSA. Intra-observer reproducibility improved for the 4 readers without the KLSSA (0.87 to 0.95) and almost all those having used the system (0.57 to 0.89). One reader's precision decreased, probably due to the modifications induced by the use of the system on his own personal points of reference.

Conclusion: Interobserver reproducibility of KL grading in HOA significantly improved using the KLSSA. This system could help for case definition or radiographic progression assessment in future trials/epidemiological studies. Further work is needed to assess the longitudinal reproducibility with this system.

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Is Matrix Gla Protein Level or Polymorphism Associated with Hand Osteoarthritis? D. Misra[1], S. Booth[2], M. McRosier[2], David T. Felson[3] and T. Neogi[1], [1]BUSM, Boston, MA, [2]USDA HNRCA, Tufts University, Boston, MA, [3]Boston University School of Medicine, Boston, MA

Purpose: Matrix Gla protein (MGP), which is present in cartilage and blood vessels, is a key regulator of vascular calcification. MGP's functionality is dependent upon vitamin K, low levels of which have been associated with increased prevalence of radiographic hand osteoarthritis (ROA). The mechanism by which vitamin K may exert its effects is not known, and may possibly be through MGP. Recently, MGP polymorphisms have been associated with coronary calcification (CAC) and kidney stones. We evaluated the relation of MGP serum concentrations and polymorphisms with hand ROA.

Method: 376 community dwelling elderly men and women (aged 60-80) who had hand x-rays, serum MGP levels and DNA evaluated for three MGP SNPs in a parent study assessing the effect of vitamin K supplementation on BMD and CAC were evaluated. Presence of hand ROA was defined on a per-joint basis as Kellgren and Lawrence grade ≥2. We evaluated the relation of serum MGP concentrations categorized into quartiles with the presence of hand ROA using logistic regression with GEE to account for correlated data, adjusting for potential confounders including age, sex, BMI, education, smoking, physical activity, baseline 25(OH)D, and phylloquinone (vitamin K). We also evaluated the relation of three MGP SNPs (rs2800802 (T-138C) [MGP802], rs1800801 (G-7A) [MGP801], rs4236 (A-102T) [MGP4236]) with hand ROA, adjusting for the same potential confounders, using the dominant, recessive, and additive modes of inheritance.

Results: Of the 376 participants, 59% were female, with mean age 70.6±5.5 and mean BMI 28.1±5.1. 70.5% had at least one hand joint with ROA. There was no significant association between serum MGP and presence of hand ROA (adjusted OR 1.34, 1.18, and 1.19 for quartiles 2-4, respectively, compared with the lowest quartile). See Table for the adjusted mean serum MGP concentrations for the 3 SNPs. The prevalence of hand ROA was 0.54 times lower in homozygous carriers of the minor allele of MGP802 (95% CI 0.30-0.96), and not significantly associated with the minor allele of MGP801 (adj OR 1.24) or MGP4236 (adj OR 1.22) compared with the respective major alleles, using the dominant mode of inheritance. Analyzed separately, the effect estimates were similar in men and women.

Conclusion: Our findings suggest that there may be an association between hand ROA and MGP polymorphism that is not reflected in concurrent MGP serum concentrations**.** The finding of an association with the minor allele of MGP802 is consistent with findings from other

studies for lower risk of kidney stones and CAC. Further studies are warranted to replicate and elucidate potential mechanisms underlying these observed associations as well as the role of vitamin K.

MGP SNP	Allele	Serum MGP (nM) (adjusted mean)	Hand ROA (adjusted OR (95% CI))
rs1800802 (MGP802)	AA	196.5	1.0 (ref)
	AG	204.0	
	GG (MAF: 0.25)	214.4	0.54 (0.30-0.96)
rs1800801 (MGP801)	GG	213.9	1.0 (ref)
	AG	191.3	
	AA (MAF: 0.39)	188.0	1.24 (0.88-1.75)
rs4236 (MGP4236)	TT	213.7	1.0 (ref)
	TC	192.3	
	CC (MAF: 0.41)	190.4	1.22 (0.87-1.70)

Adjusted for age, sex, BMI, smoking, education, activity, 25(OH)D, and phylloquinone

MAF=minor allele frequency

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The Ghent University Scoring System (GUSS™), An Optimised Scoring System to Monitor Disease Progression in Erosive Osteoarthritis of the Interphalangeal Finger Joints. Gust Verbruggen, Ruth Wittoek, Bert Vander Cruyssen and Dirk Elewaut, University Hospital Ghent, UGent, Ghent, Belgium

Purpose: To develop a quantitative radiographic scoring system, the Ghent University scoring system, GUSS™, to detect progression over shorter periods of time than an existing categorical anatomic phase scoring system (1) in erosive OA of the IP finger joints and to prove its reliability, responsiveness and sensitivity to change.

Method: Plain radiographs were obtained from 18 patients recruited into a randomized placebo-controlled trial of anti-tumour necrosis factor α therapy, at baseline, 6 and 12 months. Erosive progression and signs of repair or remodelling of the IP joints were scored by indicating the proportion of normal subchondral bone, subchondral plate and joint space on a 10-point incremental Likert scale from 0 to 100. Thirty joints showing tissue destruction typical of erosive OA were selected. All 90 radiographs were read twice in single order (i.e. blinded for patient and time) by two experienced readers. Cross sectional analysis was performed on all 90 radiographs and a longitudinal analysis on the change observed over time was done after unblinding for patient and time sequence. Inter- and intra-reader reproducibilities were studied using intraclass coefficients of correlation (ICC). Based on the within-variance of the two readers, the smallest detectable change (SDC) was calculated and allowed identifying joints as ‘progressors’ or remaining stable over time. Sensitivity to change was studied by calculating the standardised response means.

Results: Cross-sectional intra-observer reproducibilities ICC ranged from 0.73 to 0.99. Good inter-observer reproducibility was proven for the three variables and the total score (ICC 0.71 – 0.89). In order to identify ‘real’ change over background noise, a change of at least 40

units on the total score (range: 0-300) over 12 months (SDC 0-12: 36.0), and at least 50 units over 6 months (SDC 0-6: 47.6) had to be present. This allowed identifying 60% of all 30 joints as 'progressors' over 6 months compared to 33.3% with the classical anatomical scoring system, and 70% vs. 56.6% over 12 months. Standardised response means ranged from 0.19 to 0.32 for reader 1, and 0.19 to 0.47 for reader 2.

Conclusion: The new radiographic scoring system, GUSS™, is a reliable method to score radiographic change over time in erosive OA of the IP finger joints and detects more progression over a shorter period of time than the classical categorical anatomic phase scoring system.
(1) Verbruggen G and Veys EM. Arthritis Rheum 1996;39:308-20.

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Ultrasound Detection of Bone Erosions in Erosive and Non-Erosive Osteoarthritis of the Interphalangeal Joints: A Comparison to Routine Radiographs. Ruth Wittoek, Philippe Carron and Gust Verbruggen, University Hospital Ghent, UGent, Ghent, Belgium

Purpose: To determine if ultrasound (US) of the interphalangeal (IP) joints can detect more erosions than radiography and establish the presence of erosive disease in patients with erosive osteoarthritis (OA) of the IP joints earlier than conventional radiography (CR).

Method: The total number of IP joints examined was 684: 558 IP joints of 31 patients with erosive OA and 126 IP joints of 7 patients with non erosive OA. US exams and CR were independently graded for the presence of erosions by RW and GV, respectively. CR were scored by a well-described anatomic phase scoring system [1] in which the "E" (erosive) phase corresponds to the phase in which erosions are present. All US scans were performed using a MyLab 25 (Esaote, Italy) machine with a 10-18 MHz linear array transducer. US exams were scored for the presence or absence of erosions. Percentage of absolute agreement between both examinations was calculated. Ten images were read by a second US reader (PC) allowing calculation of the inter-observer reliability by Kappa (κ) statistics.

Results: Seventy-two of 558 joints of erosive OA patients were in the 'E' phase according to the radiographic scoring system (12.9%), 192/558 normal (N) and 168/558 stationary (S) joints were identified (34.4% and 30.1%). Partial or complete loss of the joint space (J) was seen in 55/558 joints (9.9%) and 66/558 joints were in the remodeled phase (R) (11.8%). No 'E' phase was identified in the non-erosive patients, 62/126 (49.2%) and 63/126 (50.0%), respectively were in the normal phase (N) and stationary (S) (showing degenerative features as osteophytes, ossicles, or joint space narrowing) phase. Only one joint (0.8%) showed loss of joint space ('J' phase). US detected erosions in 113/558 joints (20.3%), which are 41 more joints than radiography. US detected 94.4% of the radiographic erosive joints (68/72). Moreover, 45 erosions were identified in non-'E' phases: 30 in early disease (11 in 'N' (5.7%), 15 in 'S' (8.9%), 4 in 'J' (7.3%), and 15 in 'R' (22.7%) phases. US missed erosions in 4 joints in 'E' phase. Also six erosive joints were identified by US in the non-erosive patients (4.8%). A statistically different percentage of erosions in joints was seen in the radiographic normal joints in erosive vs. non-erosive OA (5.7% vs. 3.2%, $p < 0.05$), but not in the joints in 'S' phase. A very good percentage of absolute agreement between radiography and US was found for the detection of erosions (91.8%). Compared to CR as reference method to identify erosions, sensitivity of US was found 94.4% and specificity 90.7%. Accuracy of US in the detection of erosions in erosive OA is 91.2%. Inter-observer reliability for assessing the presence of erosions by US was very good ($\kappa = 0.91$).

Conclusion: US of the IP joints in erosive OA can detect erosions not seen with CR and may be supplementary to radiography in establishing erosive features in early disease.

[1] Verbruggen G and Veys E. Arthritis Rheum 1996;39:308-20.

Disclosure: R. Wittoek, None; **P. Carron**, None; **G. Verbruggen**, None.

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Erosive Osteoarthritis Is a Progressive Disease That Commonly Affects the Feet. Allen P. Anandarajah[1], Ralf G. Thiele[2] and Johnny Monu[3], [1]Univ of Rochester Med Ctr, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]University of Rochester Medical Center, Rochester, NY

Background: Erosive osteoarthritis (EOA) is considered to be an aggressive subset of generalized osteoarthritis, characterized by the appearance of symmetrical erosions, mainly in the distal (DIP) interphalangeal and proximal interphalangeal (PIP) joints. Patients with EOA often experience pain, swelling and joint deformities. Previous studies indicate that hand deformities often contribute to a functional decline but few studies have systematically examined disease progression or the prevalence and severity of foot involvement.

Purpose: To follow disease progression over time and to determine extent of foot erosions in EOA.

Method: All patients with EOA were identified from the Rheumatology Clinic at the University of Rochester Medical Center over a period of 5 years. Patients with EOA were evaluated based on predetermined criteria for diagnosis of EOA. EOA was defined as the presence of erosions (≥ 2) in DIP joints on plain radiographs of hands, normal acute phase reactants (ESR and/or CRP), a negative rheumatoid factor and/or anti-CCP antibody, absence of psoriasis and a family history negative for psoriatic arthritis. The frequency of radiographs and treatment was based on individual physician preference. Radiographs were read by experienced musculoskeletal radiologists.

Results: A total of 51 patients fulfilled criteria for the diagnosis of EOA. To date results have been analyzed for 43 subjects that consisted of 36 females (F) and 7 males (M) with a mean age of 66.2 years. 20 patients (16F and 4M) had repeat x-rays of hands, of which 13 (10F and 3M) patients (65%) had an increase in extent and/or number of erosions while 7 (6 F and 1M) patients had no evidence for progression of erosive disease. The mean duration between repeat x-rays was 20.1 months. 7 of the 13 patients with radiographic progression were on the following medications: 4 hydroxychloroquine, 1 methotrexate, 1 sulfasalazine and 1 on glucosamine chondroitin sulfate (GCS) and 6 were not on anti-inflammatory agents. Among the patients with no change in erosions, 4 were on no therapy, 1 on hydroxychloroquine, 1 on methotrexate and 1 on GCS. Foot X-rays were available for 24 subjects. Of these, 10 (41.7%) had erosions in the MTP joints while 14 were without erosions. Repeat x-rays of feet were available in 6 patients with a mean time duration between x-rays of 13.1 months. Increase in extent of erosions was seen in one while 5 showed no evidence for radiographic progression.

Conclusion: EOA is characterized by a progression of erosive disease in the majority of patients. Foot involvement was observed in over a third of the patients who had x-rays but radiographic progression was more likely to occur in the hands. Although, often asymptomatic, erosions are a common finding in the feet of patients with EOA. Further studies are needed to assess the long-term impact of this disorder on quality of life and function.

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Grey-Scale and Power Doppler Sonographic Findings in Patients with Erosive Osteoarthritis of the Interphalangeal Joints as Compared with Patients with Non-Erosive Osteoarthritis. Ruth Wittoek[1], Philippe Carron[1] and Gust Verbruggen[2], [1]University Hospital Ghent, University Ghent, Ghent, Belgium, [2]University Hospital Ghent, UGent, Ghent, Belgium

Purpose: To compare sonographic findings in patients with erosive osteoarthritis (OA) of the Interphalangeal (IP) finger joints and non-erosive OA of the IP joints, in order to evaluate the diagnostic value of ultrasound in distinguishing between erosive and non-erosive OA of the IP joints.

Method: A total of 310 proximal IP (PIP) and 248 distal IP (DIP) joints of 31 patients with radiographic erosive OA of the IP joints and 70 PIP and 56 DIP joints of 7 patients with non-erosive IP OA were examined by ultrasound using dorsal longitudinal and transverse scanning. One experienced examiner (RW) performed the scans using a MyLab 25 (Esaote, Italy) machine with a 10-18 MHz linear array transducer. Both Grey-scale and power Doppler (PD) sonography were performed. Representative images were digitally scored and were read under blinded conditions. Presence of effusion, synovitis, osteophytes, cartilage and PD signals intracapsular were scored in a dichotomous way (absent/present).The images of ten patients were reread by another investigator (PC), blinded for all clinical data, allowing to calculate the interobserver reliability by Kappa statistics (κ).

Results: Bone erosions, identified by a bone cortex discontinuation in the area adjacent to the joints, visualized in two perpendicular planes, were observed in 20.3% of joints of patients with erosive OA compared to 4.8% of joints of patients with non-erosive OA ($p < 0.01$). Remarkably more erosions were identified in the DIP than in the PIP joints (26.2% vs. 15.5%, $p < 0.05$) in the erosive OA group. Bone proliferations or osteophytes were seen in 55.9% and 58.7% of joints respectively, in patients with erosive and non-erosive OA. Effusion, represented by an anechoic signal in the joint space, different from cartilage, was found in 45.3 % of the erosive and 48.4% of the joints of patients with non-erosive OA. Grey-scale synovitis, represented by an anechoic or hypoechoic signal in the intracapsular area, was present in

respectively 16.3% and 12.7% of the joints in patients with erosive and non-erosive OA. No difference in PD signals were localized in the intracapsular area of the joints of patients with erosive and non-erosive OA (2.2% and 0.7% of joints, respectively).

Interobserver reliability was very good for all parameters ($\kappa = 0.91$ for erosions, $\kappa = 98$ for osteophytes, $\kappa = 0.98$ for hydrops, $\kappa = 0.99$ for synovitis, and $\kappa = 0.94$ for PD signal).

Conclusion: Ultrasound seems to be able to differentiate between erosive and non-erosive OA of the IP joints by identifying more erosions in the erosive form. Presence of osteophytes, effusion, synovitis and PD signals are comparable in both diseases.

Disclosure: R. Wittoek, None; **P. Carron**, None; **G. Verbruggen**, None.

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ICAM-1 and VCAM-1 Concentrations in Synovial Fluid Correlate to the Degree of Synovitis Measured by MRI in Moderate to Severe Osteoarthritis of the Knee. Signe E.B. Andersen[1], Annette Jørgensen[1], Torkell Ellingsen[1], Niels Egund[2] and Kristian Stengaard-Pedersen[1], [1]Rheumatology Universityhospital, Aarhus, Denmark, [2]Radiology Aarhus Universityhospital, Denmark

Purpose: To quantify intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) in plasma and synovial fluid (SF) from patients with moderate to severe osteoarthritis (OA) of the knee with and without joint effusion and to relate these findings to both the morphological changes measured by magnetic resonance imaging (MRI) and to parameters for pain and function.

Methods: The 24 OA patients fulfilled the ACR Criteria for primary OA of the knee joint and had a Lequesne Functional Index (LFI) score of 10 or more and a normal C-reactive protein (CRP). Exclusion criteria were secondary OA, inflammatory joint disease, significant OA symptoms of the other knee or co-morbidity. ICAM-1 and VCAM-1 concentrations in plasma and SF were quantified by validated ELISA kits. Synovitis, bone marrow lesions (BML) and effusion were estimated by MRI. The Western Ontario and McMaster Universities (WOMAC) index and LFI were performed, pain was estimated by visual analogue scale (VAS) and effusion was clinically assessed by presence or absence of ballottable patella sign (BPS).

Results: Levels of plasma ICAM-1 (median 234.47 ng/mL, range 143.92-338.82) and SF ICAM-1 (median 99.78 ng/mL, range 35.06-282.16) were positively correlated ($p < 0.0001$), ($r = 0.73$). Levels of ICAM-1 in SF differed between patients with and without PBS ($p = 0.012$). SF ICAM-1 correlated positively to MRI effusion ($p = 0.009$, $r = 0.54$), MRI synovitis (max) ($p = 0.004$, $r = 0.59$) and MRI synovitis (sum) ($p = 0.003$, $r = 0.61$). Plasma VCAM-1 (median 913.67ng/mL, range 509.81-1655.76) and SF VCAM (median 852.48 ng/mL, range 273.1-1710.01) did not correlate. SF VCAM-1 correlated positively to MRI effusion ($p = 0.041$, $r = 0.44$), MRI synovitis (max) ($p = 0.041$, $r = 0.43$) and MRI synovitis (sum) ($p = 0.025$, $r = 0.48$). SF VCAM-1 did not correlate to other parameters.

Conclusion: Our main finding in moderate to severe OA of the knee was that SF ICAM-1 and VCAM-1 correlated to the degree of synovitis measured by MRI. The plasma levels of ICAM-1 and VCAM-1 differed significantly between controls, OA patients without joint effusion and OA patients with joint effusion. Patients with joint effusions had the highest plasma concentration of ICAM-1 and VCAM-1.

In patients with moderate to severe knee OA and joint effusion; the concentrations of ICAM-1 and VCAM-1 in SF correlates to the degree of synovitis and effusion measured by MRI, which suggests a possible pathogenetic role for ICAM-1 and VCAM-1.

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Baseline Effusion but Not Synovitis Predicts Cartilage Loss Over 30 Months in Subjects without Tibiofemoral Osteoarthritis - Results From the Multicenter Osteoarthritis (MOST) Study. Frank W. Roemer[1], Ali Guermazi[1], David T. Felson[1], Jingbo Niu[1], Michael C. Nevitt[2], Michel D. Crema[3], John A. Lynch[4], C. Lewis[5], James Torner[6] and Yuqing Zhang[1], [1]Boston University School of Medicine, Boston, MA, [2]University of California, San Francisco, San Francisco, CA, [3]BUSM, Boston, MA, [4]UCSF, San Francisco, CA, [5]UAB, Birmingham, AL, [6]UIowa, Iowa City, IA

Purpose: Synovitis and effusion are frequently present in knee osteoarthritis (OA) and correlate with pain and other clinical outcomes. If synovitis or effusion in OA appears to predispose to further structural progression has been questioned. Synovitis present in OA is thought to be triggered by cartilage detritus, and thus seems to be a secondary phenomenon. However, the clinical data supporting this theory is

limited. Synovial inflammation is regularly observed in early OA, but as to whether it occurs prior to damage of other tissues remains unclear. Aim of the study was to assess if presence of baseline synovitis and effusion in knees without OA, predicts future cartilage loss.

Method: The Multicenter Osteoarthritis (MOST) Study is a longitudinal observational study of subjects with OA or at risk of developing OA. The MRI protocol included axial and sagittal proton-density weighted fat-suppressed fast spin echo and coronal STIR sequences. MRI was performed at a 1.0 T extremity system. MRIs were assessed semiquantitatively according to the WORMS scoring system. Only knees without radiographic OA and no baseline tibio-femoral cartilage damage were included. A synovitis-surrogate of signal changes in the infrapatellar and intercondylar areas of Hoffa's fat pad, and effusion were both scored from 0-3. Presence of definite synovitis and effusion was defined as any grade ≥ 2. Knees with scores of either 0 or 1 were the reference. Logistic regression was used to estimate the risk of cartilage loss at follow-up. Cartilage loss was defined as an increase of at least 0.5 grade (subtle within-grade progression, that did not fulfill the criteria of a full-grade change) in any subregion. Adjustment was performed for possible confounders of future tibio-femoral cartilage damage, i.e. baseline effusion for synovitis model, synovitis for effusion model, patellofemoral cartilage damage, meniscus damage, meniscal extrusion, body mass index, age, gender, malalignment, bone marrow lesions.

Results: 514 knees were included (55.6% women, mean age 60.1 ± 7.2, mean BMI 29.1 ± 4.5). 43 (8.4%) knees showed synovitis, and 53 (10.3%) presented with joint effusion at baseline. 137 (26.7%) knees showed cartilage loss at follow-up. After adjustment, baseline synovitis was not associated with an increased risk of cartilage loss at follow-up (adjusted odds ratio 1.0 [95% confidence intervals 0.5-2.1, p=0.89]). Knees with baseline effusion had an increased risk for cartilage loss (adjusted odds ratio 2.7 [95% confidence intervals 1.4-5.1, p=0.002]).

Conclusion: Baseline synovitis does not predict cartilage loss, but joint effusion. However, contrast-enhanced MRI, which is able to directly depict the inflamed synovium, might yield different results. Baseline effusion as a reflection of synovial activation seems to play a role in predicting structural progression in early or pre-OA.

Disclosure: F. W. Roemer, Boston Imgaing Core Lab, LLC, 4 ; **A. Guermazi**, GE HealthCare, 2, MerckSerono; Facet Solutions , 5, Boston Imaging Core Lab, LLC, 4, Synarc, Inc., 1 ; **D. T. Felson**, None; **J. Niu**, None; **M. C. Nevitt**, None; **M. D. Crema**, Boston Imaging Core Lab, LLC, 4 ; **J. A. Lynch**, None; **C. Lewis**, None; **J. Torner**, None; **Y. Zhang**, None.

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Anatomical Distribution of Synovitis in Knee Osteoarthritis and Its Association with Joint Effusion Assessed On Contrast-Enhanced MRI. Frank W. Roemer[1], M. Kassim Javaid[2], Ali Guermazi[1], Matthew Thomas[3], Amit Kiran[4], Leonard King[5], Richard Keen[6] and Nigel K. Arden[4], [1]Boston University School of Medicine, Boston, MA, [2]University of Oxford, Oxford, United Kingdom, [3]University of Southampton, Southampton, United Kingdom, [4]Oxford University, United Kingdom, [5]University of Southampton, United Kingdom, [6]University College London, United Kingdom

Purpose: Degenerative joints commonly demonstrate signs of synovitis, even in the early phase of disease, which is thought to be a secondary phenomenon due to damaged intraarticular tissues. Only assessment of synovitis on contrast-enhanced T1-weighted images correlates with microscopically proven synovitis, which is the rationale for using contrast-enhanced MRI. Aim of our study was to describe the distribution of synovial enhancement patterns and presence of joint effusion in patients with radiographic knee osteoarthritis (OA) using a novel comprehensive semiquantitative (SQ) scoring system.

Method: We used the baseline MRI from participants of a randomized treatment trial in knee OA including axial proton density (PD)-weighted (w) fat suppressed (FS), axial T1w FS contrast enhanced (CE) and sagittal T1w FS CE sequences. Synovial enhancement was scored semi-quantitatively from 0-3: 0 = no synovial thickening, 1 = <2 mm (equivocal synovial thickness), 2 = 2-4 mm (moderate synovitis) and 3 ≥4mm (severe synovitis). The following 11 subregions were assessed: suprapatellar, infrapatellar, medial parapatellar, lateral parapatellar, intercondylar, around the anterior cruciate ligament (ACL), posterior to the posterior cruciate ligament (PCL), medial perimeniscal, lateral perimeniscal, Baker's cysts and around loose bodies. Maximum synovial enhancement was grouped as absent (grade 0), equivocal (grade 1) and definite (grades 2 and 3). Effusion was scored from 0-3 on PD fs and T1w FS CE sequences according to the amount of capsular distension. We described the distribution of synovitis in the whole cohort and also by effusion status.

Results: 111 subjects were included (mean age 64.4 [range 51-81], 64% women, mean body mass index 29.3 [range 21-43]). All knees exhibited at least one subregion with equivocal synovial thickness, 89% of knees had at least one subregion with at least grade 2 and 40% had a maximum grade 3. The commonest sites for definite synovitis were posterior to the PCL in 71% and the suprapatellar region in 60% of all knees. The median number of affected sites with definite synovitis was 3. Overall percent agreement of effusion scored on PD fs and T1w

FS CE sequences was 65%, with a weighted kappa of 0.69. On T1w FS CE 73% of knees showed effusion, with 38% of knees exhibiting a grade 2/3 size effusion. Definite synovitis in at least one location was present in 78/81 (96.3%) knees with an effusion and in 21/30 knees (70%) without an effusion.

Conclusion: Disagreement of effusion assessment is due to overestimation of effusion on the PD fs sequence. Definite synovitis was present in the majority of knees without a measurable effusion. Synovitis in OA is common with the commonest site being the region posterior to the PCL. The clinical consequences of synovial enhancement at the different sites need to be explored.

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Association of Contrast Enhanced MRI Demonstrated Synovitis in Knee Osteoarthritis with Clinical Signs. Matthew Thomas[1], Amit Kiran[2], Frank W. Roemer[3], Ali Guermazi[3], M. Kassim Javaid[2], Leonard King[1], Madeleine Sampson[4], Richard Keen[5], John A. Lynch[6] and Nigel K. Arden[2], [1]Southampton University, Southampton, United Kingdom, [2]Oxford University, Oxford, United Kingdom, [3]BUSM, Boston, MA, [4]Southampton University Hospital, Southampton, United Kingdom, [5]University College London, United Kingdom, [6]UCSF, San Francisco, CA

Purpose: Osteoarthritis (OA) is the most prevalent form of arthritis, a major cause of morbidity worldwide. Synovitis is common in OA and thought to be a secondary phenomenon related to structural changes. Its presence has been documented in early phases of OA. Only contrast (C) enhanced (E) T1 weighted images are proven to correlate with histologically proven synovitis. Few studies have been performed assessing the link between active synovitus and clinical signs of inflammation. The aim of our study was to describe the link between synovitus measured by contrast enhanced MRI and these signs of inflammation.

Method: Participants of the VIDEO study of knee OA were included. MRI was performed at baseline using axial proton density (PD) weighted fat suppressed (FS), axial T1 weighted FSCE and sagittal T1 weighted FSCE sequences. Synovitis enhanced was scored semi-quantitively from 0-3: 0= no synovial thickening, 1 = <2mm (equivocal synovial thickening), 2 = 2-4 mm (moderate synovitis) and 3 = ≥ 4mm (severe synovitis). 11 regions were assessed in this fashion (suprapatellar, infrapatellar, medial parapatellar, lateral parapatellar, intercondylar, ACL, posterior to PCL, medial perimeniscal, lateral perimeniscal, Baker's cyst and around loose bodies). A cumulative grade was obtained from summation of these individual scores to provide an estimate of the volume of synovitis, subsequently divided into quartiles for secondary analysis. Effusion was scored from 0-3 on PD FS and T1 FS CE sequences according to the amount of capsular distension. All participants were examined by a trained research nurse for effusion, joint line tenderness (JLT) and warmth. We describe the association of vol of synovitis with joint effusion, warmth and JLT. We also explored the association of perimeniscal and peripatellar synovitis with JLT. Correlation of clinical versus radiological grading of effusion is determined.

Results: 111 subjects were included. Age: mean=64.4, median(IQR) = 64 (58,70), range =51,81. Gender: m = 36.04% (40/111), f= 63.96% (71/111). BMI: mean = 29.3, median(IQR) = 28.2 (26.0,32.0), range =21.3,42.7. cumulative synovitis mean=8, median(IQR)=9(7,10), range=2,11

Table 1: association of clinical variable with cumulative synovitis MRI score.

Explanatory Variable	Outcome Variable	OR (CI)
cumulative synovitis score	Any clinical effusion	1.66 (1.32,2.09)
cumulative synovitis score	Severe clinical effusion	1.65 (1.24, 2.18)

There was no significant association of synovitis with warmth or JLT. There was no significant association of radiological effusion and clinical effusion.

Conclusion: We have demonstrated a strong association of cumulative synovitis score with radiological effusion but surprisingly no association with warmth or of JLT.

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Association of Plasma n-3 and n-6 Fatty Acids with Synovitis in the Knee: The MOST Study. K. Baker[1], N. R. Matthan[2], A. H. Lichtenstein[2], A. Grainger[3], J. Niu[4], M. Clancy[4], C. Lewis[5], J. Buckwalter[6], M. Nevitt[7] and David T. Felson[8], [1]BUMC, Boston, MA, [2]Tufts University, Boston, MA, [3]U Leeds, Leeds, United Kingdom, [4]BUSM, Boston, MA, [5]UAB, Birmingham, AL, [6]U Iowa, Iowa City, IA, [7]UCSF, SF, CA, [8]Boston University School of Medicine, Boston, MA

Purpose: Studies have shown that fatty acids modulate the inflammatory response by multiple mechanisms. Specifically the n-6 fatty acid arachidonic acid (AA) and the n-3 fatty acids eicospentaenoic (EPA) and docosahexaenoic (DHA) can serve as precursors for the synthesis of bioactive lipid mediators including eicosanoids. Eicosanoids produced from AA induce eicosanoind-mediated inflammation while those produced from EPA and DHA inhibit inflammation. Synovitis represents an inflammatory process in the knee and has been shown to be a common feature in those with or at high risk of knee OA. We assessed the relationship of plasma n-6 and n-3 fatty acids with knee synovitis.

Methods: The MOST study is a NIH-funded longitudinal study of risk factors for knee OA in persons age 50-79 with or at high risk of knee OA. Participants were those who volunteered to obtain a 1.5 contrast enhanced MRI of one knee and had fasting blood drawn at the 30-month clinic visit. Synovitis was scored 0-3 in 4 compartments (suprapatellar pouch, medial and lateral parapatellar recesses and infrapatellar fat pad) and 0-1 in 2 compartments (medial and lateral posterior condylar) (Rheumatol 44:1569 2005). Synovitis in the whole knee was categorized as "extensive" ($\geq$ 1 compartment scored 3), "a lot" ($\geq$ 2 compartments scored 2 but no 3s), "some" ($\geq$ 4 compartments scored 1 or 1 scored 2), "none/questionable" ($<$ 4 compartments scored as 1). Inter-reader kappa was 0.9 ($p<.001$). Plasma samples stored at -80^{o}C were measured for fatty acid concentrations using gas chromotagraphy. We analyzed the concentration of 3 fatty acids, AA, EPA, and DHA in quartiles, with synovitis using a logistic regression model adjusting for age, sex, BMI, MRI bone marrow lesions.

Results: Of 500 subjects with a fatty acid measure, 28 were excluded, 11 were missing synovitis variables and 17 were taking fatty acid supplements. Mean age was 59.9 ± 7.3 years, mean BMI 29.5 ± 4.8 kg/m^2, and 50% were women. 49% had "some" synovitis and 16% "a lot/extensive". The odds of having "a lot/extensive" synovits was 3.4 times more (95% CI 1.4, 10.5) in the highest quartile of AA versus the lowest. Levels of EPA and DHA were not associated with synovitis.

Conclusion: These data suggest that higher tissue levels of AA may be associated with synovitis in the knee. The lack of a relationship of synovitis with EPA and DHA may be due to relatively low dietary intakes relative to those achieved with supplementation, which has resulted in decreased inflammatory mediators. Our findings indicate the potential for dietary manipulation as a therapy for synovitis.

	Arachidonic Acid				
Synovitis	4.99-9.17 (n=120)	9.19-10.41 (n=118)	10.42-11.82 (n=115)	11.85-17.66 (n=119)	
None/ Questionable	47 (39%)	42 (35%)	43(37%)	38 (32%)	
Some	59 (49%)	61 (52%)	54 (47%)	54(45%)	
A lot/extensive	14 (12%)	15 (13%)	18 (16%)	27(23%)	P for trend
Adj OR for some vs no synovitis (95% CI)	1.0	1.1 (0.6, 1.9)	1.1 (0.6, 2.0)	1.2 (0.7, 2.2)	0.5
Adj OR for a lot/extensive vs. no synovitis (95% CI)	1.0	1.7 (0.5, 5.1)	2.1 (0.7, 5.8)	3.4 (1.4, 10.5)	0.01

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Relationship Between Active Appearance Modelling Score of DXA Images and Whole Organ Magnetic Resonance Imaging Score (WORMS) in Knee Osteoarthritis. Kanako Yoshida[1], Jennifer S. Gregory[1], Rebecca J. Barr[1], Sandro Galea-Soler[2], Salvatore Alesci[3], Fiona Gilbert[2], David M. Reid[2] and Richard M. Aspden[1], [1]Univeristy of Aberdeen, Aberdeen, United Kingdom, [2]University of Aberdeen, Aberdeen, United Kingdom, [3]Wyeth Research, Collegeville, PA

Purpose: The use of plain radiographs for the assessment of Osteoarthritis (OA) is well established. More recently, Magnetic Resonance Imaging (MRI) has been used. We have shown that Active Shape Modelling (ASM) of hip radiographs can quantify OA severity and predict the risk of rapid progression. Active Appearance Modelling (AAM), an extension of ASM, allows assessment of simultaneous changes in both joint shape and intensity (i.e., bone mineral density (BMD) distribution), expressed in terms of "modes of variation", using dual energy X-ray absorptiometry (DXA) images.

The aim of this study was to examine the relationship between AAM score derived from DXA images, and Whole Organ Magnetic Resonance Imaging Score (WORMS) derived from MRI images, in patients with knee OA.

Methods: Thirty five subjects, with Kellgren-Lawrence grades (KLG) based on radiographs taken in the previous year were invited to undergo bilateral knee DXA scans (iDXA scanner, GE Medical Systems) and an MRI scan (3-T Achieva, Philips) of the knee with a higher KLG. An 85-point model template, developed using the AAM toolkit (Manchester University, Manchester, UK), was applied to DXA images. The model included the femur, tibia, osteophytes, tibial plateau, femoral condyles and intercondylar notch. WORMS was derived from the MRI images. Pearson's correlation was used for analysis.

Results: Appearance Modes (AppM) 1-7 were all significantly correlated with KLG, and AppM2 and 4 were also significantly correlated with total WORMS. A low AppM2 score was associated with higher KL grade (r=-0.68, $P<0.001$) and captured joint space narrowing, uneven distribution of BMD, bilateral osteophytes on femur and tibia, a wider medial femoral condyle, and a shallower intercondylar notch, all features typical of OA (Fig. 1). This mode had the strongest correlation with total WORMS and the constituents examined (marrow abnormality r=-0.68; cartilage r=-0.82; cyst r=-0.61; osteophytes r=-0.81; total WORMS r=-0.82; P<0.001). Marrow abnormality was observed in 11/18 knees (61%) classified as having doubtful OA.

Conclusion: This is the first report to examine relationships between the appearance of the knee joint, captured from DXA, and MRI signs of knee OA. Some appearance modes (2 and 4) are strongly linked with bone features, such as oedema and cysts, which suggest a link between the two. Use of AAM on DXA images, which are more economical and accessible than MRI, hold promise as a potential biomarker for knee OA.

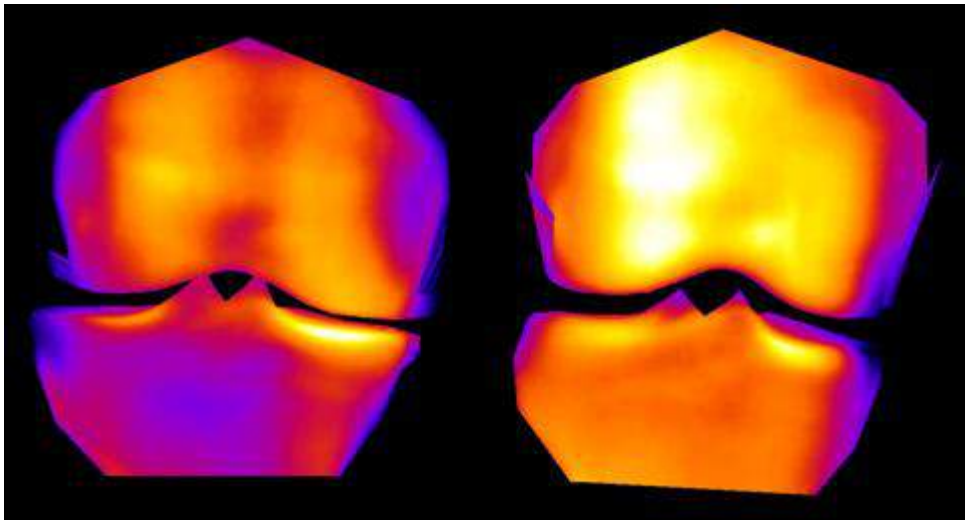

Fig 1

False-colour images of mode 2 (±2 SD) from AAM of the knee built from DXA images (medial compartment on the right). Low AppM2 scores (left image) show concurrent changes in joint space width, osteophytes, joint geometry and BMD distribution

Disclosure: K. Yoshida, TMRI, 2 ; **J. S. Gregory**, TMRI, 2 ; **R. J. Barr**, TMRI, 2 ; **S. Galea-Soler**, TMRI, 2 ; **S. Alesci**, Wyeth Research, 3 ; **F. Gilbert**, TMRI, 2 ; **D. M. Reid**, TMRI, 2 ; **R. M. Aspden**, TMRI, 2 .

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Serum Transforming Growth Factor-Beta 1 as a Biomarker of Incident and Progressive Radiographic Hip and Knee Osteoarthritis: The Johnston County Osteoarthritis Project. A.E. Nelson[1], Y.M. Golightly[1], T. Stabler[2], V.B. Kraus[2], Jordan B. Renner[3] and J.M. Jordan[4], [1]Thurston Arthritis Research Center, Chapel Hill, NC, [2]Duke University Medical Center, Durham, [3]The University of North Carolina, Chapel Hill, NC, [4]UNC, Chapel Hill, NC

Purpose: To test whether serum transforming growth factor-beta 1 (sTGF-β1) predicts incident and progressive radiographic OA (rOA) in African Americans (AAs) and Caucasians.

Method: Serum TGF-β1 (sTGF-β1) was measured for 330 participants in the Johnston County OA Project, using a sandwich ELISA kit from Biosource International (Camarillo, CA). Among participants with sTGF-β1 data, paired longitudinal films were available for 658 hips and 618 knees. Incident rOA was defined as 1) development of K-L grade ≥2 from a baseline K-L grade <2, or 2) development of K-L grade ≥1 from a baseline K-L grade=0. Progression of rOA was defined as 1) an increase of ≥1 K-L grade from a baseline K-L grade ≥2, or 2) an increase by ≥1 K-L grade from a baseline K-L grade ≥1. Incident osteophytes (OST) and joint space narrowing (JSN) were identified in joints with grade=0 at baseline and ≥1 at follow-up; progression was defined as an increase of ≥1 grade from a baseline grade ≥1. Natural logarithm transformation was used to produce near-normal distributions for continuous sTGF-β1 (lnTGF-β1). Separate multivariable Weibull regression models were used to provide hazard ratios (HR) for a 1-unit increase lnTGF-β1 with each rOA outcome, accounting for variable follow-up times and clustering by individual, adjusted for age, race, gender, and body mass index (BMI). Interaction terms were considered statistically significant at $p < 0.1$.

Results: The mean (±SD) age of the sample was 62 ± 10 years, the mean BMI was 30 ± 7 kg/m2, with 61% women and 42% AA. The mean (± SD) sTGF-β1 was 17.8 ± 6.1 ng/ml (range 6.1-40.9 ng/ml); mean (± SD) follow up time was 6.1 ± 1.3 years. There were no significant interactions by race or gender. The HRs (Table) showed no significant relationship between higher lnTGF-β1 and incident rOA, OST, or JSN, before or after adjustment. There were no significant associations between lnTGF-β1 levels and progressive hip rOA; very few hips progressed from a baseline K-L ≥2, or had progressive JSN. The odds of progressive knee rOA by either K-L definition were 40-50% higher in association with higher lnTGF-β1 levels, but this was not statistically significant.

Conclusion: Levels of sTGF-β1 do not predict development of incident rOA, OST, or JSN at the hip or knee in this longitudinal, population-based study including AAs and Caucasians. That our findings failed to reach statistical significance, even in this largest study to date of this biomarker, make it unlikely that sTGF-β1 will be a robust, stand-alone biomarker for future studies.

Table. Adjusted* hazard ratios for lnTGF-β1 and rOA outcomes

Definitions of rOA Outcomes	n (hips with outcome)	Adjusted HR* for Hip rOA (95% CI)	n (knees with outcome)	Adjusted HR* for Knee rOA (95% CI)
Incident rOA (from baseline K-L<2 to K-L = 2)	**45**	**0.61 (0.25-1.47)**	**103**	**1.10 (0.46-2.63)**
Incident rOA (from baseline K-L<1 to K-L = 1)	54	1.05 (0.31-3.51)	94	1.04 (0.41-2.65)
Incident OST (from grade 0 to grade = 1)	**49**	**1.41 (0.38-5.25)**	**94**	**1.41 (0.56-3.56)**
Incident JSN (from grade 0 to grade = 1)	29	0.65 (0.20-2.09)	99	1.39 (0.50-3.88)
Progressive rOA (increasing = 1 grade from baseline K-L =2)	**10**	**2.74 (0.31-24.30)**	**86**	**1.36 (0.63-2.91)**
Progressive rOA (increasing = 1 grade from baseline K-L =1)	47	1.02 (0.46-2.28)	160	1.51 (0.82-2.79)
Progressive OST (increasing = 1 grade from baseline OST =1)	**19**	**0.55 (0.12-2.59)**	**76**	**0.55 (0.24-1.26)**
Progressive JSN (increasing = 1 grade from baseline JSN =1)	7	4.14 (0.62-27.7)	84	1.40 (0.64-3.03)

***Adjusted for age, race, gender and body mass index**

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Longitudinal Rate and Sensitivity to Change in Knee Cartilage Morphology in Osteoarthritis as a Function of Radiographic Disease Grades (KLG 0 to 4) – Results From 716 Participants From the Osteoarthritis Initiative (OAI). Felix Eckstein[1], Marie-Pierre Hellio Le Graverand[2], Olivier D. Benichou[3], Donatus Dreher[4], Richard Y. Davies[5], Michael Nevitt[6], Jennifer Lee[7], Fred Baribaud[8], Alberto Gimona[9], Martin I. Hudelmaier[1], Wolfgang Wirth[1] and OAI investigators, [1]Paracelsus Medical Unversity & Chondrometrics Gmbh, Salzburg, Austria, [2]Pfizer Inc., New London, CT, [3]Lilly, Indianapolis, IN, [4]Merck Serono, Geneva, Switzerland, [5]Glaxo Smith Kline, Collegeville, PA, [6]UCSF, San Francisco, CA, [7]Wyeth Research, Collegeville, PA, [8]Centocor, PA, [9]Novartis, Basel, Switzerland

Purpose: The Osteoarthritis Initiative (OAI) is a large public study designed for identifying sensitive (imaging) biomarkers and risk factors of knee OA. To select suitable participants and adequately power clinical trials, reliable information on the rate and sensitivity to change in structural outcomes is required. Here we describe the rate of cartilage loss in 716 OAI participants across all radiographic grades.

Methods: One knee of 716 participants from the OAI was studied (public releases 0/1E1 and 0/1F1). Kellgren Lawrence grades were calculated (cKLG) from osteophyte and joint space narrowing scores from baseline fixed flexion radiographs: 65 knees were cKLG 0, 36 cKLG 1, 272 cKLG 2, 274 cKLG 3, and 69 cKLG 4. Cartilage segmentation was performed on baseline and year 1 follow up coronal FLASHwe MR images by 7 experienced readers, blinded to time point and cKLG. Changes in cartilage thickness (ThCtAB) were computed in femorotibial cartilage plates and in 16 subregions, 5 in the medial (MT) and lateral tibia (LT), and 3 in the weight-bearing femoral

condyles (cMF and cLF), respectively. The standardized response mean (SRM) was used to express the sensitivity to change. The changes for the subregions in each knee (in µm) were sorted in ascending order (Ranks 1-16), starting with the region showing the greatest thinning (Rank1). One way ANOVA with Bonferroni Dunn correction was used to compare rates of change (in µm) in the medial femorotibial compartment (MFTC=MT+cMF) and in Rank 1 between KL grades.

Results: The annual rate of change in MFTC cartilage thickness (MT+cMF) differed significantly with KLG (overall p=0.012); it was -8µm (-0.2%; SRM -0.12) in KLG 0, -71 µm (-2.1%; SRM -0.27) in KLG 1, –17 µm (-0.5%; SRM -0.17) in KLG 2, -45 µm (-1.3%; SRM -0.35) in KLG 3, and -42 µm (-1.5%; SRM -0.28) in KLG 4 knees. None of the between-KLG differences were, however, significant after Bonferroni-Dunn correction for multiple testing. Changes in rank1 (subregion with greatest reduction in each knee) showed a strong relationship with KLG (overall p<0.001). Rank 1 reductions were significantly greater in KLG 1,3 and 4 compared with KLG 0 or with KLG 2 knees.

Conclusion: Changes in cartilage thickness, measured quantitatively with MRI over 1 year, were relatively modest across all KL grades. A ranking system of subregional cartilage changes was more sensitive in detecting differences in rates of change between KL grades than analysis of cartilage plates. The rates of change in KLG 1, 3 and 4 knees were greater than those in KLG 0 knees. Surprisingly, the rates of cartilage thinning in KLG 1, 3 and 4 were also greater than those in KLG 2 knees, a subcohort commonly studied in drug trials.

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The Relation of Reversible Knee MRI Features to Knee OA Symptom Fluctuation. David J. Hunter[1], Michel D. Crema[2], Ali Guermazi[3], Frank W. Roemer[3], Monica D. Marra[3], Marie-Pierre Hellio Le Graverand[4], Ling Li[1], Bradley T. Wyman[4] and Yuqing Zhang[3], [1]New England Baptist Hospital, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]BUSM, Boston, MA, [4]Pfizer Inc., New London, CT

Purpose: The osteoarthritis (OA) symptoms of pain and functional limitation are characterized by marked fluctuation. To date the time-varying risk factors for these dynamic fluctuations remain unknown. The objective of this analysis was to investigate the relation of change in specific structural features to the risk of knee pain and functional limitation fluctuation.

Method: 62 obese women with radiographic knee OA and 99 non-obese female controls (mean age 56.6 yrs) were imaged using 3T MRI during a longitudinal 24-month observational study (A9001140 study). Knee pain and functional limitation were defined using WOMAC questionnaire. Fluctuation in pain/ functional limitation was defined as a change ≥20% and absolute change of ≥10 (on 100mm scale). We identified knees that have experienced pain/ functional fluctuation at least at one but not at all visits. Each MRI was scored for subchondral bone marrow lesions (BMLs), synovitis, and effusion using the BLOKS instrument at baseline, 6, 12 and 24 months. Synovitis was scored 0-3 in Hoffa's fat pad, effusion was scored 0-3 for each knee, and BMLs were scored 0-3 in each of 5 sub-regions in the medial and lateral tibiofemoral compartments and 4 subregions in the patellofemoral compartment. Given the small number of observations with Grade 3 synovitis or effusion these were collapsed into Grade 2. We summarized BMLs within each knee to use data across sub-regions. We performed a self-matched case-control study, using each knee as its own control, to evaluate the relation of BMLs, synovitis, and effusion to the risk of pain/ functional fluctuation using a conditional logistic regression model.

Results: 77 participants experienced fluctuation in pain in at least one, but not all 4 visits for a total of 305 observations. 69 participants experienced fluctuation in function in at least one, but not all 4 visits for a total of 274 observations. The table below displays the results of the relation between MRI feature and symptom fluctuation. A 1 unit difference in effusion was associated with an increased risk of function fluctuation (OR 2.54 (95%CI 1.02-6.29). There were also strong trends to increased risk of pain fluctuation with effusion.

Predictor		Pain fluctuation OR (95% CI)	Function fluctuation OR (95% CI)
Synovitis	1	1.18 (0.43 -3.26)	0.64 (0.22 -1.90)
(0 as Ref.)	2	1.07 (0.23 – 4.97)	0.56 (0.11 – 2.74)

Effusion (0 as Ref.)	1	1.94 (0.85 – 4.40)	**2.54 (1.02 – 6.29)**
	2	3.01 (0.80- 11.39)	3.30 (0.86 – 12.67)
BML (0 as Ref.)	1	0.88 (0.31 – 2.46)	2.02 (0.61 – 6.70)
	2	2.08 (0.64 – 6.71)	1.84 (0.49 – 6.87)
	3	1.39 (0.42 – 4.58)	0.89 (0.24 – 3.38)

Conclusion: Change of MRI-detected effusion appears to be the most potent reason for fluctuation in functional limitation in persons with knee OA. The potential for clinical interventions to decrease effusion volume and by so doing reduce short term fluctuation in symptom severity warrant further investigation.

Disclosure: D. J. Hunter, Pfizer Inc, 2 ; **M. D. Crema**, None; **A. Guermazi**, BICL, LLC, 4, Synarc, inc, 1, GE Healthcare, 2, MerckSerono, Facet Solutions, 5 ; **F. W. Roemer**, None; **M. D. Marra**, None; **M. P. Hellio Le Graverand**, Pfizer Inc, 3 ; **L. Li**, None; **B. T. Wyman**, Pfizer Inc, 1, Pfizer Inc, 3 ; **Y. Zhang**, None.

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Stage of Knee OA and Odds of Cartilage Thickness Loss or Gain Over Two Years. L. Sharma[1], J. S. Chmiel[1], O. Almagor[1], W. Wirth[2], S. Cahue[1], M. Marshall[1] and F. Eckstein[2], [1]Northwestern Univ, Chicago, IL, [2]Paracelsus Med Univ, Chondrometrics Gmbh, Salzburg, Austria

Purpose: Small average annual loss of cartilage (C) in OA knees by quantitative MRI may be due to heterogeneous sampling of knees with C thinning and thickening (from swelling or hypertrophy). An understanding of the stage at which thickening and thinning reach peak prevalence aids conceptualization of knee OA natural history and trial design. C thickness should increase in more knees at early OA stages when swelling or anabolic processes may dominate. We determined %knees with subregional C thinning and thickening and tested if knees with moderate-severe OA were more likely to experience C loss and less likely to experience C thickening over 2 years than mildly diseased knees.

Method: Participants had knee OA, and underwent MRI including double oblique coronal FLASHwe, at baseline and two years. C thickness was determined in the medial tibia and weightbearing femur and in 8 subregions using custom software. We used logistic regression with GEE to analyze the relationship between baseline medial OA disease severity and the odds of baseline-to-2 year C thickness loss or gain (defined as ≥ 5%).

Results: We studied 244 knees (150 persons, 66 yrs, BMI 30, 74% women). At most subregions, %knees with C thickness loss (Table 1) was higher and %knees with thickness gain (Table 2) was lower in knees with worse OA at baseline than knees with less severe OA. Baseline medial joint space grade (mjsg) 2-3 (vs. 0-1 reference) was significantly associated with greater odds of thickness loss (right column Table 1), and with reduced odds of thickness gain in almost all subregions, although these did not reach significance (Table 2).

Conclusion: C thickness increase occurred in a subset of knees within each subregion. In most medial surfaces and subregions, worse baseline medial OA disease severity was associated with significantly greater odds of C thickness loss and a consistent although not statistically significant reduction in odds of C thickness gain.

Table 1. Baseline MJSG and Baseline-to-2-Year C THICKNESS LOSS

Medial subregion	In knees (195) baseline mjsg = 0-1, % with thickness LOSS	In knees (34) baseline mjsg = 2, %with thickness LOSS	In knees (15) baseline mjsg = 3, %with thickness LOSS	OR (95% CI) for thickness LOSS associated with baseline mjsg 2-3 (vs. 0-1 reference)
Tibia (T)	16	50	67	6.25 (3.17, 12.33)
WB Femur (F)	28	44	53	2.31 (1.15, 4.64)

T, central	25	62	80	6.15 (2.84, 13.28)
T, external	29	74	80	7.65 (3.45, 17.00)
T, internal	18	32	27	2.02 (0.99, 4.09)
T, anterior	31	47	73	2.76 (1.46, 5.22)
T, posterior	22	44	60	3.50 (1.77, 6.93)
F, central	33	50	60	2.31 (1.22, 4.39)
F, external	27	53	67	3.57 (1.76, 7.24)
F, internal	29	29	47	1.32 (0.70, 2.48)

Table 2. Baseline MJSG and Baseline-to-2-Year C THICKNESS GAIN

Medial subregion	In knees (195) baseline mjsg = 0-1, % with thickness GAIN	In knees (34) baseline mjsg = 2, % with thickness GAIN	In knees (15) baseline mjsg = 3, % with thickness GAIN	OR (95% CI) for thickness GAIN associated with baseline mjsg 2-3 (vs. 0-1 reference)
Tibia (T)	9	3	0	0.22 (0.03, 1.62)
WB Femur (F)	13	9	7	0.58 (0.19, 1.74)
T, central	15	9	0	0.37 (0.11, 1.25)
T, external	14	9	13	0.68 (0.26, 1.75)
T, internal	13	6	13	0.60 (0.20, 1.85)
T, anterior	21	18	7	0.63 (0.22, 1.81)
T, posterior	15	21	0	0.95 (0.36, 2.51)
F, central	18	12	27	0.86 (0.34, 2.16)
F external	22	15	13	0.61 (0.24, 1.55)
F, internal	12	9	20	1.04 (0.41, 2.65)

Disclosure: L. Sharma, NIH, 2 ; **J. S. Chmiel**, NIH, 2 ; **O. Almagor**, NIH, 2 ; **W. Wirth**, Chondrometrics, Gmbh, 3 ; **S. Cahue**, NIH, 2 ; **M. Marshall**, NIH, 2 ; **F. Eckstein**, Chondrometrics GmbH, 4, Chondrometrics GmbH, 3, Pfizer, MerckSerono, Novartis, Novo Nordisk, Wyeth, 5, Pfizer, MerckSerono, Eli Lilly, GlaxoSmithKline, Wyeth, Centocor, Novartis, 2, OARSI Board of Directors, 6 .

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Clinical Examination Findings of the Painful OA Knee and Correlation with MRI Abnormalities. C.Y. Wenham[1], A. Grainger[2], E.M Hensor[1], R.A. Maciewicz[3], J.C. Waterton[3] and P. Conaghan[4], [1]LIMM, University of Leeds, Leeds, United Kingdom, [2]U Leeds, Leeds, United Kingdom, [3]AstraZeneca, Macclesfield, United Kingdom, [4]U of Leeds, Leeds, United Kingdom

Purpose: Multiple clinical examination findings are common when examining the painful OA knee yet there is little literature on correlation with MR imaging. This study examined the relationship between compartment specific clinical findings and associated MR abnormalities.

Method: This was a cross-sectional study of people with painful, ACR OA knee. Detailed examination of the most painful knee was recorded within 48 hrs of 1.5 T contrast enhanced MR imaging of the knee. Logistic regression controlling for BMI, disease duration and gender was used to assess any association.

Results: 123 subjects were included. 64 (52%) women, mean age 63.4, mean pain VAS 61.3 mm. Crepitus was present in the patellofemoral (PF) compartment in 85 subjects (69%), lateral compartment in 39 (32%) and medial compartment in 44 (35%). 71 subjects (58%) had tenderness on PF compression, 101 (82%) medial joint line tenderness and 64 (52%) lateral joint line tenderness. 23 (19%) had medial knee pain on knee flexion and 50 (41%) medial pain with the joint held in maximal flexion.

At least one site with complete cartilage loss in the medial compartment was associated with medial crepitus (OR 2.15 (0.98-4.73) p=0.056). Lateral compartment crepitus was significantly associated with moderate-severe osteophytosis (OR 4.4 (1.68-9.69) p=0.02). Lateral compartment cartilage damage was uncommon but was associated with increased odds of lateral crepitus. Medial joint line tenderness was more common in those with a higher medial synovitis score (OR 2.12 (0.74-6.03) p=0.16). There was no association between lateral joint line tenderness and lateral synovitis scores (1.03 (0.46-2.28) p= 0.95) or between tenderness on PF compression and infrapatellar synovitis (0.74 (0.33-1.68) p=0.48). Greater area/thickness of cartilage loss and >1 site of complete cartilage loss were associated with greater odds of medial or lateral joint line tenderness or tenderness on PF compression (not statistically significant). Medial knee pain on knee flexion was significantly associated with medial synovitis (OR 3.23 (1.17-8.89) p=0.023). Medial knee pain with the joint held in maximal flexion was associated with medial MR findings of >75% area cartilage loss (2.61 (1.16-5.89) p=0.021), full thickness cartilage loss (3.07 (1.33-7.0) p=0.009) and medial meniscal maceration (2.80 (1.2-6.52) p=0.017).

Conclusion: This was a hypothesis generating dataset. Most examination findings did not correlate with specific pathologies. Crepitus was significantly associated with moderate-severe osteophytosis and was more common in those with complete cartilage loss. Compartment-specific tenderness was also associated with cartilage loss, but not significantly with synovitis. Medial compartment synovitis was significantly associated with medial pain both on knee flexion and with the knee held in maximal flexion.

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Body Mass Index and Baseline Walking Speed as a Predictor for Longitudinal Cartilage Loss in Knee Osteoarthritis (KOA). Ji Yeon Lee, Grace H. Lo, Lori Lyn Price and Timothy McAlindon, Tufts Medical Center, Boston, MA

Purpose: Although BMI is a major risk factor for KOA its influence on progression of cartilage loss is less certain. Studies that examined the relationship between BMI and change in cartilage volume have generated inconsistent results. In this study, we sought to further explore this relationship controlling for covariates including walk speed.

Method: We studied participants in a double-blinded randomized controlled trial of vitamin D for KOA (Kellgren Lawrence grade 2-4). At present, treatment allocation remains blinded. 1.5 Tesla knee MRIs were obtained at baseline, 1 and 2 year follow-up visits. At baseline, we measured height, weight, and a timed 20m walk at a self-selected speed. A single reader used ANALYZE© software to register baseline and follow-up knee MRIs for each participant, and segmented the medial femoral (MFC) and medial tibial cartilage (MTC) volumes (intra-reader root mean square CV% was 1.2-2.5%). For participants without a 2-year MRI, 2-year cartilage loss was assumed to be double the 1-year change. We expressed cartilage loss as continuous (% change) and dichotomous outcomes (>3% loss). We used stepwise linear regression to evaluate baseline BMI as a predictor of change in cartilage volume, adjusting for age, sex, change in BMI and habitual walking speed. We used logistic regression to compute odds ratios for exposures classified in quantiles.

Results: Among 146 trial enrollees, analyzable data were available from 119 (complete 2-year data for 109 MTC and 104 MFC; 1-year data from 15). Their mean age was 63.0 ± 8.5yrs, 58% were female, mean baseline BMI was 30.0 ± 5.4 and 2-yr BMI change was 0.14 ± 1.9 kg/m². The mean 2-yr change for MFC was -4.22 ± 2.7% and for MTC was -4.14 ± 3.6%. Of the covariates, baseline BMI was the most consistent predictor of cartilage loss in the stepwise linear models (beta= 0.12, p=0.02 for MFC change, and 0.12, p= 0.05 for MTC). In the

logistic analyses, significant effects on MFC were also evident from age and walking speed (see Table). Other tested covariates had no substantial effects in these models.

Conclusion: In KOA, baseline BMI independently predicts medial compartment cartilage loss, although the magnitude of this effect is small. We did not observe an influence of BMI change, but the study may have been underpowered to evaluate this relationship as BMI change was minimal in this sample. Notably, slower habitual walking speed appeared protective for femoral cartilage loss. This could be mediated by biomechanical mechanisms such as lower adduction moment.

Table. Odds Ratio for >3% 2-yr Medial Femoral Cartilage Loss

BMI (kg/m²)		**p trend**
≤ 26	referent	
>26 - 29	0.6 (95% CI: 0.2 – 2.0)	
>29 - 34	1.3 (95% CI: 0.4 – 4.0)	
> 34	4.1 (95% CI: 1.1 – 15.6)	0.009
Age (yrs)		
≤ 56	referent	
>56 – 62	1.3 (95% CI: 0.4 – 4.2)	
>62 – 70	3.5 (95% CI: 1.0 – 11.4)	
> 70	3.6 (95% CI: 0.9 – 13.9)	0.009
20m walk time (sec)		
≤ 13 (fastest)	referent	
>13 - 15	1.6 (95% CI: 0.5 – 5.0)	
>15 – 17	0.5 (95% CI: 0.1 – 1.0)	
> 17 (slowest)	0.2 (95% CI: 0.4 – 4.0)	0.01

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Biochemical Markers of Wnt–Frizzled–b-Catenin Pathway and VEGF and Their Association with MRI Markers of Knee Osteoarthritis Progression. M. Corr[1], J. Niu[2], D.J. Hunter[3], A. Guermazi[4], N.E. Lane[5] and David T. Felson[4], [1]University California School o, La Jolla, CA, [2]BUSM, Boston, MA, [3]NEBH, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]UCDMC, Sacramento, CA

Purpose: The objective of this analysis was to assess the potential relationship between novel markers for bone and cartilage homeostasis (sFRP3 and DKK-1), and an angiogenic factor (VEGF) and 1) the progression of knee OA and 2) the presence of bone marrow lesions (BMLs).

Method: We conducted an analysis of data from the Boston Osteoarthritis of the Knee Study (BOKS).) All subjects in the study met ACR criteria for knee OA. Knee Magnetic resonance images (MRI) were scored for BMLs, attrition, osteophytes, synovitis and cartilage using the WORMS semi-quantitative grading scheme at baseline and at 30 months. Serum VEGF, sFRP3 and DKK-1 levels were assayed by ELISA on archived sera that was stored at -70 C. Because of nonparametric distribution of the data the natural log of each biomarker was used. To facilitate comparison between the biomarkers we used the standardized distribution of each biomarker as the predictor. We assessed whether increased levels of each biomarker was predictive of subsequent cartilage loss on knee MRI as defined by an increase in cartilage score in any of the plates from baseline to 30 month visit. We classified each subject according to maximum score of BML>0. Logistic regression

models were fit using BML as the outcome and biomarkers, age, sex and BMI as predictors. A Receiver Operating Characteristic (ROC) curve was generated for each model and the area under the curve was assessed. We also performed exploratory analyses to assess if the biomarkers were associated with attrition, osteophyte size, synovitis using the same methods.

Results: 124 subjects with knee OA were assessed. The mean (SD) age was 65 (9) years and 56% were male. At baseline 74% of participants had a maximum BML score > 0, 53% a maximum attrition score > 0, 78% a maximum osteophyte score > 2, and 64% had a maximum synovitis score > 0.

We found no relation between sFRP3, DKK-1 and VEGF with either presence of BML or OA progression defined as MRI cartilage loss (see table). Similarly we found no relation between these markers and attrition, osteophyte size, or synovitis.

	Prevalence of BML			**Cartilage loss**		
	OR (95% CI)	p-value	c-statistic	OR (95% CI)	p-value	c-statistic
Standardized Log VEGF	1.2 (0.8, 1.8)	0.44	0.66	1.1 (0.8, 1.6)	0.45	0.58
Standardized Log DKK	1.5 (0.9, 2.4)	0.08	0.66	1.3 (0.9, 1.7)	0.13	0.61
Standardized Log SFRP	1.2 (0.8, 1.9)	0.44	0.65	1.1 (0.8, 1.6)	0.44	0.59

Conclusion: We found no associations between sFRP3, DKK-1 and VEGF with either presence of BML or progression of cartilage loss. We would not advocate their use as markers for these structural changes in persons with knee OA.

Disclosure: M. Corr, None; **J. Niu**, None; **D. J. Hunter**, None; **A. Guermazi**, Synarc, Inc., 1, Boston Imaging Core Lab, LLC, 4, MerckSerono; Facet Solutions , 5, GE HealthCare, 2 ; **N. E. Lane**, None; **D. T. Felson**, None.

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Varus Thrust Is Associated with Cartilage Loss in Knee Osteoarthritis. William F. Harvey, J.Y. Lee, K.A. Carr, Melanie A. Ripley, Melynn Nuite, T. E. McAlindon and G.H. Lo, Tufts Medical Center, Boston, MA

Purpose: Varus thrust (VT), rapid lateral knee bowing during ambulation, can be recognized in the clinical setting without expensive gait lab equipment. VT has been shown to be predictive of longitudinal joint space narrowing (JSN) in knee osteoarthritis (KOA). JSN on radiograph is due to loss of cartilage, meniscal malposition or both. We sought to further characterize this by examining the relationship between VT and change in cartilage volume over 2 years.

Methods: We studied subjects enrolled in a double blind, placebo controlled study of Vitamin D to slow the progression of KOA over 2 years. The parent study is still blinded to treatment allocation. The primary outcome was cartilage volume based on MRIs of the study knee obtained at baseline and 2 years. The MRIs from each subject were registered using ANALYZE software for accurate comparison. Medial femoral and tibial cartilage were segmented manually using ANALYZE by one reader to generate volume. The percent change from baseline to year 2 was calculated. A convenience sample of consecutive subjects were videotaped at the 2 year visit walking on a flat surface at a self selected speed with a standard digital video camera (60 Hz) in the frontal plane. The videos were viewed on separate occasions by two rheumatologists trained to evaluate VT. Videos were scored as definite VT, possible VT and no VT. Both evaluators read all videos and disagreements were adjudicated by consensus of both. Stratifying by VT score, ANOVA and chi-square were used to compare the baseline subject characteristics. ANCOVA with Tukey's procedure was used to compare the mean percent change in cartilage volume (baseline – 2 years), controlling for age, sex, weight, height, 20 meter walk time and WOMAC pain.

Results: Of the 146 subjects enrolled in the trial, 78 had cartilage volumes at both time points and video recordings. Baseline characteristics are shown in the table. The prevalence of definite VT was 28%. Definite VT was associated with greater cartilage loss in the tibia compared to no VT and trended towards significance in the femur.

Conclusion: Definite VT was highly prevalent in a clinical trial of knee OA. Measurement of VT in the research setting may be of use in determining which subjects are more likely to develop cartilage loss, increasing the power of a study for detecting a difference. The videos were recorded at 2 years rather than baseline, a limitation to the study, precluding our ability to assign causality.

Table. Subject characteristics and results of ANCOVA for change in cartilage volume

	No VT N=41	Possible VT N=15	Definite VT N=22	p-value
Age (yrs - mean (SD))	63.0 (8.4)	63.1 (9.6)	63.6 (8.8)	*p=0.96
Sex (% female)	78%	53%	32%	**p=0.001
Height (m - mean (SD))	1.7 (0.1)	1.6 (0.1)	1.7 (0.1)	*p=0.38
Weight (kg - mean (SD))	80.9 (14.7)	81.1 (21.8)	87.0 (16.0)	*p=0.35
WOMAC pain (0-10 - mean (SD))	4.4 (3.5)	2.5 (2.9)	6.1 (4.1)	*p=0.01
20 meter walk (sec - mean (SD))	15.5 (2.9)	15.1 (2.0)	16.8 (3.5)	*p=0.15
Medial Tibia % Δ in cartilage volume (mean (SE))	3.2% (0.6)	3.9% (1.0)	6.6% (0.9)***	*p=0.06
Medial Femur % Δ in cartilage volume (mean (SE))	4.2% (0.5)	3.3% (0.8)	5.8% (0.7)	*p=0.08

* p-value based on ANOVA / ANCOVA (for volume)

** p-value based on chi-square

*** p=0.01 vs No VT based on Tukey's procedure after ANCOVA controlling for the above covariates

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Risk of Subregional Cartilage Thickness Loss Associated with Malalignment in Knee OA. K. Moisio[1], F. Eckstein[2], A. Chang[1], J. S. Chmiel[1], O. Almagor[1], P. Prasad[1], W. Wirth[2], S. Cahue[1], M. Marshall[1] and L. Sharma[1], [1]Northwestern Univ, Chicago, IL, [2]Paracelsus Med Univ, Chondrometrics Gmbh, Salzburg, Austria

Purpose: Varus (VAR) and valgus (VAL) malalignment stress the medial and lateral tibiofemoral compartments, respectively. Recent studies suggest that cartilage loss is more pronounced in certain subregions, depending in part upon alignment (Eckstein 2008). We tested whether baseline VAR is associated with baseline-to-2-year cartilage thickness loss at the central and external (medial-most) medial tibial (T) and weightbearing femoral (F) subregions, and that VAL is associated with loss at the central and external (lateral-most) lateral T and F subregions.

Method: All participants had knee OA (K/L ≥2) and underwent full-limb x-ray for alignment at baseline and MRI at baseline and 2 years using double oblique coronal FLASHwe sequences. Cartilage thickness was determined in 5 subregions of each medial and lateral T surface and 3 subregions of each weightbearing F surface using custom software. Logistic regression with GEE was used to analyze the relationship of VAR (≥2° in VAR direction vs. non-VAR) and VAL (≥2° in VAL vs. non-VAL) with baseline-to-2-year cartilage thickness loss of ≥5% at each subregion, adjusting for age, gender, BMI, and baseline K/L grade.

Results: The sample included 261 knees (159 persons, 66 yrs, BMI 30, 75% women). 38% of knees were VAR and 31% were VAL. VAR at baseline was associated with a significant increase in the adjusted OR for cartilage thickness loss in the central and external subregions of the medial T and F surfaces (Table 1). Baseline VAL was associated with cartilage thickness loss in the central and external subregions of the lateral T and F surfaces and in the posterior and interior subregions of the lateral T surface (Table 2). VAR and VAL were each associated with reduced odds of thickness loss, significant in some subregions, in the unloaded compartment (Tables 1 and 2).

Conclusion: VAR at baseline was associated with baseline-to-2 year cartilage thickness loss in the central and external subregions of the medial T and weightbearing F surfaces. Similarly, baseline VAL was associated with cartilage thickness loss in the central and external subregions of the lateral T and F surfaces and the lateral T posterior and interior subregions.

Table 1. Adj OR (95% CI) for MEDIAL Cartilage Thickness Loss Associated with Baseline Malalignment

	Medial T, central subregion	Medial T, external	Medial T, internal	Medial T, anterior	Medial T, posterior	Medial F, central	Medial F, external	Medial F, internal
VARUS	2.69 (1.40, 5.16)	4.42 (2.37, 8.22)	1.24 (0.61, 2.52)	1.35 (0.78, 2.36)	1.42 (0.76, 2.63)	2.44 (1.40, 4.26)	3.29 (1.78, 6.09)	0.82 (0.44, 1.53)
VALGUS	0.40 (0.20, 0.81)	0.36 (0.18, 0.74)	0.62 (0.32, 1.23)	0.61 (0.31, 1.19)	1.03 (0.54, 1.98)	0.79 (0.41, 1.52)	0.46 (0.24, 0.91)	1.04 (0.53, 2.02)

Table 2. Adj OR (95% CI) for LATERAL Cartilage Thickness Loss Associated with Baseline Malalignment

	Lateral T, central subregion	Lateral T, external	Lateral T, internal	Lateral T, anterior	Lateral T, posterior	Lateral F, central	Lateral F, external	Lateral F, internal
VARUS	0.82 (0.44, 1.52)	0.34 (0.17, 0.71)	1.04 (0.56, 1.93)	1.36 (0.73, 2.53)	0.49 (0.25, 0.94)	0.71 (0.36, 1.43)	0.65 (0.33, 1.28)	1.11 (0.58, 2.12)
VALGUS	2.97 (1.66, 5.33)	2.71 (1.44, 5.10)	2.04 (1.14, 3.65)	1.16 (0.64, 2.11)	3.16 (1.69, 5.92)	2.02 (1.07, 3.84)	2.34 (1.32, 4.13)	1.19 (0.63, 2.26)

Disclosure: K. Moisio, NIH, 2 ; **F. Eckstein**, NIH, 2, Chondrometrics GmbH, 3, Chondrometrics GmbH, 4, Paizer, MerckSerono, Novartis, Novo Nordisk, Wyeth, 5, Pfizer, MerckSerono, Eli Lilly, GlaxoSmithKline, Wyeth, Centocor, Novartis, 2 ; **A. Chang**, NIH, 2 ; **J. S. Chmiel**, NIH, 2 ; **O. Almagor**, NIH, 2 ; **P. Prasad**, NIH, 2 ; **W. Wirth**, Chondrometrics GmbH, 3 ; **S. Cahue**, NIH, 2 ; **M. Marshall**, NIH, 2 ; **L. Sharma**, NIH, 2 .

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Serum Levels of Inflammatory Markers, Knee Radiographic Osteoarthritis, and Knee Cartilage Loss in Older Adults. Changhai Ding[1], Flavia Cicuttini[2] and Graeme Jones[1], [1]University of Tasmania, Hobart, Australia, [2]Monash University, Melbourne, Australia

Purpose: The role of inflammation in osteoarthritis (OA) is unclear and the associations between serum levels of inflammatory markers and knee cartilage loss have not been reported.

Methods: A total of 172 randomly selected subjects (mean 63 years, range 52-78, 47% female) were studied at baseline and 2.9 years later. Serum high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were assessed by

radioimmunoassay. T1-weighted fat-suppressed MRI of the right knee was performed to determine knee cartilage volume. Knee radiographic osteoarthritis (ROA) was also assessed.

Results: At baseline, quartiles of IL-6 and TNF- α were associated with increased prevalence of medial tibiofemoral joint space narrowing (grade ≥1) in multivariate analyses (OR: 1.42 and 1.47 per quartile, respectively, both P<0.05). Longitudinally, baseline IL-6 (but not TNF- α) predicted loss of both medial and lateral tibial cartilage volume (β: -0.89% and -1.02% per annum per quartile, P<0.05 and P<0.01, respectively), which was independent on TNF- α. Change in IL-6 was associated with increased loss of medial and lateral tibial cartilage volume (β: -0.95% and -0.79% per annum per quartile, both P<0.05) and change in TNF- α was also negatively associated with change in medial and lateral tibial cartilage volume (β: -0.81% and -0.82% per annum per quartile, both P<0.05). Serum hs-CRP was not associated with ROA and cartilage loss.

Conclusion: Serum levels of IL-6 and, to a lesser extent, TNF- α are associated with knee cartilage loss in older people suggesting low level inflammation plays a role in the pathogenesis of knee OA.

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The Effect of Tears in Specific Meniscal Segments On Subregional Tibiofemoral Cartilage Thickness Loss in Knee OA. A. Chang[1], F. Eckstein[2], A. Guermazi[3], K. Moisio[1], J. S. Chmiel[1], O. Almagor[1], W. Wirth[2], P. Prasad[1], M. Marshall[1], S. Cahue[1] and L. Sharma[1], [1]Northwestern Univ, Chicago, IL, [2]Paracelsus Med Univ, Chondrometrics Gmbh, Salzburg, Austria, [3]Boston Univ, Boston, MA

Purpose: Meniscal (M) tears have been linked to knee OA progression, presumably via impaired load attenuation. How M tears influence OA pathogenesis is unclear; subregional examination may elucidate whether any impact is local. We tested if baseline medial M tear in a specific segment is associated with baseline-to-2 year cartilage thickness loss in subregions that the damaged segment overlies.

Method: Persons with knee OA by K/L ≥ 2 and symptoms had 1.5T MRI at baseline and 2 years later using double oblique coronal FLASH sequences, coronal T1-weighted spin-echo (SE), and sagittal fat-suppressed dual-echo turbo SE. M tears were graded separately (0-4, WORMS) for each segment [posterior horn (PH), body, anterior horn (AH)]. Mean cartilage thickness of 5 tibial (T) and 3 weightbearing femoral (F) subregions was determined using proprietary software. We used logistic regression with GEE to analyze the relationship between baseline tear (score ≥2) in each M segment and baseline-to-2 year cartilage thickness loss (of ≥5%), adjusting for age, gender, BMI, and M tear in the other two segments.

Results: Our sample consisted of 261 knees from 159 persons (66 yrs, BMI 30, 75% women). Table 1 shows the % of knees with M tears in each segment. The % knees losing cartilage in the medial T subregions was 33% (central), 36% (external), 20% (internal), 33% (anterior), and 28% (posterior), and in the F subregions was 36% (central), 33% (external), and 31% (internal). As in Table 2, baseline PH tear was significantly associated with T posterior subregion cartilage loss. Body tear was significantly associated with cartilage loss in the T central, external, and anterior subregions as well as F external subregion. There was no significant association between AH tear and cartilage thickness loss in any subregion.

Conclusion: Knees with medial M body tear had substantially increased odds of subsequent cartilage thickness loss in the subregions that the M body overlies, T external and F external, as well as in T central and anterior. PH tears were associated with T posterior region thickness loss. The lack of findings for AH tears may relate to the small numbers with tears in this segment. These findings suggest that at least some of the M tear effect is experienced locally.

Table 1. Medial Meniscal Tear Location (261 knees)

	PH	Body	AH	PH & body	AH & body	AH & PH	All segments	No tear
# (%) of knees	29 (11%)	10 (4%)	1 (0.4%)	40 (15%)	4 (2%)	0 (0%)	8 (3%)	169 (65%)

Table 2. Medial Meniscal Segment Tear Associated OR (95% CI) for Cartilage Thickness Loss in Medial Subregions (adjusted for age, gender, BMI, and tears in other meniscal segments)

Independent variable	T, central	T, external	T, internal	T, anterior	T, posterior	F, central	F, external	F, internal
PH tear	1.02 (0.50, 2.08)	0.97 (0.44, 2.13)	1.11 (0.47, 2.59)	0.57 (0.26, 1.27)	**2.63 (1.23, 5.62)**	1.58 (0.82, 3.04)	1.30 (0.63, 2.69)	0.54 (0.26, 1.16)
Body tear	**4.18 (1.80, 9.72)**	**5.39 (2.44, 11.88)**	1.19 (0.50, 2.82)	**3.22 (1.49, 6.96)**	0.95 (0.42, 2.11)	1.79 (0.89, 3.61)	**2.61 (1.20, 5.66)**	1.10 (0.46, 2.62)
AH tear	0.76 (0.23, 2.47)	1.39 (0.45, 4.31)	1.07 (0.25, 4.54)	0.86 (0.25, 3.00)	2.99 (0.83, 10.74)	0.48 (0.14, 1.73)	1.34 (0.39, 4.57)	1.55 (0.45, 5.30)

Disclosure: A. Chang, NIH, 2 ; **F. Eckstein**, NIH, 2, Chondrometrics GmbH, 4, Pfizer, MerckSerono, Novartis, Novo Nordisk, Wyeth, 5, Pfizer , MerckSerono, Eli Llly, GlaxoSmithKline, Wyeth, Centocor, Novartis, 2 ; **A. Guermazi**, BICL, LLC, 4, Synarc, Inc, 1, GE Healthcare, 2, MerckSerono, Facet Solutions, 5 ; **K. Moisio**, NIH, 2 ; **J. S. Chmiel**, NIH, 2 ; **O. Almagor**, NIH, 2 ; **W. Wirth**, Chondrometrics, GmbH, 3 ; **P. Prasad**, NIH, 2 ; **M. Marshall**, NIH, 2 ; **S. Cahue**, NIH, 2 ; **L. Sharma**, NIH, 2 .

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Active Appearance Modelling of DXA Images to Assess Severity of Osteoarthritis of the Hip. Rebecca J. Barr[1], Jennifer S. Gregory[1], Kanako Yoshida[1], Salvatore Alesci[2], Richard M. Aspden[1] and David M. Reid[1], [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Wyeth Research, Collegeville, PA

Purpose: The use of plain radiographs for the assessment of Osteoarthritis (OA) is well established. Our recent studies have found that new generation Dual Energy X-ray Absorptiometry (DXA) scanners, normally used for measuring Bone Mineral Density (BMD), produce images of sufficient quality to allow grading of OA severity using the Kellgren Lawrence (KLG) scoring system. We have also shown that Active Shape Modelling (ASM), a method for quantifying variations in the shape of the femur, can identify early onset and progression of hip OA from radiographs. The aim of this study was to develop this further by using Active Appearance Modelling (AAM) and DXA images to model not only the shape, but also the variation in image intensity (BMD distribution) within the femur.

Method: Sixty two subjects with hip OA were identified as having had a pelvic radiograph in the last 12 months using the local Radiology Information System, and invited to undergo a dual femur DXA scan using an iDXA scanner (GE Medical Systems). DXA images of each hip were graded using the KL system. An 85 point AAM template, that included the proximal femur, osteophytes, and parts of the pelvis, was applied to each image to provide a comprehensive model of the hip joint. Outputs from the AAM are independent “modes of variation” that describe changes in the shape of the hip and BMD distribution occurring together in the dataset. Correlations between the first 10 modes and KLG were assessed to identify modes likely to be of interest for assessing OA progression. These were then analysed using one-way ANOVA.

Results: Significant correlations were found between KLG and modes 2, 4 and 7 ($P < 0.001$, $r = 0.22 – 0.49$, Fig 1A). These modes reflected changes in BMD distribution, identifying common areas of sclerosis as well as changes in the shape of the femur, the pelvis and joint space narrowing (Fig 1B).Results were confirmed by one-way ANOVAs ($P < 0.001$).

Conclusion: Active Appearance Modelling can be used with DXA images to extend the ASM of the hip to collect information on BMD distribution. This additional information may further improve our ability to assess the early onset, severity and progression of hip OA.

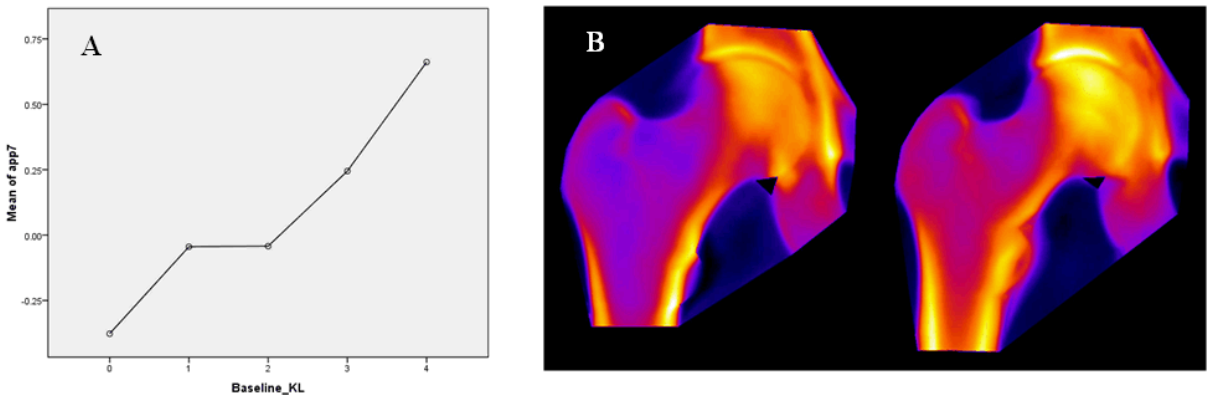

Fig. 1

Disclosure: R. J. Barr, TMRI Ltd, 2 ; **J. S. Gregory**, TMRI Ltd, 2 ; **K. Yoshida**, TMRI Ltd, 2 ; **S. Alesci**, Wyeth Research, 3 ; **R. M. Aspden**, TMRI Ltd, 2 ; **D. M. Reid**, TMRI Ltd, 2 .

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Is Severe Osteoarthritis of the Knee Heritable: A Population Based Study. Allen D. Sawitzke[1], Josep Vergés[2], Eulàlia Montell[2], Marta Herrero[2] and Daniel O. Clegg[3], [1]Univ of Utah, Salt Lake City, UT, [2]Bioibérica S.A., Barcelona, Spain, [3]University of Utah Medical Ctr, Salt Lake City, UT

Purpose: Osteoarthritis (OA) is the most common rheumatologic diagnosis and is increasing in frequency with the aging of the populace. OA of the knee arguably accounts for the largest clinical costs as knee replacement is common and effective medical therapies to slow progression have not been described. While genetic predispositions to OA, are described, different genetic underpinnings may predispose to specific disease presentations. Clinical trial design of agents for OA structural modification would benefit from identifying and recruiting individuals at highest risk of progression at a time when their disease is potentially modifiable. The first step in defining patients at high risk for disease progression is to better understand the heritability of OA and if it is strongly heritable, genetic biomarkers can be identified. Ideally, the approach to identifying patients at risk for rapidly progressive OA would concurrently provide insight into selection of persons for development of specific biomarkers and for enrollment into studies.

Method: A unique resource, the Utah Population Data Base (UPDB) was used to test the heritability of severe OA of the knee. The UPDB is a genealogic resource with records on more than 7.1 million individuals that are used to define patterns of genetic inheritance. For this study, severe OA of the knee cases were defined as persons who underwent total knee arthroplasty (TKA) for OA in Utah over the years of study as found by search of the statewide hospital discharge data (1996-2007) using billing coding. Whenever possible, the cases were mapped to UPDB pedigrees for further analysis. Measures of risk to relatives of 1, 2 and 3 degree to cases was calculated. Control families were randomly selected from the UPDB as well to allow the calculation of risk accounted for by genetic factors.

Results: Over 18,000 OA patients who underwent TKA in Utah hospitals were linked to the UPDB and analysis performed. 683 Founder families were identified who had at least 5 affected cases for analysis as multiplex families. Members of these families had 1.1 to 60.8 times the likelihood of having OA complicated by a TKA as did members of control families. The population attributable risk was 21%. Siblings of affected cases were most likely to be affected with a relative risk of 2.07, followed by parents (1.79), children (1.74) and more distant relatives. All relations closer than second cousins were statistically at increased risk. Interestingly, spouses were also statistically at increased risk (RR 1.33).

Conclusion: Severe OA of the knee pedigrees can be identified and the risk for TKA due to OA of the knee in these families shows a graded heritable effect for 1, 2 and 3 degree relatives of the cases. Carefull selection of and analysis of these families at highest risk may help to outline a unique strategy for a biomarker development and ultimately to define selection criteria for studies of structural modification in OA of the knee.

Disclosure: A. D. Sawitzke, Bioiberica S.A., 9 ; **J. Vergés**, Bioiberica S.A., 3 ; **E. Montell**, Bioiberica S.A., 3 ; **M. Herrero**, Bioiberica S.A., 3 ; **D. O. Clegg**, Bioiberica SA, 2 .

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Measures of Alignment in Knee OA: How Valid Are Clinical Methods?- Data From the Osteoarthritis Initiative. KD Gross[1], J. Niu[2], JP Goggins[2], TDV Cooke[3], MC Nevitt[4] and David T. Felson[5], [1]MGH Inst Health Prof, Boston, MA, [2]BUSM, Boston, MA, [3]Queens Univ, Kingston, ON, [4]UCSF, SF, CA, [5]Boston University School of Medicine, Boston, MA

Purpose: Standing long limb (LL) x-ray measures of Hip-Knee-Ankle (HKA) alignment provide valid information about load distribution and the likelihood of knee OA progression. In many clinics however, LL x-rays are unavailable and decisions about intervention to improve alignment are based on clinical measures whose validity is unknown. We determined the concurrent validity of clinical measures of standing knee alignment by comparing them to measures from LL x-rays.

Method: The Osteoarthritis Initiative (OAI) is a multi-center study that includes a progression subcohort of individuals with symptomatic knee OA. From this subcohort, bilateral fully extended LL x-rays were obtained as part of a 12-month follow-up exam. To these, we applied reference standard methods to measure HKA alignment in each knee (inter-rater ICC=0.98). At the same exam, clinical examiners used long-arm goniometers to obtain bilateral measures of standing tibiofemoral (TF) alignment (data from OAI public use data set). Varus angles were assigned negative values. We used Bland-Altman analysis to determine the limits of agreement between the two measures. Weighted kappa coefficients were calculated to assess agreement between categories of varus, neutral, and valgus alignment. While categories of varus, neutral, and valgus HKA alignment were defined according to traditional ≤-2º, -2º to 2º, and ≥2º cutpoints, a range of gender-neutral and gender-specific offset values were used to adjust TF measures before determining categorical agreement.

Results: 1175 subjects (55% female), mean age 62.0 +/- 9.2 yrs and mean BMI 29.6 +/- 4.7, contributed 2309 knees. Mean x-ray HKA alignment was -1.3º +/- 3.9º (range -16.0º, 17.9º). Mean clinical TF alignment was -0.2º +/- 4.1º (range -15.0º, 14.0º). On average, clinical alignment was 1.1º more valgus than x-ray alignment with 95% limits of agreement ranging from 6.3º more varus to 8.5º more valgus. At the highest level of categorical agreement (when clinically measured neutral alignment was defined as 1º to 3º in both genders), weighted kappa was only 0.36 (95% CI: 0.33, 0.39). When using a different offset for women and men, agreement did not rise substantially (weighted kappa=0.37, 95% CI: 0.34, 0.40). In 7.1% of knees, there was extreme disagreement between clinical and x-ray measures, such that one measure indicated varus while the other indicated valgus alignment (see table).

Table: Clinical vs. X-ray Alignment

X-ray HKA Alignment	**Clinical TF Alignment**			
# knees % knees	**Varus** (≤0º)	**Neutral** (1 to 3º)	**Valgus** (≥4º)	**Total**
Varus (≤-2º)	814 35.3	125 5.4	60 2.6	999 43.3
Neutral (-2º to 2º)	483 20.9	230 10.0	183 7.9	896 38.8
Valgus (≥2º)	103 4.5	90 3.9	221 9.6	414 17.9
Total	1400 60.6	445 19.3	464 20.1	2309 100.0

Conclusion: The 95% limits of agreement between clinical and x-ray alignment include important discrepancies of up to 8.5º. Despite adjusting clinical measures to maximize agreement in the categorization of varus, neutral, and valgus knees, the two methods agree only modestly.

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Patella Alta Is Associated with Patellofemoral Malalignment: The MOST Study. J.J. Stefanik[1], Y. Zhu[1], A.C. Zumwalt[1], K.D. Gross[2], M. Clancy[1], J.A. Lynch[3], L.A. Frey Law[4], C.E. Lewis[5], A. Guermazi[6], C.M. Powers[7] and David T. Felson[6], [1]BUSM, Boston, MA, [2]MGH Inst Health Prof, Boston, MA, [3]UCSF, San Francisco, CA, [4]UIowa, Iowa City, IA, [5]UAB, Birmingham, AL, [6]Boston University School of Medicine, Boston, MA, [7]USC, Los Angeles, CA

Purpose: Research on risk factors for patellofemoral joint (PFJ) osteoarthritis (OA) has focused on patellar malalignment (patellar tilt angle and lateral displacement or bisect offset) and trochlear morphology (sulcus angle). Patella alta (PA), a high riding patella, has received much less attention despite being a known risk factor for patellar subluxation and dislocation in young persons. Patella alta is measured on a lateral knee radiograph by the Insall-Salvati ratio (ISR), a ratio between the length of the patellar tendon and length of the patella. Subjects with higher ISRs are hypothesized to have increased patellar malalignment due to the lack of osseous stability when the patella articulates superior to the femoral trochlea. The purpose of this study was to determine the association between the ISR and measures of PFJ malalignment, specifically patellar tilt angle (PTA) and bisect offset (BO).

Methods: The MOST study is an NIH funded cohort study of persons aged 50-79 years with or at risk for knee OA. We measured the ISR on weight bearing and flexed lateral knee radiographs and PTA and BO on baseline knee MRIs in 486 knees, one knee per subject. PTA was defined as the angle between a line connecting the posterior femoral condyles and a line defining the maximal patellar width. BO is a measure of the percent of the patellar lateral to the midline of the trochlea. ANOVA was used to determine the association between quartiles of the ISR and BO and PTA in two separate analyses.

Results: The mean ISR was 1.10, mean BO 59.79%, and mean PTA 8.81 degrees. The mean age of the sample was 62, mean BMI 30, and 60% of subjects were female. The means for BO and PTA were 9.82 and 3.56 greater in the highest ISR quartile compared to those in the lowest ISR quartile (see table). Similar results were seen when adjusting for isokinetic knee extensor strength, age, sex, and BMI.

Conclusion: Our results support the hypothesis that high ISRs, indicative of patella alta, are associated with increased PFJ malalignment. Since the ISR is unlikely to change over time, patella alta may be an important risk factor for PFJ OA, as it may cause patellofemoral malalignment.Longitudinal studies are needed to determine if higher ISRs increase the risk for PFJ malaignment.

Insall-Salvati Ratio (ISR)

	Quartile 1	Quartile2	Quartile 3	Quartile 4	P for trend
	0.64-0.99	1.00-1.08	1.09-1.20	1.21-1.58	(continuous ISR)
	n=128 knees	n=106 knees	n=128 knees	n=124 knees	
	(low)			(high)	
Bisect Offset					
Mean (%)	55.98	58.76	58.60	65.80	<0.0001
Patellar Tilt Angle					
Mean (degrees)	7.54	8.17	8.34	11.13	<0.0001

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Persons with Patellofemoral Osteoarthritis Exhibit Increased Hip and Knee Moments During A Sit-to-Stand Task. Lisa T. Hoglund[1], Mary F. Barbe[2], Ann E. Barr[3], Howard J. Hillstrom[4], Margery A. Lockard[5], Jinsup Song[2], William R. Reinus[2] and Benjamin P. Heilman[6], [1]University of the Sciences in Philadelphia, Philadelphia, PA, [2]Temple University, Philadelphia, PA, [3]Thomas Jefferson University, Philadelphia, PA, [4]Hospital Special Surgery (HSS), New York, NY, [5]Drexel University, Philadelphia, PA, [6]Biomet Manufacturing Corporation, Warsaw, IN

Purpose: Patellofemoral (PF) osteoarthritis (OA) is common in middle-aged and older adults. Isolated radiographic PFOA has been reported in 24% of females and 15.4% of males ≥ 55 years. Increased joint stress is one factor in the development and progression of PFOA. Forceful quadriceps contraction with the knee in extreme flexion, e.g., during sit-to-stand (STS), produces high PF joint reaction force (JRF) and PF stress. Increased tibial abduction during STS was recently reported in persons with PFOA, a position reported to increase PF stress. The purpose of this study was to quantitatively examine the triplanar hip and knee kinetics during STS in persons with patellofemoral osteoarthritis.

Method: A cross-sectional study with 2 groups was conducted: subjects with bilateral, symptomatic, radiographic PFOA (PFOA) compared to asymptomatic subjects free from radiographic PFOA (control). Thirty-two adults (40-65 years) participated; 15 subjects remained after radiographic exclusions (30 lower extremities [LE]) with 8 in the PFOA group and 7 in the control group. Anthropomorphic and LE strength data were collected. Subjects performed STS from a stool at 110% knee height without hand use. Biomechanical data were collected in 3 anatomical planes with a Vicon 460™ system (5 cameras) and 2 Kistler™ force plates (one per foot). Hip and knee joint moments were normalized by body mass and examined at 4 events: Maximum (MAX), Minimum (MIN), Seat-Off (SO), and End of STS. The Temple University Institutional Review Board approved the protocol. A mixed model 2 factor ANOVA was used (group, limb); $\alpha = 0.01$.

Results: Increased hip and knee internal moments during STS were present in the PFOA group versus the control group. Hip extension (EXT), abduction (ABD), and external rotation (ER) moments were increased at the events of MAX, SO, and End of STS. Knee EXT and adduction (ADD) moments were increased at SO. Significant between-limb differences were present at the hip; the dominant (stronger) LE had increased ABD and ER hip moments at MAX and End. Significant group x limb interactions were found at the knee at MAX and End.

Conclusion: Increased knee EXT and ADD moments indicate that increased knee JRF are present during STS in persons with PFOA. The PF joint stress is likely to be increased and may be a factor in the progression or development of PFOA. Increased hip ABD and ER moments in the PFOA group may be a compensation to prevent "medial collapse" of the LE, reported in persons with PF pain syndrome and PFOA. This is the first study to report kinetics during STS in persons with PFOA. It indicates that increased hip and knee joint moments are associated with PFOA. Future research should examine interventions to decrease joint moments as a method of joint protection.

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Minimum Joint Space Width (minJSW) and Mean JSW at a Constant Location in Evaluating Joint Space Narrowing (JSN) in Medial Tibiofemoral Osteoarthritis (OA)-Data From the Osteoarthritis Initiative. Thierry Conrozier[1], Muriel Piperno[1], Kenneth D. Brandt[2], Marie-Pierre Hellio Le Graverand[3], D.J. Hunter[4] and Eric Vignon[5], [1]Lyon Sud University Hospital, Pierre Bénite, France, [2]Kansas Univ Medical Center, Fairway, KS, [3]Pfizer Inc., New London, CT, [4]NEBH, Boston, MA, [5]Claude Bernard University, Lyon, France

Purpose: Measurement of a change in the minimum JSW (minJSW) is widely used to evaluate JSN in knee OA. Measurement of mean JSW at a constant location has recently been suggested as an alternative. The purpose of this study was to compare both methods of measurement in terms of their reproducibility and sensitivity to change.

Method: Knee radiographs from a subset of subjects in the OA Initiative (OAI) (Clinical Datasets 0.1.1 and 1.2.1 and Image Release 0.C.1 and 1.C.1) were used in this analysis. MinJSW and mean JSW in each of 16 consecutive slices of the medial tibiofemoral compartment in films of the left knee of a subset of subjects from the OAI Progression Cohort were measured at baseline and 1-year, using HOLY's software (Lyon, France). The 16 slices comprised 70% of the distance between the tibial axis and inner non-osteophytic limit of the medial compartment. Slices were numbered 1–16, with Slice 1 the most medial. The slice that contained minJSW was determined in each film.

Results: ***JSW:*** In baseline films, radiograph quality limited the measurement of JSW in all 16 slices to 71.1% of knees. Notably, JSW measurement in Slices 1, 2 and 3 was possible in only 69.1, 76.1 and 87.0% of knees Reproducibility of minJSW measurement was much

greater than that for slice JSW: SD of test-retest difference was only 0.02 mm for minJSW, but 0.09 - 0.14 mm for Slices 3- 11 and 0.17 - 0.49 mm for innermost and outermost slices. The magnitude of the mean difference in JSW between KL0 (n= 21) and KL4 (n=24) decreased progressively from Slice 1 to 16. In Slices 1, 2 and 3 the difference in JSW between KL 0 and KL 4 was greater than the difference between KL 0 and 4 in minJSW (4.13, 3.59, 3.34 mm vs. 3.28 mm). The mean location of minJSW shifted from Slice 5 in KL 0 knees to Slice 3 in KL 4 knees (p=0.021).

***JSN*:** 1-year JSN was evaluated in 123 knee pairs. JSN was significant only in Slices 3, 4 and 5 of KL3 knees ($p<0.02$) and in Slices 5- 9 of KL4 knees ($p<0.005$). JSN was 0.15 ± 0.36 mm ($p=0.009$, SRM = 0.41) and 0.15 ± 0.41 mm ($p=0.016$; SRM = 0.39), respectively, for minJSW and for the best-performing slice (Slice 3). The location of minJSW did not vary significantly over the 1-year interval.

Conclusion: Comparison of KL0 and KL4 knees suggests that the largest decrease in JSW occurs in the innermost portion of the medial compartment. However, measurement of JSW at a constant location in this region was often not technically possible. MinJSW and Slice 3 JSW offered similar sensitivity to change over 1 year but Slice 3 JSW was less reproducible and frequently could not be measured accurately. Thus, minJSW appears to be preferable to Slice JSN for evaluation of JSN in a series of radiographs .

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Reduced Peripheral Nerve Function as a Risk Factor for Radiographic Knee Osteoarthritis. Sunil Abraham[1], C. Kent Kwoh[2], Robert M. Boudreau[1], Michael J. Hannon[1], Michael C. Nevitt[3], Anne B. Newman[1], Annemarie Koster[4], Suzanne Satterfield[5], Tuhina Neogi[6] and Elsa S. Strotmeyer[1], [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh, VA Pittsburgh Healthcare System, Pittsburgh, PA, [3]University of California, San Francisco, San Francisco, CA, [4]National Institute on Aging, Bethesda, MD, [5]University of Tennessee, Memphis, TN, [6]Boston Univ Schl of Med, Boston, MA

Purpose: Neural deficits are postulated to play a role in the etiology of knee osteoarthritis (KOA), but few studies have examined this. One study with a small sample size has suggested an association between decreased vibratory perception threshold in the lower extremities and KOA.

We hypothesized that reduced peripheral nerve function would be associated with radiographic KOA (RKOA) in community dwelling older adults in a nested case control substudy of the Health Aging and Body Composition (Health ABC) cohort.

Method: The Health ABC Study is a longitudinal cohort of 3075 ambulatory, community-dwelling elderly aged 70-79 years at 1997-98 entry. The KOA substudy within Health ABC obtained fixed-flexion knee x-rays on participants who reported knee pain (most days of a month in the past year or moderate or worse WOMAC pain with any activity in past 30 days) at the Year 2 visit as well as a sample of controls without pain by this definition. Peripheral nerve function was assessed on the index (right if possible) leg at the Year 4 visit using peroneal motor nerve conduction studies (amplitude and velocity), 1.4-g and 10-g monofilament testing at the great toe, and average vibration threshold (quantitative sensory method) at the great toe in the index leg. RKOA was defined as a Kellgren-Lawrence grade ≥ 2 on fixed-flexion knee x-rays.

Multivariable logistic regression was used to determine the association of nerve function measures with knee OA with, while adjusting for height, weight, depression, age, race, gender, and diabetes.

Results: The sample of Health ABC participants with any peripheral nerve function testing and a knee x-ray (n = 978) was 60% women, 55% white, and 74+SD years of age; with a mean weight of 76+SD kg and a mean height of 1.65+SD m. The bivariate results comparing differences in peripheral nerve function in participants with RKOA vs. those without RKOA is summarized in Table 1.

Table 1	+ROA		-ROA		p-values
	Mean	(SD)	Mean	(SD)	
Peroneal motor nerve conduction velocity					
Amplitude (mV)	3.6	(1.9)	3.7	(1.7)	0.28
Nerve conduction velocity (m/s)	43.9	(5.5)	43.6	(5.5)	0.40

Average Vibration threshold (microns)	55.8	(37.9)	49.6	(34.9)	0.01
Monofilament testing	N	(%)	N	(%)	
Neither	30	(9.68)	54	(8.36)	0.75
10g	125	(40.32)	257	(39.78)	
1.4g	155	(50.00)	335	(51.86)	

Only reduced vibratory sense was significantly associated with an increased odds of RKOA in MV models. Adjusted OR=1.20 (95%CI: 0.84-1.3) per SD increase of vibration threshold.

Conclusion: In an elderly community-dwelling cohort, higher vibration thresholds, but not other measures of nerve function, were associated with greater odds of RKOA, supporting a possible role for large afferent nerve fiber dysfunction in the etiopathogenesis of knee OA. Further studies are needed to elucidate this relationship.

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Relationship Between Self- Reported Comorbidity and Health Status in Early OA: The CHECK Study. Janet Wesseling[1], Sita MA Bierma- Zeinstra[2], Joost Dekker[3], Johannes WJ Bijlsma[4] and on behalf of CHECK study group, [1]University Medical Center, Utrecht, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]VU University Medical Center, Amsterdam, Netherlands, [4]University Medical Center, Utrecht

Purpose: Osteoarthritis (OA) is the most common diagnosis made in older patients with knee or hip pain in primary care. The prevalence of many other disabling conditions rises with age, and some chronic conditions can be found together with OA. An important question is to whether comorbidity and the presence of specific diseases impairs the clinical status of patients with early OA. The objective is to describe the relationship between comorbidity and the health status of participants with early osteoarthritis.

Method: In the Netherlands a prospective 10-year follow-up study was initiated by the Dutch Arthritis Association with participants with early OA related complaints of hip and/or knee: CHECK. Inclusion criteria were pain and/or stiffness of knee and/or hip, age 45- 65 years, and had never or not longer than 6 months ago visited the general practitioner for these symptoms for the first time. The WOMAC was utilized to measure pain, stiffness, and limitations in activities. Physical functioning and mental functioning were measured by SF-36, a generic measure of self-reported health related quality of life (HRQL). The presence of chronic disease was assessed with a standard consensus based list (self- reported health module of Statistics Netherlands), which consists of 24 diseases and disorders. It was investigated if the number of comorbidities influenced outcome and if specific conditions from this score had an effect beyond the comorbidity score.

Results: In CHECK 1002 participants were included, a mean age of 56 years, mean BMI of 26 kg/m^2 and 79% female. Over 64% of the included participants had comorbidity: severe disorders of neck, shoulder, elbow, wrist or hand (23%), hypertension (20%) and severe or persistent back disorder (18%) being most prevalent. After controlling for age, gender, and BMI, participants with more comorbidities had more pain (beta 0,5; $p \leq 0{,}001$), limitation in activities (beta 2,2 ; $p \leq 0{,}001$) and a worse health related quality of life (HRQL) (beta -2,2; $p \leq 0{,}001$). Beyond the score, results (controlling for age, sex, BMI) show that back disorder has the most negative effect on pain and function. Disorders of elbow, shoulder, wrist, or hand have the most negative effects on HRQL (Physical function subscale). On the contrary, participants with hypertension reported less pain and disability when controlling for the number of diseases.

Conclusion: The number of comorbidities deteriorates the health status of participants with complaints of early OA. Next to this, specific disease, like severe back disorder, further increases pain and impairs function. Also disorders of neck, elbow, shoulder, wrist or hand decrease the physical function in HRQL.

Disclosure: J. Wesseling, None; **S. M. Bierma- Zeinstra**, None; **J. Dekker**, None; **J. W. Bijlsma**, None.

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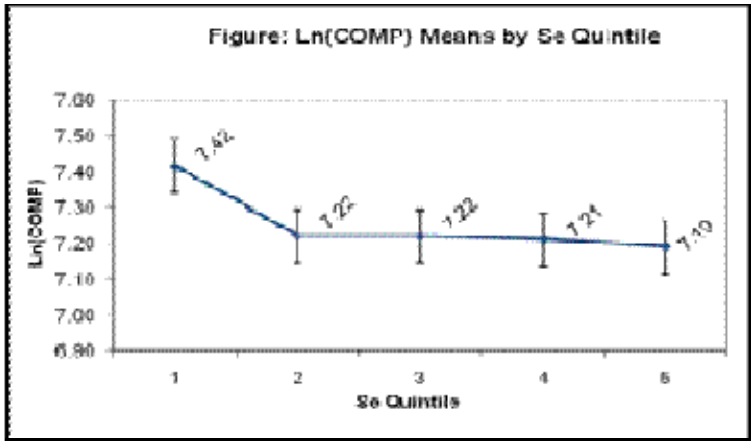
Selenium and Biomarkers of Joint Tissue Metabolism in a Community-Based Cohort: The Johnston County Osteoarthritis Project.

S. Addison[1], X. Shi[2], Todd A. Schwartz[3], V.B. Kraus[4], T. Stabler[5], C.G. Helmick[6] and J.M. Jordan[7], [1]University of North Carolina, Chapel Hill, NC, [2]Thurston Arthritis Research Center, Chapel Hill, NC, [3]The University of North Carolina, Chapel Hill, NC, [4]Duke University Medical Center, Durham, NC, [5]Duke University Medical Center, Durham, [6]Centers for Disease Control and Prevention, Atlanta, GA, [7]UNC, Chapel Hill, NC

Purpose: Selenium (Se) is an essential trace element required for the reduction of antioxidant enzymes that may be important in osteoarthritis (OA). We have observed that low Se levels are associated with radiographic osteoarthritis (rOA). The objective of this analysis was to examine associations between toenail Se levels and various putative OA biomarkers reflecting specific metabolic processes that may be influenced by Se level.

Method: A cross-sectional analysis was performed on 678 participants (36.6% African American; 48.8% male; mean age 63.7 (10.2) years) from the Johnson County Osteoarthritis Project to determine the association of Se with 6 biomarkers: cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), two markers of collagen turnover (C2C and CPII), and two markers of bone degradation (CTX-II and NTX-I). Toenail Se was measured by Instrumental Neutron Activation Analysis and mass spectroscopy. Biomarkers were measured by enzyme-linked immunosorbent assays. Spearman correlation coefficients were calculated between Se and the natural logarithm of each biomarker, as well as ln C2C/CPII, a ratio that reflects net collagen degradation or synthesis. Separate linear regression models were used to explore these associations, adjusting for age, gender, race, body mass index, and current smoking status. In addition, mean biomarker levels were calculated for each Se quintile and plotted with 95% confidence intervals.

Results: Mean Se levels were 0.80 ppm (range 0.31-2.10). In linear regression models, Se was correlated with ln COMP ($r = -0.15$, $p = <0.0001$). There was a borderline association between Se and ln NTX-I ($r = 0.07$, $p = 0.076$), but no significant association with ln HA, ln CTX-II, ln C2C, ln CPII, or ln C2C/CPII. Mean ln COMP was significantly higher in those in the first Se quintile (7.42 ppm) when compared to the other four Se quintiles (7.19-7.22 ppm) (Figure). Compared to the highest quintile of Se (quintile 5), the p-values for the effect of the other Se quintiles (quintiles 1-4) on ln(COMP) are 0.001, 0.763, 0.663, and 0.765.



Conclusion: Se levels were inversely associated with ln COMP, suggesting that cartilage and/or bone turnover may be the specific metabolic process linking low Se to rOA. The effect of Se appears limited to those in the lowest quintile, mirroring our prior findings in rOA. This suggests that Se deficiency may be important in OA, but that increases in Se levels above repletion may not have a significant impact.

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Morphological Variations in Hip Shape: Validation of New Hip Measurement Software and Provisional Association with Total Hip Replacement-The Chingford Study. Alexander S. Nicholls[1], Harinderjit Gill[2], Tom Pollard[3], Debbie Hart[4], David W. Murray[5], Andrew Carr[6], TD. Spector[4], Amit Kiran[7] and Nigel K. Arden[8], [1]University of Oxford, Oxford, OX2 6HG, United Kingdom, [2]University of Oxford, [3]University of Oxford, Oxford, United Kingdom, [4]St Thomas Hospital, London, United Kingdom, [5]Univeristy of Oxford and Nuffield Orthopaedic Centre, WIndmill Rd, OX3 7LD, United Kingdom, [6]Oxford University, Oxford, OX3 7LD, United Kingdom, [7]Oxford University, United Kingdom, [8]Oxford University, Oxford, United Kingdom

Purpose: Over the past decade measures of hip morphology, including femoroacetabular impingment (FAI), have been recognised as a biomechanical risk factors for individuals who develop osteoarthritis (OA) in the hip. Few studies have examined this in combination with pelvic morphology in a cohort of healthy volunteers with prolonged follow-up. The present study validates a new software process that quantifies morphologoical parameters of the hip and pelvis.

Method: We developed a software program that measures 24 morphological parameters in the pelvis, acetabulum and proximal femur. We tested inter-user reproducibility by 4 trainee orthopedic surgeons (OS) measuring the same 10 blinded radiographs. Intra-user reproducibility was measured by one trainee OS measuring 10 blinded radiographs on three separate occasions.

We performed a nested case-control study using women from a well-described cohort of 1003 women who were recruited in 1989 and followed up for 20 years. A group of 45 age-matched individuals (aged 50-59 years at baseline; 15 total hip replacements & 30 controls) were randomly selected. Pelvis radiographs taken at study-year 2 were analyzed for variations in hip morphology using the new software. These measurements were correlated with current total hip replacement (THR) records, which were used as a clinical end-point for end-stage OA.

Result: Most morphological measures were reproducible, with the exception of horizontal toit externe (HTE). The alpha-angle was significantly greater in the cases than the controls (67.9 vs 49.4; $p = 0.002$). The Gosvig triangular index was positive in 50% of the caes and 0% of the controls ($p < 0.001$). In all other measurements, there were no significant differences between cases and controls.

	Inter-User Variability (Coefficient of Variation, %)	Intra-User Variability (Coefficient of Variation, %)
Alpha-angle	6	4
Femoral neck length	2	7
Femoral neck width	3	1
Femoral neck-shaft angle	1	1
Lateral centre edge angle (Wiberg Angle)	6	4
Extrusion Index	6	4
Horizontal Toit Externe	106	15

Conclusion: This software reproducibly measures a wide variety of hip morphological parameters. In this provisional nested case-control study, the alpha angle and Gosvig triangular index are strongly associated with future need for THR. This software allows us to look for interactions between these morphological parameters and subsequent formation of additive OA risk pathways.

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Prevalence of Femoral Neck Protuberance On Hip MRI in a Swiss Male Population: A Cross-Sectional Study. Stephan Reichenbach[1], Peter Jüni[1], Stefan Werlen[2], Eveline Nüesch[1], Christian W. Pfirrmann[3], Sven Trelle[1], Reinhold Ganz[1] and Michael Leunig[4], [1]University of Bern, Bern, Switzerland, [2]Hospital Sonnenhof, Bern, Switzerland, [3]University Hospital Balgrist, Zurich, Switzerland, [4]Schulthess Clinic, Zurich, Switzerland

Purpose: Based on experimental and clinical studies, femoro-acetabular impingement was proposed to cause early osteoarthritis (OA) in the non-dysplastic hip. Femoro-acetabular impingement usually occurs as one of two different types, either 'cam' or 'pincer'. Cam impingement is predominantly seen in males, and is caused by the presence of a femoral neck protuberance (FNP) with a non-spherical femoral head and/or a decreased anterior head-neck offset. The increased radius of the femur entering the acetabulum results in decreased joint clearance with repeated shearing forces occurring between the femoral neck and the acetabular rim during flexion and internal rotation. The aim of this study was to determine the prevalence of FNP as a potential risk factor for hip OA in a population-based inception cohort study of young males.

Method: Study subjects were consecutively recruited young males undergoing conscription for the Swiss army, which is required for all citizens regardless of their health status. Participants completed a set of questionnaires pertaining to pain, stiffness, and physical function, and internal rotation was measured reliably using a newly developed examination chair. A random sample of the examined participants was subsequently invited to obtain magnetic resonance images (MRI) of the hip. FNP was assessed semiquantitatively using scores from grade 0 to grade 3: 0=normal, 1=mild, 2=moderate, 3= severe FNP. Overall prevalence estimates with 95% confidence intervals (95% CI) accounted for the oversampling of participants with decreased (<30°) and increased (≥40°) internal rotation using posts-stratification weights. Prevalence of different grades of FNP was calculated separately for participants with decreased, normal (≥30° and <40°) and increased internal rotation.

Results: Subjects who underwent imaging included 244 asymptomatic participants with a mean age of 19.9 years and a mean body mass index of 23.1 kg/m^2. Grade 1 FNP was found in 112 MRIs, grade 2 in 54 MRIs, and grade 3 in 13 MRIs. The prevalence of definite FNP (grade ≥ 2) was 0.24 (95% CI 0.19 to 0.30). FNP was more prevalent in participants with decreased internal rotation compared to normal or increased internal rotation (table 1, p-value for trend < 0.001).

Conclusion: Definite femoral neck protuberance on MRI can be found in every fourth young asymptomatic male individual, and in every second participant with decreased internal rotation. Table1: Prevalence of femoral neck protuberance in the general male population

	No. of MRI examined	**MRI with femoral neck protuberance grade≥2**	**Prevalence (95% CI)**
Overall	**244**	**67**	**0.24 (0.19 to 0.30)**
IR < 30°	83	40	0.48 (0.37 to 0.59)
30° ≤ IR < 40°	81	17	0.21 (0.13 to 0.31)
40° ≤ IR	80	10	0.13 (0.06 to 0.22)

IR: internal rotation

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ACR Poster Session A

Pediatric Rheumatology - JIA, Uveitis, Autoinflammatory Diseases, Education

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Interim Safety Data of Gardasil® in a Trial in Females with JIA and Seronegative Arthritis. Nora G. Singer[1], Michelle Wallette[2], Ingrid Tomanova-Soltys[3] and Gina Montealegre-Sanchez[3], [1]University Hospitals/Case Medical Center and Rainbow Babies & Childrens Hospital, Cleveland, OH, [2]University Hospitals/Case Medical Center, Cleveland, OH, [3]University Hospitals/Case Medical Center and Rainbow Babies and Children's Hospital, Cleveland, OH

Purpose: The purpose of the study is to assess the efficacy and safety of Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine Recombinant (qHPV vaccine) in females age 9-26 who have been diagnosed with juvenile idiopathic arthritis or seronegative inflammatory arthritis including SEA syndrome, psoriatic arthritis, anyklosing spondylitis and inflammatory bowel disease related arthritis are eligible for an open-label, Phase IV clinical trial. We hypothesized 9-26 y.o. females with inflammatory arthritis will have protective responses following qHPV vaccine. Measurement of serum mean geometric titers is planned. The purpose of this abstract is to report the safety profile of qHPV vaccine the 22 patients enrolled to date. We further hypothesized that qHPV vaccine would have an acceptable safety profile in this population despite concerns that the vaccine could trigger arthritis flare.

Method: This trial is actively enrolling. Data are descriptive and are taken from adverse event reporting during the conduct of the study.

Results: 22 adverse events (AE) in 13 patients were reported. No serious adverse events were reported. One AE, a vasovagal reaction was considered to be study related. AEs that were possibly related included: achiness (1), fever (1), fatigue (1), headache (1), dizziness (2) light-headed (2), arthralgia (1), exacerbation patellar enthesitis (1), arm stiffness (1). AEs considered not to be study related included: common cold (4), thrush (1), varicella zoster infection (1), flu symptoms (1), rash (1), sinusitis (1), whiplash (1).

Conclusion: Vaccination with qHPV vaccine in the first 22 subjects has been associated with AEs but not SAEs. Among AEs associated with vaccination, vasovagal reaction was considered study related. AEs that were possibly associated included stiffness in the extremity where vaccine was administered, mild exacerbation of underlying enthesitis and limited constitutional symptoms. Practices regarding the recommendation and use of qHPV vaccine in females with inflammatory arthritis vary within the rheumatology community. Our data indicate an acceptable safety profile for subjects participating in an open label Phase IV clinical trial of qHPV vaccine. Information regarding the efficacy of this vaccine is likely to impact medical decision-making of practitioners who counsel patients regarding vaccination and patients and their parents who will decide whether or not to undergo vaccination.

Disclosure: N. G. Singer, Merck , 2 ; **M. Wallette**, None; **I. Tomanova-Soltys**, None; **G. Montealegre-Sanchez**, None.

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Immunologic Responsiveness in Patients with JIA On Methotrexate and Etanercept: Candida Skin Test and Tetanus Vaccination. Ankur Kamdar[1], Patricia C. Giclas[2] and Barry L. Myones[1], [1]Baylor College of Medicine, Houston, TX, [2]National Jewish Health, Denver, CO

Background: There is a paucity of data regarding response to vaccinations in patients with JIA treated with methotrexate (MTX). It is also unclear whether newer biologic agents affect vaccination response.

Purpose: To investigate delayed hypersensitivity response and vaccination response to protein (secondary) and polysaccharide (primary) in these patients.

Method: Patients with a diagnosis of polyarticular JIA on stable doses of NSAIDS and/or MTX were enrolled into this prospective study. All patients received 0.5cc Td vaccine IM, 0.5cc Pneumovax (23-valent) subcutaneously, and 0.1cc Candida antigen (1:100) intradermal skin test. Serum samples were obtained at time of vaccination and after 4-6 weeks. Tetanus toxoid (TT) titers were measured by standard EIA. Positive response was considered a 2-fold increase in titer (4-fold responses also reported), 0.10 IU/ml was considered a clinically protective titer by the clinical laboratory. Patients were educated on how to measure a Candida skin test response, and were asked to mail in the results. 10mm diameter erythema and/or induration reaction was considered positive. Serum samples were subjected to C4 allotyping, complement and Ig levels to examine alternative causes for non-response.

Results: 50 patients were included for primary analysis in this study. 3 additional patients were excluded because of reaction to vaccination requiring steroid treatment. Patients were subdivided into MTX and non-MTX groups for analysis. 38 patients were on MTX (including 16

on MTX + etanercept), and 12 patients were on NSAIDS (n=9) or no medications (n=3). For the Candida skin test, results for 38 patients were available for analysis. 92% (n=35) had a positive skin test. All 3 non-responders were in the MTX group with 1 on MTX and etanercept. The serologic response rate (2-fold increase) for Tetanus vaccination was 82% and 75% and was similar to vaccine failure in normals. The post geometric mean titers (GMT) were significantly different at 8.82 IU/ml (95% CI 6.41, 12.1) and 12.34 IU/ml (95% CI 7.61, 20) for the MTX and non-MTX group respectively ($p<0.001$). Additional analysis revealed significantly higher pre-vaccination TT titers in those that did not respond to the vaccination ($p=<0.0001$). Of 16 patients on both MTX and etanercept, 93% responded to Candida skin test and 87% responded to tetanus vaccination. If a positive response is defined as a 4 fold increase, the serologic response rate for Tetanus vaccination was 66% and 66% for both groups (69% for the MTX + etanercept group).

Conclusion: Tetanus vaccination appears safe and effective in patients with JIA on background of both methotrexate and etanercept. Methotrexate use in patients with JIA does not appear to impair delayed hypersensitivity response or secondary response to protein vaccination although post GMT differences suggest a slightly decreased level of response with patients on methotrexate. Continued investigation is ongoing to evaluate polysaccharide response in this cohort.

Disclosure: A. Kamdar, None; **P. C. Giclas**, None; **B. L. Myones**, None.

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Analysis of Intracellular Methotrexate Polyglutamates in Juvenile Idiopathic Arthritis. M. L. Becker[1], L. van Haandel[2], A. S. Lasky[1], M. F. Hoeltzel[1], J. E. Neal[1], C. N. Palmer[1], J. F. Stobaugh[2] and J. S. Leeder[1], [1]Children's Mercy Hospitals and Clinics, Kansas City, MO, [2]University of Kansas, Lawrence, KS

Purpose: Recently, intracellular MTX polyglutamates ($MTXglu_n$) have been shown to be potentially useful biomarkers of response in adult RA patients. We aimed to measure total intracellular MTX glu_{TOT} concentrations in a cohort of JIA patients and determine predictors of $MTXglu_{TOT}$ variability and association with outcome.

Methods: After obtaining informed consent, 5 ml of blood was obtained from JIA patients maintained on a stable dose of MTX for 3 months or longer. Demographic characteristics, efficacy and toxicity outcomes were collected by chart review. $MTXPG_{1-7}$ in RBC lysates were quantitated using an innovative ion-pairing chromatographic procedure with mass spectrometric detection with improved sensitivity and specificity over existing HPLC separation followed by photochemical/fluorescence detection methods.

Results: Patients (n=85; 61 female) from a single center aged 10.1 ± 4.5 years (mean ± SD; range 1.5 to 19.5 yr) were included in the analysis. Mean MTX dose was 0.51 ± 0.25 mg/kg/dose (range 0.11 to 1.05 mg/kg/dose) for a median of 19 months (range 3 to 156 months). MTX was given SC in 54 (64%) subjects; 50 (59%) subjects had active arthritis.

Total intracellular $MTXglu_n$ ($MTXglu_{TOT}$) concentrations varied 40-fold, from 4.80nmol/L to 210.3nmol/L (median 75.5nmol/L), in our cohort. Concentrations of $MTXglu_{1-7}$ were measured individually and as a percentage of each patient's $MTXglu_{TOT}$. $MTXglu_6$ and $MTXglu_7$ concentrations were detected in 68 and 15 patients, respectively. $MTXglu_3$ was the most prominent subtype identified, comprising 41±10.3% of $MTXglu_{TOT,}$ and was most highly correlated with $MTXglu_{TOT}$ (r =0.96). Principal components and cluster analyses revealed that $MTXglu_{1+2}$ and $MTXglu_{3-6}$ formed two internally correlated subgroups, and $MTXglu_{3-6}$ correlated highly with $MTXglu_{TOT}$ (r=0.94). $MTXglu_{1+2}$ constituted 38.1 ± 19.5% of $MTXglu_{TOT}$ (range 5.2 to 92.9%).

Bi-variable analyses revealed the following were associated with $MTXglu_{TOT}$: age, weight, mg/kg dose, months on MTX, NSAID use and MTX route. Multivariable analyses with inclusion of these variables in the model resulted in only mg/kg dose ($p=0.03$), route ($p=0.01$), and months of MTX ($p=0.03$) remaining significant predictors of $MTXglu_{TOT}$ variability. Months on MTX had a negative association. Response to MTX (no active arthritis) was not associated with $MTXglu_{TOT}$ or any individual absolute $MTXglu_n$ concentration, however, responders tended to have higher proportions of $MTXglu_1$ ($p=0.04$) and lower proportions of $MTXglu_4$ ($p=0.04$).

Conclusion: In our cohort of JIA patients, $MTXglu_{TOT}$ varied 40-fold, but only 32% of this variability was attributed to dose, route and duration of treatment. Longer use of MTX was associated with lower intracellular $MTXglu_n$ levels. Up to $MTXglu_7$ was detected by our analysis, not previously reported. Unlike adults, long chain $MTXglu_n$ absolute concentrations were not associated with response to MTX, however, the proportion of glutamate substrates differ between responders and non responders and may be worthy of further investigation.

Disclosure: M. L. Becker, Kansas City Area Life Sciences Institute Research Grant, 2, Children's Mercy Hospital Young Investigator Grant, 2, Katherine B. Richardson Foundation Grant, 2 ; **L. van Haandel**, None; **A. S. Lasky**, None; **M. F. Hoeltzel**, None; **J. E. Neal**, None; **C. N. Palmer**, None; **J. F. Stobaugh**, None; **J. S. Leeder**, Kansas City Area Life Sciences Institute, 2 .

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Effect of Route of Administration On Intracellular Methotrexate Polyglutamate Patterns in Juvenile Idiopathic Arthritis. M. L. Becker[1], R. Gaedigk[1], L. van Haandel[2], A. S. Lasky[1], M. F. Hoeltzel[1], J. E. Neal[1], C. N. Palmer[1], J. F. Stobaugh[2] and J. S. Leeder[1], [1]Children's Mercy Hospitals and Clinics, Kansas City, MO, [2]University of Kansas, Lawrence, KS

Purpose: The effects of methotrexate (MTX) in adults and children are unpredictably variable. The addition of glutamates to intracellular methotrexate ($MTXglu_n$) has been shown to enhance intracellular drug retention and folate pathway enzyme inhibition and may be a promising predictor of drug response. In JIA, the proportions of $MTXglu_{1-7}$ may be more important than absolute concentrations in association with drug response. We evaluated differences in demographics, genotype, and outcomes in 2 subgroups of JIA patients exhibiting specific patterns of MTX polyglutamation.

Methods: After obtaining informed consent, 5 ml of blood was obtained from JIA patients on a stable dose of MTX for 3 months. Demographic characteristics, efficacy and toxicity outcomes were collected by chart review. Genomic DNA was extracted from 200µl of whole blood and amplified in gene specific PCR reactions. An innovative ion-pairing chromatographic procedure with mass spectrometric detection was developed for the detection of $MTXPG_{1-7}$ in patient RBCs.

Results: JIA patients (n=85) from a single center were included in the analysis. Hierarchical clustering of the proportions of $MTXglu_{1-5}$ was performed. $MTXglu_{6-7}$ were excluded due to their relative minimal concentrations. Two distinct clusters were identified: group 1 (n=50) had low proportions of $MTXglu_{1+2}$ and high proportions of $MTXglu_{3-5}$ and group 2 (n=35) had high proportions of $MTXglu_{1+2}$ and low proportions of $MTXglu_{3-5}$. Bi-variable analyses revealed group 1 had a higher mean MTX dose (0.56mg/kg/dose vs. 0.44mg/kg/dose, p=0.02), had higher mean $MTXglu_{TOT}$ (92 nMol/L vs. 66.1, p=0.01) and were more likely to be dosed via the SC route (90% vs 26%, p<0.0001). Notably, of the patients on SC dosing, 83% were in group 1; and of the patients on oral dosing, 84% were in group 2. When all significant variables were entered into a multivariable regression model, only route remained significantly associated with subgroup (p<0.0001, 95% CI -2.22, -0.96). No differences were noted in demographics, outcome or genotype between the groups. Within each group, there were responders and nonresponders defined by the presence of active arthritis. There were no statistically significant differences between responders and nonresponders within groups, except for a higher liklihood of receiving an anti-TNF medication in the patients with active arthritris within group 2 (p=0.01).

Conclusion: Different routes of MTX administration were associated with opposite proportions of intracellular $MTXglu_n$, with higher proportions of long chain MTX polyglutamates ($MTXglu_{3-5}$) seen in patients using the subcutaneous route, and higher proportions of shorter chain polyglutamates ($MTXglu_{1+2}$) seen in patients using the oral route. There are likely additional factors contributing to therapeutic response beyond intracellular $MTXglu_n$ patterns. This observation may be better explained with additional measurements of intracellular folate polyglutamate concentrations and SNP combinations to determine other potential factors which may drive glutamation patterns intracellularly.

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High Prevalence of Methotrexate-Related Gastrointestinal Side Effects in Children with Juvenile Idiopathic Arthritis. Maja Bulatovic[1], Marloes Heijstek[1], Marleen Verkaaik[1], Pieter Van Dijkhuizen[1], Wineke Armbrust[2], Esther Hoppenreijs[3], Sylvia Kamphuis[4], Carin Rademaker[1], Toine Egberts[1], Gerben Sinnema[1], Wietse Kuis[1] and Nico Wulffraat[1], [1]University Medical Centre Utrecht, Utrecht, Netherlands, [2]University Medical Centre Groningen, Netherlands, [3]University Medical Centre st. Radboud Nijmegen, Netherlands, [4]Erasmus Medical Centre Rotterdam, Netherlands

Purpose: Methotrexate (MTX) is the most commonly used disease-modifying anti-rheumatic drug in children with juvenile idiopathic arthritis (JIA). A major drawback of MTX is the induction of gastrointestinal side effects in many JIA patients. Gastrointestinal complaints,

termed MTX intolerance, occur upon intake as well as prior to and when thinking of MTX. The latter two aspects are probably the result of a classical conditioning reaction. Intolerance to MTX could lead to refusal and premature discontinuation of an otherwise very efficacious drug. The aim of this study was to determine the prevalence of MTX intolerance in a large cohort of JIA patients.

Method: We performed a cross-sectional study in 283 JIA patients between 4 and 18 years of age from four University Medical Centres in the Netherlands. In order to establish MTX intolerance, all patients filled in a previously validated questionnaire consisting of five domains: abdominal pain, nausea, vomiting, oral pain and behavioural problems. Each domain contained three questions, pertaining to a respective complaint upon intake, prior to (anticipation) and when thinking (association) of MTX. Behavioural problems consisted of restlessness, crying, irritability and refusal of MTX. A patient could score 0 (no complaints), 1 (mild), 2 (moderate) or 3 (severe) points on each question. A patient with a total score of ≥5 with ≥1 point on anticipatory and/or associative complaints or ≥1 point on behavioural problems was considered intolerant to MTX. Analysis was performed with the SPSS statistical package.

Results: We evaluated 283 questionnaires. Hundred and fifty-five patients (54.8%) exhibited MTX intolerance independently of the route of administration. Out of 206 patients on oral MTX, 49.5% experienced intolerance, whereas a significantly higher percentage was intolerant to the drug if on subcutaneous (s.c) MTX, namely 68.8% out of 77 patients (p=0.006). Further analysis of patients intolerant to MTX in each domain separately revealed that significantly more patients showed behavioural problems and had vomiting complaints if on s.c. MTX.

Conclusion: The prevalence of MTX intolerance is high. Although it is present in patients on both oral and s.c. MTX, it is significantly higher in patients on s.c. MTX. This striking finding suggests a strong classical conditioning component in the development of MTX intolerance. Cognitive-behavioural therapy could be effective in reducing MTX intolerance. Currently we are performing a randomised multicentre trial comparing the effect of cognitive-behavioural therapy on MTX intolerance with either a switch to s.c. MTX or continuation of oral MTX.

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Predictors of Hip Disease in Systemic Juvenile Idiopathic Arthritis (S-JIA). Michelle Batthish, Pascal N. Tyrrell, Rayfel Schneider and Brian Feldman, The Hospital for Sick Children, Toronto, ON

Purpose: Hip involvement occurs in 20-40% of all JIA cases. Patients with S-JIA are affected most frequently. The aim of this study is to investigate the predictors of clinical hip disease and radiographic hip damage in S-JIA.

Method: The medical records of all children (n = 101) with S-JIA – seen at The Hospital for Sick Children – from 1997 to 2007 were reviewed. 59 patients met the inclusion criteria and were further examined: (1) satisfied the ILAR classification criteria for S-JIA; (2) were first seen within 3 months of symptom onset; and (3) were followed for at least 6 months. Potential clinical and laboratory predictors were examined at presentation, and at 3 and 6 months. Clinical data included: fever, S-JIA rash, hepatomegaly or splenomegaly, lymphadenopathy, and arthritis. Laboratory data comprised: hemoglobin, leukocyte count, platelet count, ESR, serum albumin concentration, and quantitative immunoglobulin concentrations. To account for censored observations, we used survival analysis.

Results: During the study period, 59 children (32 girls) met our inclusion criteria. The mean age at diagnosis was 7.8 years and the mean duration of follow up was 4.3 years. 30 (51%) developed clinical hip disease; with 9 (15%) developing radiographic evidence of hip damage. The median time to develop clinical hip disease was 24 months. Gender and age at diagnosis did not predict time to develop hip disease. At presentation, patients in whom clinical hip disease later developed had large joint involvement (HR=1.22, p=0.0001), elevated IgG (HR=1.12, p=0.01) and IgM (HR=2.71, p=0.02) levels and higher CHAQ scores (HR=1.65, p=0.02). 3 months after disease onset, the 3 factors that were most predictive of hip disease were leukocytosis (HR=1.19, p=0.0009), an elevated IgG (HR=1.14, p=0.04) and the CHAQ score (HR=2.24, p=0.005). At 6 months, large joint involvement was most predictive for hip disease (HR=1.15, p=0.004). Given the small number of patients who developed radiographic evidence of hip damage, no significant predictors were found.

Conclusion: About half of S-JIA patients will develop hip disease within 2 years of diagnosis. Early presentation with large joint involvement, higher inflammatory markers and more marked disability predict an earlier development of hip disease. The early identification of an increased risk of hip disease in patients with S-JIA might suggest earlier, more aggressive interventions to prevent joint destruction.

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Distinction of a Psoriatic Subset Within a SoJIA Clinic Population. Brandt P. Groh, Jennifer Lindenmuth, Barbara E. Ostrov, Catherine A. Bingham and Lisabeth V. Scalzi, Hershey Medical Center, Hershey, PA

Purpose: SoJIA is a somewhat heterogeneous disease process in terms of initial presentation and disease course over time. In our clinic population, 12 SoJIA patients have also been diagnosed with psoriatic rash, raising the question as to whether these patients might be more correctly classified as psoriatic arthritis with systemic onset.

Methods: All patients diagnosed with SoJIA onset between July 1991 and May 2009 were included. All patients met the ILAR SoJIA diagnostic criteria. There were 53 patients total: 12 in the "psoriatic" group, and 41 in the "classic" group. Clinical exam findings, lab findings and course details of interest were tabulated for comparison between the two groups. Intergroup differences were tested for significance by nonparametric statistical methods.

Results: Patients in the psoriatic group presented initially in a manner indistinguishable from the classic group. Both groups were comparable in age, sex and race distribution. The only significant differences in the disease course between the groups were the frequent development of enthesitis ($p < 0.0001$) and non-cervical spine axial involvement ($p < 0.0001$) in the psoriatic group. These disease features were not present near onset, and only became apparent later in the disease course of the psoriatic patients. There were no significant differences comparing presence of rash near onset, development of macrophage activation syndrome (MAS), family history of psoriasis in 1st or 2nd degree relatives, duration of the systemic phase, or duration of active arthritis between the two groups. Lab studies throughout indicated a comparable inflammatory response in both groups. Only peak ferritin values were significantly different ($p = 0.0018$), the psoriatic group mean of 5,810 mg/dL (CI 3231, 8389) being higher than the classic group mean of 1,995 mg/dL (CI 1255, 2735). There we no significant differences in ESR, CRP, ASO, ANA, PTT, fibrinogen, platelets, WBC and hemoglobin values at disease onset.

Conclusion: We describe a subset of soJIA patients who developed psoriasis. By clinical course, the psoriatic group was distinct from the other soJIA patients in the development of enthesitis and non-cervical spine axial involvement. Higher mean ferritin values in the psoriatic group did not translate into any increased incidence of MAS, but perhaps a larger population of similar patients would be disproportionately affected by this complication. Based on cytokine profiles and disease course, SoJIA is perhaps best classified as an autoinflammatory disorder. Psoriatic arthritis might also be autoinflammatory in some cases, based on the demonstration of substantial genetic overlap with autoinflammatory disorders (Arthritis & Rheum, 2006;58:2142-6). Although now clinically defined as a unique disorder, SoJIA may prove to be the final common pathway for at least two autoinflammatory disorders.

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FSTL-1 Is Elevated in the Serum and Synovial Fluid of Patients with Systemic Juvenile Idiopathic Arthritis. David C. Wilson, Anthony D. Marinov, Yury Chaly and Raphael Hirsch, Childrens Hospital of Pittsburgh, Pittsburgh, PA

Purpose: Follistatin-like protein 1 (FSTL-1) is a secreted glycoprotein that is over-expressed in rheumatoid arthritis (RA) synovium. We have previously demonstrated a pro-inflammatory role for FSTL-1 in arthritis by showing that over-expression of FSTL-1 exacerbated murine collagen-induced arthritis (CIA) while its neutralization suppressed CIA. We also demonstrated that FSTL-1 over-expressed in the joint of mice with CIA and humans with rheumatoid arthritis. The current study was designed to determine whether FSTL-1 might represent a novel biomarker in juvenile idiopathic arthritis (JIA).

Methods: A sandwich type immunoassay was developed for detection of FSTL-1 protein using the Meso Scale Discovery (MSD) assay platform. Sera from patients with oligoarticular (n=27), polyarticular (n=10), and systemic (n=9) JIA were assayed and compared to sera from normal children (n=13). We also assayed FSTL-1 in synovial fluids from patients with oligoarticular (n=41), polyarticular (n=18), and systemic (n=12) JIA. These were assayed and compared to synovial fluid from normal arthritic children (n=4).

Results: The mean FSTL-1 serum titer in systemic JIA patients was increased 20% over that of controls ($p=0.004$ by Student's T-test). Synovial fluids had a mean FSTL-1 serum titer 5-fold higher than that of serum. FSTL-1 synovial fluid titer in polyarticular and systemic JIA was increased 2 fold over that of non-arthritic synovial fluid ($p=0.04$ and $p=0.005$, respectively, by Student's T-test).

Conclusion: The high levels of FSTL-1 in the synovial fluid, compared to the blood, suggests that it plays a role in the local inflammatory response in the joint and may be a novel biomarker of disease severity and course. Studies to address this possibility are currently underway.

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Rapid and Sustained Remission of Macrophage Activation Syndrome (MAS) Associated with Systemic-Onset Juvenile Idiopathic Arthritis (SoJIA) by Treatment with Anakinra but without Cyclosporine. Normi Bruck, Juliane Hamel, Meinolf Suttorp, Manfred Gahr and Frank Pessler, Technical University Dresden Children's Hospital, 01307 Dresden, Germany

Purpose: To describe the dramatic response of two patients with MAS associated with SoJIA to treatment with Anakinra and a corticosteroid, but without cyclosporine.

Methods: We established a protocol for the treatment of MAS associated with SoJIA, allowing for a two week trial of Anakinra and a corticosteroid as initial treatment. Inclusion criteria: SoJIA as defined by the International League of Associations for Rheumatology classification of juvenile idiopathic arthritis (1) and MAS as defined by Ravelli et al. (2).

Results: Between September 2008 and March 2009, two patients met entry criteria.

Patient 1 was an 8-year-old Caucasian boy. At initial diagnosis of SoJIA, treatment with prednisolone and indomethacin led to almost complete resolution of clinical symptoms and normalization of laboratory abnormalities. However, during the prednisolone taper he suddenly developed thrombocytopenia and a dramatic rise in liver transaminases, ferritin, and D-dimers, accompanied by a paradoxically mild elevation of ESR and CRP. A bone marrow aspirate (performed after a 3 day methylprednisolone pulse) showed reduced cellularity and dysfunctional maturation in myelopoiesis, but no hemophagocytosis, but the patient nonetheless satisfied criteria for SoJIA-associated MAS (2). Treatment with oral prednisolone (2 mg/kg/day) and Anakinra (2 mg/kg/d s.c.) led to resolution of fevers and restoration of the patient's sense of well being within 3 days. All lab values normalized within 20 days. At 6 months follow-up, the patient remains in complete remission on monotherapy with Anakinra (2 mg/kg/d s.c.).

Patient 2 was a 12-year-old Caucasian girl. SoJIA-associated symptoms and laboratory abnormalities improved initially under treatment with prednisolone and ibuprofen. At the beginning of the prednisolone taper, the patient developed recurrent fevers, hepatosplenomegaly, general lymphadenopathy, pancytopenia with complete agranulocytosis, and highly elevated ferritin, D-dimer, LDH, ASAT, ALAT, and GGT levels. The bone marrow aspirate showed hemophagocytosis and complete absence of granulopoiesis. Treatment with dexamethasone (10 $mg/m^2/d$) led to a decrease in serum ferritin and liver transaminases, but did not affect fever or agranulocytosis. The patient defervesced within 48 h of starting Anakinra (2 mg/kg/d s.c.), and the granulocyte count normalized within 7 days. All other laboratory indices normalized within 14 days despite a dexamethasone taper. 14 weeks later, complete remission has been sustained on Anakinra monotherapy at a stable dose of 2 mg/kg/d.

Conclusion: Early initiation of IL-1 directed therapy may be effective for the treatment of MAS and could reduce the necessity for potentially toxic long-term treatment with corticosteroids, cyclosporine and/or etoposide.

References:
(1) Petty E.R. et al., J Rheumatol. 2004; 31:390-392
(2) Ravelli A. et al., J. Pediatr. 2005; 146:598-604

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Patterns of Non-Steroidal Anti-Inflammatory Drug Use for Juvenile Idiopathic Arthritis in the Era of Modern Aggressive Treatment. Rabina Kochar[1], Steven J. Spalding[2], Anil Jain[2], Kyle M. Walsh[3] and Philip J. Hashkes[2], [1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Yale University School of Public Health, New Haven, CT

Purpose: To describe trends in NSAID use for JIA and explore factors associated with anti-inflammatory use of NSAIDs by conducting a retrospective cohort study of treatment of patients with JIA.

Method: Through our electronic health record (EHR) system, we identified all individuals seen in pediatric rheumatology from 1/2003 to 6/2008 with a diagnosis of JIA. Subjects were excluded if they did not meet criteria for JIA or were seen only for a second opinion. Of 377 eligible patients, 100 were randomly selected for detailed analysis (EHR measureable characteristics not significantly different than the entire cohort, including medication use). Longitudinal data was extracted through a combination of manual review and automated extraction from the EHR. Background demographics and disease type data were collected, and data for disease activity status (number of active joints, joints with LOM, CHAQ score, pain score, physician assessment, inflammatory labs), medication use (NSAIDs, and other JIA medications) and adverse events were collected for each outpatient encounter. Longitudinal data were analyzed for factors predictive of NSAID use at an anti-inflammatory dose using Nonlinear Mixed Effects Regression analysis accounting for intra-subject correlation.

Results:

	N=100	
	N	**n**
DEMOGRAPHICS		
Sex (Female)	66	--
Ethnicity (Caucasian)	87	--
Oligoarticular	49	--
Systemic	5	--
Polyarticular RF-	25	--
Polyarticular RF+	2	--
Enthesitis-related	6	--
Psoriatic	6	--
Other	7	--
MEDICATIONS	Ever used	Used at last visit
NSAID any dose	90	40
NSAID anti-inflammatory	40	19
Methotrexate	58	42
Other DMARD	14	4
Biologic	17	17
Intra-articular Injection	45	--
Oral Corticosteroids	11	3

56% of patients were in a state of inactive disease and 20% had one active joint at last visit. NSAID use decreased by >50% over the study period. Less than 50% of NSAID users used at an anti-inflammatory dose. Factors associated with anti-inflammatory use included year of visit (OR = 0.605 for each subsequent year since 2003; p = 0.0076), number of joints with active arthritis (OR = 1.26 per joint; p = 0.0047), number of joints with limitation of motion (OR = 1.12 per joint; p = 0.0189), uveitis (OR = 0.013; p = 0.0078), and use of MTX (OR = 0.053; p = 0.023). The number of patients on biologics was not sufficient to analyze their effect on NSAID use.

Conclusion: While NSAIDs were used at some point by nearly all patients, only a minority ever used NSAIDs at an anti-inflammatory dose. This proportion of all types of NSAID use significantly decreased over time. Reduced anti-inflammatory use was associated with decreased disease activity, use of MTX, and treatment of isolated uveitis. The role of NSAIDs in treating JIA has changed markedly since past literature reports from the 1990s.

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Performance of the RA Disease Activity Measures and JADAS in Polyarticular-Course Juvenile Idiopathic Arthritis. Sarah Ringold[1], Rachel Bittner[1], Tuhina Neogi[2], Carol A. Wallace[1] and Nora G. Singer[3], [1]Seattle Children's Hospital, Seattle, WA, [2]BUSM, Boston, MA, [3]University Hospitals/Case Medical Center/Rainbow Babies and Children's Hospital, Cleveland, OH

Purpose: To measure the abilities of the continuous measures of disease activity used in rheumatoid arthritis (RA) and the 3 Juvenile Arthritis Disease Activity Scores (JADAS-10, JADAS-27, JADAS-71) to classify the Pediatric ACR measures of response, flare, and inactive disease (ID) in polyarticular-course JIA (poly JIA).

Method: Secondary analysis of a randomized, controlled trial of infliximab in poly JIA (n=97). Disease activity was calculated at baseline and weeks 14, 28, and 52 using the DAS (Disease Activity Score), DAS28, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and JADAS. Pediatric ACR response, flare, and ID were assessed contemporaneously. The ability of each continuous disease activity measure to classify each pediatric outcome was determined by area under receiver operating characteristic curves (AUC). The AUC of each of the scores for each of the outcomes were compared using empirical estimation methods. Positive predictive values (PPV) for ID were calculated by determining the maximum PPV value for which both the sensitivity and specificity were >= 0.5.

Results: The mean DAS, DAS28, CDAI, and SDAI at study entry were 3.46, 4.41, 27.22, and 29.55, corresponding to moderate (DAS/DAS28) and high (CDAI/SDAI) disease activity. At 52 weeks, mean values for each score corresponded to low/minimal disease activity. The AUCs for each pediatric outcome ranged from 0.73-0.94. The PPV of these scores for ID were 0.56-0.65. The mean JADAS-10, -27, and -71 at study entry were 20.6, 24.3, and 30.5. At 52 weeks, mean values for each score were 8.1, 8.6, and 9.7. The AUCs for each pediatric outcome ranged from 0.75-0.97. The PPV of these scores for ID were 0.83-0.86. The JADAS-10 had statistically significantly higher AUCs for the Pediatric ACR50, 70, and 90 measures than the SDAI, CDAI, JADAS-27, and JADAS-71 (95% CI: 0.01-0.20). The 3 JADAS also had statistically significantly higher AUCs for ID than the SDAI and CDAI (95% CI: 0.01-0.06). The AUC for the JADAS-27 and -71 for flare were statistically significantly higher than those of the DAS28 (95% CI: 0-0.13).

Conclusion: Each of the RA measures and JADAS versions showed good ability to classify participants based on the Pediatric ACR measures, flare, and ID in this specific cohort. There were some statistically significant differences between the scores AUC for the Pediatric ACR measures, flare, and ID, and the clinical significance of each of these comparisons requires additional exploration. Misclassification of active versus inactive disease by the RA scores and JADAS versions was not uncommon. Modification of these scores will be required if they are to be used to detect accurately both change in disease activity and ID.

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Pilot Study of the Illness Perception Questionnaire-Revised (IPQ-R) in Children with Juvenile Idiopathic Arthritis (JIA). Alexandra I. Barsdorf[1], Kathleen M. Schiaffino[2], Lisa F. Imundo[3] and Deborah M. Levy[4], [1]Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center, New Yok, NY, [2]Fordham University Graduate School of Arts & Sciences, Bronx, NY, [3]Morgan Stanley Children's Hospital of NY-Presbyterian, New York, NY, [4]Columbia University, New York, NY

Purpose: The way in which a child or adolescent comes to understand and form beliefs about his/her illness is called illness representation. Little research exists on how children and adolescents with a chronic disease, such as juvenile idiopathic arthritis (JIA), cognitively represent their illness. The goal of this pilot was to determine if the Illness Perception Questionnaire –Revised (IPQ-R) could be used to assess illness representations in children and adolescents with JIA who are 10 – 20 years old. The IPQ-R has been adapted for use in several chronic adult diseases, including asthma, chronic pain, diabetes, HIV, hypertension, and rheumatoid arthritis, but has not been tested for use with children or adolescents with JIA.

Methods: The IPQ-R was administered to 15 children recruited from a pediatric rheumatology clinic. The questionnaire was revised by substituting the term “JIA” in place of the term “my illness”. In addition, symptoms specific to JIA were added to the Identity list, and causes specific to JIA were added to the Causal subscale. Feedback was elicited using a semi-structured interview. Children were asked

"Tell me what you think about this questionnaire. Do you think it was easy or hard to answer?" and "What words did you find difficult to understand?"

Results: Internal consistency coefficients greater than .60 were found to be acceptable for IPQ-R subscales and were retained in the questionnaire. Chronbach alphas obtained included .63 for Personal Control, .81 for Timeline Acute/Chronic, .81 for Illness Coherence, .84 for Consequences, and .88 for Emotional Representations. . The domain "Treatment Control", demonstrated and alpha of .56 and .67 when item #19 ("There is very little that can be done to improve my arthritis") was deleted. Timeline Cyclical had an unacceptable reliability of .34. Reliability was not calculated for Causal items because of the small sample size.

Qualitative feedback demonstrated that children had minimal or no difficulty understanding questions on the IPQ-R. Average time to complete the questionnaire was approximately 13 minutes. Younger subjects (aged 10-12 years) required further explanation of the words "permanent, temporary, consequences, depressed, hereditary, germ, virus, financial consequences, immune system, and mental attitude".

Conclusion: The IPQ-R, with minor changes, is easily understood and completed by children and adolescents with JIA, and it can be used to accurately assess perceptions of illness. Results demonstrate that children and adolescents with JIA form illness representations along the same illness dimensions as adults with a chronic disease. Modifications to the IPQ-R for use in this population should include deletion of the Timeline Cyclical domain and item #19.

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Feasibility Testing of An Online Self-Management Program for Adolescents with Juvenile Idiopathic Arthritis (JIA): A Pilot Randomized Controlled Trial. Jennifer N. Stinson[1], Patrick J. McGrath[2], Ellen E. Hodnett[3], Brian Feldman[1], Ciaran M. Duffy[4], Adam Huber[2], Lori B. Tucker[5], Ross Hetherington[1], Shirley ML. Tse[1], Lynn R. Spiegel[1], Sarah SC. Campillo[4], Navreet K. Gill[1] and Meghan White[1], [1]The Hospital for Sick Children, Toronto, ON, [2]IWK Health Centre, Halifax, NS, [3]University of Toronto, Toronto, ON, [4]Montreal Children's Hospital, Montreal, QC, [5]BC Childrens Hospital, Vancouver, BC

Purpose: To determine the feasibility of a 12-week internet-based self-management program of disease specific information, self-management strategies and social support with telephone support for youth with JIA and their parents aimed at improving their quality of life.

Method: A single-blinded pilot RCT was conducted to test the feasibility of the "Teens Taking Charge: Managing Arthritis Online" internet intervention across 4 tertiary level centres in Canada. Accrual rates were high ranging from 45% to 68% of eligible subjects at each site. Participants comprised 48 adolescents with JIA ages 12 to 18 years and one of their parents who were randomized to the attention control arm (n=24) or the internet intervention (n=24).

Results: There were no significant differences between groups on age (Mean=14.5 years ± 1.48), gender (86.7 % female), disease severity (Mean = 2.2 ± 2.3 rated on 10 cm VAS), onset subtype, or disease duration (Mean = 6.6 years ± 4.6) at baseline. Attrition rates were 4.2% (n=1, went into remission) and 16.7% (n=2 after randomization and n=2 during Week 1 due to problems accessing website) respectively from the control and intervention groups. 83.3% of participants randomized to experimental group completed all 12 online modules and weekly phone calls with coach in an average of 14.7 weeks (SD=2.08). Control group completed 90% of weekly attention control phone calls. Participants received a mean of 1.4 phone calls to maintain attention control contact and the experimental group received an average of 1.6 phone calls per week. Intervention group participants felt the website content, videos and weekly calls with coaches were very helpful. Two-thirds of participants found the email system helpful; while only half found the discussion board helpful. 94.1% of participants rated the website as easy to use and would recommend the website to other families. Overall participants liked the website finding it "very helpful", "straightforward" and "easy to navigate".

Conclusion: This pilot RCT was the crucial first step in ensuring the feasibility of an internet-based self-management treatment for adolescents with JIA. Findings from this study will be used to lay the ground work for a large scale multi-centered RCT to determine the effectiveness of the online self-management intervention in improving health-related quality of life and symptoms (physical and emotional) in youth with JIA.

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Are Children with Juvenile Idiopathic Arthritis and Their Parents Reliable Reporters of Joint Involvement? Giovanni Filocamo, Angela Pistorio, Marta Bertamino, Alessandro Consolaro, Cristina Ferrari, Stefano Lanni, Bianca Lattanzi, Alessandro Parodi, Nicolino Ruperto, Alberto Martini and Angelo Ravelli, Pediatria-II, IRCCS G. Gaslini and University of Genova, Genova, Italy

Background: Quantitative joint counts are key outcome measures in children with juvenile idiopathic arthritis (JIA). However, assessment of the whole joints in all patients is time consuming and may be difficult in a busy clinical setting. Self or proxy-report of joint involvement, may help the physician to obtain information on the severity and distribution of arthritis.

Purpose: To investigate the reliability of self or proxy-report of joint involvement by children with JIA and their parents.

Methods: 220 children with JIA and 465 parents of children with JIA were asked to score the swelling or pain in 9 joints or joint groups. Afterward, a paediatric rheumatologist performed a formal joint assessment. Agreement between physician, parent, and child was assessed with Cohen's kappa.

Results: Table shows the k values for agreement in joint assessment between physicians, parents and children.

Joint	**k MD-parent**	**k MD-child**
Shoulder	0.15	0.15
Elbow	0.51	0.38
Wrist	0.41	0.47
Hand joints	0.52	0.52
Hip	0.28	0.33
Knee	0.54	0.59
Ankle	0.57	0.56
Foot joints	0.56	0.34
Cervical spine	0.35	0.69

Conclusion: Agreement between physicians and children and between physicians and parents was similar. Agreement was in the moderate range for all joints, except for the shoulder and hip, for which concordance was poor. Children agreed with physicians better than their parents in rating involvement of cervical spine. Overall, our results highlight the importance of obtaining children's' and parent's rating of joint disease but do not indicate that children's' and parent's assessment is a good surrogate for physicians' assessment.

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The Impact of Time From Symptom Onset to First Pediatric Rheumatology Visit On Quality of Life and Functional Status in Canadian Children with Juvenile Idiopathic Arthritis (JIA). NJ Shiff[1], LB Tucker[1], J. Guzman[1], KG Oen[2], R. SM Yeung[3], CM Duffy[4] and ReACCh-Out Investigators, [1]BC Children's Hospital, Vancouver, BC, [2]University of Manitoba, Winnipeg, MB, [3]Hospital for Sick Children, Toronto, [4]Montreal Children's Hospital, Montreal, QC

Purpose: The impact of time from JIA symptom onset to a child's first pediatric rheumatology (PR) visit on functional status and health related quality of life were explored in a multicentre inception cohort of patients with newly diagnosed JIA, the Research on Arthritis in Canadian Children Emphasizing Outcomes (ReACCH-Out).

Method: ReACCH-Out patients enrolled within 2 weeks of presentation to PR were included if dates of symptom onset, first PR visit, and 6 mo follow up (FU) were recorded. Parents completed the Childhood Health Assessment Questionnaire (CHAQ), and the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) at enrolment and 6 mo FU. The area under the curve (AUC) from onset to 6 month FU was calculated. Independent variables associated with CHAQ and JAQQ over time (identified in multivariable linear regression analyses) and previously identified potential confounders were entered as covariates into 2 final models in which time from symptom onset to first PR visit was the primary independent variable and AUC was the dependent variable.

Results: Eighty-two patients from the current cohort were included. Exploratory analyses, which excluded time to first PR visit, showed that the number of active joints at enrolment and enthesitis had the strongest association with AUC for both CHAQ and JAQQ. Table 1 shows the results for the final regression models with time to first PR as an independent variable and other associated factors as covariates.

Conclusion: Longer time from symptom onset to first PR visit is associated with reduced functional status and health related quality of life in children with JIA as measured by the CHAQ and JAQQ, even after adjusting for other associated factors, including the number of active joints at enrolment and the presence of enthesitis.

	CHAQ (n=82, R^2=0.37)			JAQQ (n=78, R^2=0.43)		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Onset to 1st PR*	10.09	(5.26, 14.91)	<0.001	17.72	(9.90, 25.54)	<0.001
Active joints*	8.27	(4.05, 12.49)	<0.001	12.05	(5.42, 18.67)	0.001
History of fever	6.32	(-10.56, 23.20)	0.46	14.11	(-13.04, 41.28)	0.30
History of limp	1.79	(-8.16, 11.74)	0.72	12.58	(-3.16, 28.32)	0.12
Enthesitis	9.77	(-6.32, 25.45)	0.23	19.08	(-3.52, 41.67)	0.10
South Asian	-0.94	(-17.07, 15.18)	0.91	8.43	(-19.00, 35.86)	0.54
Parental University or Postgrad	0.61	(-9.29, 10.51)	0.90	-3.64	(-19.09, 11.82)	0.64

Table 1. Coefficients for AUC regression models for the CHAQ and JAQQ. PR=first pediatric rheumatology visit, active joints are at first PR visit, *coefficients=ln(variable)

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Predictors of Poor Growth in Early JIA: Results From the Childhood Arthritis Prospective Study (CAPS). MH Obeysekera[1], S.D. Lal[2], M. Lunt[1], E. Baildam[3], L. Wedderburn[4], A. Chieng[5], J. Gardner-Medwin[6], M. Friswell[7], Helen Foster[8], J. Davidson[6], W. Thomson[9] and K. Hyrich[9], [1]arc Epidemiology Unit, Manchester, United Kingdom, [2]ARC Epidemiology Unit, Manchester, United Kingdom, [3]Royal Liverpool Children's Hospital, Liverpool, United Kingdom, [4]UCL, London, United Kingdom, [5]Royal Manchester Children's Hospital, Manchester, United Kingdom, [6]Royal Hospital for Sick Children, Glasgow, United Kingdom, [7]University of Newcastle, Newcastle, United Kingdom, [8]Newcastle University, Newcastle upon Tyne, United Kingdom, [9]University of Manchester, Manchester, United Kingdom

Purpose: Juvenile Idiopathic Arthritis (JIA) has been associated with poor growth, particularly in children with severe disease, although these data have been based primarily in retrospective studies. The aim of this analysis was to study the height, change in height and factors associated with poor growth in an inception cohort of children with JIA over the first 2 years of disease.

Method: The analysis included children with JIA participating in the CAPS study, which recruits and follows children <16 years with new onset arthritis from five UK tertiary referral centres. Heights at presentation and at 2 years were standardised using normative data from the World Health Organisation and presented as z-scores. Height velocity was calculated using change in height over the first 2 years of follow-up. Factors associated with height at baseline (BL), year 2 (Y2) and growth over the 2 years were modelled using linear regression models. Covariates included age, gender, disease duration, subtype, JIA core outcome variables, and treatment.

Results: 304 children were included (median age 7.9 years (IQR 4.0-11.3) at first presentation, 68% female, 5% systemic, 54% oligoarthritis, 18% rheumatoid factor negative polyarthritis). 89% had normal height (height z-score greater than -2 standard deviations) at BL and at Y2 although median height was slightly below the population mean (median z-score BL -0.30 (IQR -0.92, 0.48), Y2.-0.36 (IQR -1.11, 0.35)); 4% developed new short stature at 2 years. At BL and at Y2, lower height z-scores were strongly associated with younger age (βcoeff 0.065 (95% CI 0.034, 0.096) per year increase) and higher Childhood Health Assessment Questionnaire (CHAQ) scores (βcoeff -0.304 (95% CI -0.499, -0.109) per unit increase CHAQ) at first presentation. There was an inverse relationship between younger age at onset and height velocity ($p< 0.001$). Patients with lower height velocity were also found to have a higher active ($p=0.018$) and limited ($p=0.005$) joint count at the end of the 2 year period. Children who required treatment with methotrexate or biologics were more likely to have short stature, although this effect disappeared after allowing for differences in disease severity.

Conclusion: This study demonstrates that the majority of children presenting with JIA in the modern era have normal height over the first 2 years of disease. However, younger age at onset and higher disease activity were associated with poor growth, even within the first 2 years of disease. Continued follow-up of these children will indicate if modern therapies can maintain height in children with JIA.

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Balance in Juvenile Idiopathic Arthritis. KM Houghton[1] and M. MacLeod[2], [1]British Columbia Childrens Hos, Vancouver, BC, [2]BC Children's Hospital, Vancouver, BC

Purpose: Clinical observation suggests children with lower extremity arthritis have poor proprioception, demonstrated by difficulty balancing on one leg or single leg hopping. This is corroborated by studies in adults showing decreased proprioception in inflammatory and degenerative arthritis. To date there are no studies looking at balance in children with juvenile idiopathic arthritis (JIA). The objective of this study was to evaluate and describe dynamic postural balance using the Biodex Balance System® (BBS) in a cohort of children with JIA.

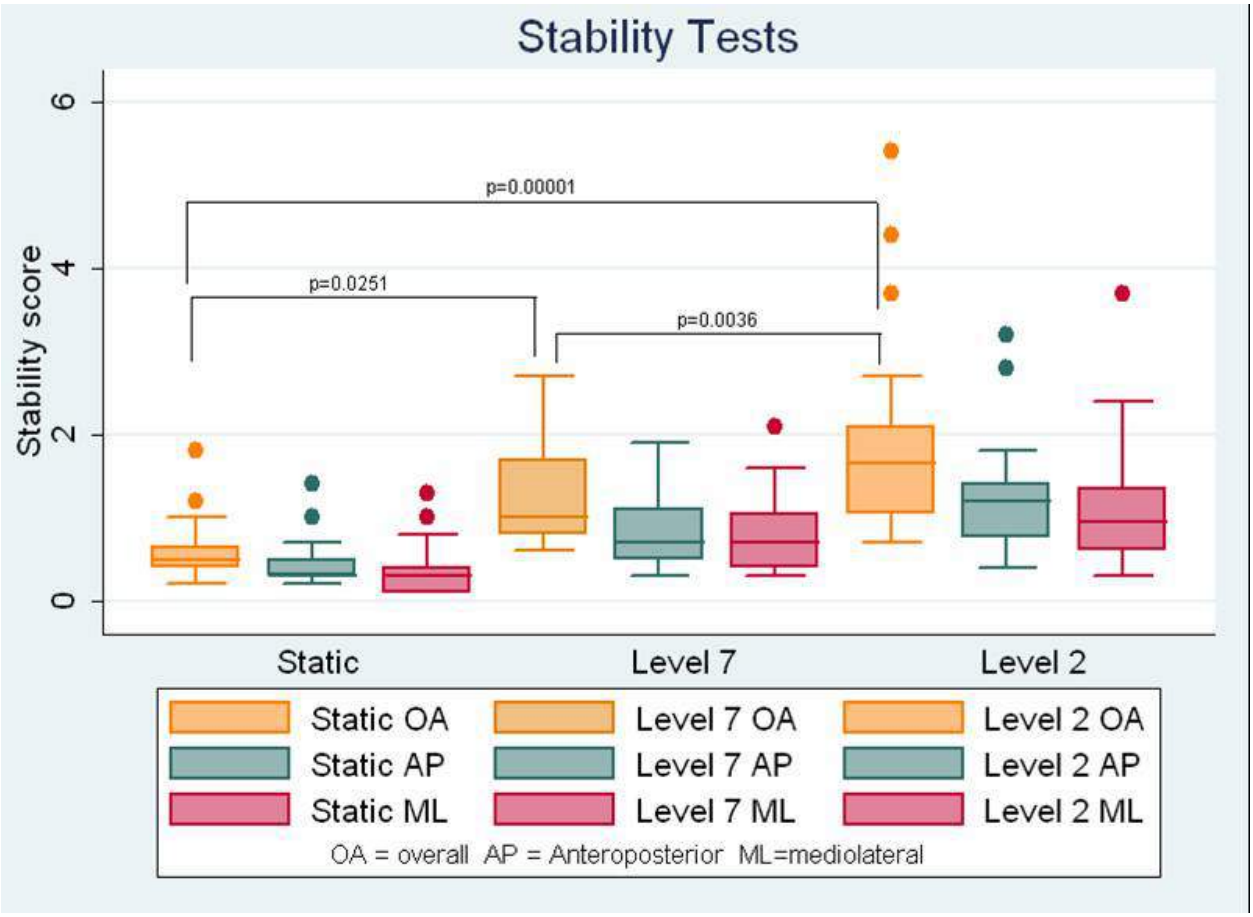
Methods: 25 patients (14 boys) with JIA aged 8.7 to 18.2 years (median 13.8) were tested using the BBS. The BBS is a multiaxial tilting platform that allows objective measurement of the ability of a subject to maintain dynamic single and double limb postural stance on an unstable platform. The stabilometric technique allows assessment of overall (OA), anterior/posterior (AP) and medial/lateral (ML) stability. All children had active lower extremity arthritis within one year prior to testing. Data was collected for age, gender, leg dominance, JIA subtype and current medications. Isometric strength of both legs was tested by manual muscle testing (hip abductor, flexor, extensor; knee extensor, flexor; foot dorsiflexor, plantarflexor). Single leg static balance (BBS level 12) and bilateral static and dynamic balance [BBS level 2 (very unstable) and level 7 (moderately unstable)] were measured as AP, ML and OA stability scores. Correlation analyses were performed between stability indices (AP, ML, OA), lower extremity strength, disease activity [articular severity index, ASI], function (Child Health Assessment Questionnaire, CHAQ) and pain (Visual Analog Scale, VAS). Correlation coefficients of 0.3-0.5, 0.5-0.7, and 0.7-1.0 indicated low, moderate, and high correlations, respectively.

Results: Twenty patients had knee arthritis, 15 ankle, 11 foot, and 7 hip arthritis. All but 1 patient had multiple joints involved. Mean ASI on the day of testing was 4.4 (5.7). Mean CHAQ score was 0.13 (0.31) and mean VAS pain 10.2 (17.2). Balance summary measures are shown in Figure 1. Single leg balance was impaired in 12 patients (48%; 1 right leg, 8 left leg, 3 both); 23 patients (92%) were right side dominant. Bilateral static balance (OA) was significantly better than dynamic balance (level 7 $p=0.0251$; level 2 $p=0.0001$). Ankle involvement significantly impaired dynamic balance (level 7 AP $p=.029$; level 2 OA $p=.011$; level 2 AP $p=.0003$). Hip abduction and hip flexion strength had low correlation with single leg balance; hip abduction, hip flexion, knee flexion and ankle plantarflexion strength had

low correlation with bilateral static and dynamic balance. Pain, but not disease activity or function, had a low negative correlation with static balance.

Conclusion: These preliminary results suggest children with leg arthritis and ankle disease in particular, have impaired dynamic balance. As strength and balance are shown here to be positively related, proprioceptive exercises are likely to emerge as an important therapy in the treatment of children with JIA and lower extremity arthritis.

Figure 1: Bilateral Stance Stability Tests



Disclosure: K. Houghton, None; **M. MacLeod**, None.

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Efficacy of Intra-Articular Steroid Injection Into the Temporomandibular Joint in Children with Juvenile Idiopathic Arthritis.

Rotraud K. Saurenmann[1], Lukas Muller[2], Silke Schroeder[1], Timo Peltomaki[2], Elvira Cannizzaro[1] and Christian Kellenberger[3], [1]University Children's Hospital, Zurich, Switzerland, [2]Orthodontics and pediatric dentistry, University of Zurich, Zurich, Switzerland, [3]Zurich University Children's Hospital, Switzerland

Background: Intra-articular steroid injection is a common treatment modality in juvenile idiopathic arthritis (JIA). Little is known about the optimal technique for the injection of the temporomandibular joint (TMJ) and about the efficacy and side effects of this method.

Purpose: To study the efficacy of TMJ steroid injections on inflammation on magnetic resonance imaging (MRI) in children with JIA.

Methods: 33 consecutive JIA patients with MRI confirmed diagnosis of TMJ arthritis received an intra-articular injection of triamcinolone hexacetonide into 57 affected joints. Immediately after injection the location of the injected medication was controlled by MRI. Follow-up MRI was performed 1-3 months later and the change of inflammatory signs on MRI was compared to the grade of successful intra-articular placement of the medication.

Results: The injection resulted in intra-articular fluid collection in 37/57 joints (65%). The amount of intra-articular fluid was a trace in 13 (23%), small in 8 (14%) and moderate/large in 16 (28%). Improvement of inflammation on follow-up MRI was found in 15% with extra-articular injection and 73% with intra-articular injection. 12/21 joints (57%) with trace/small amount of fluid after injection but 15/16 joints (94%) with moderate/large amount of fluid after injection had improvement of inflammation on follow-up MRI. No significant deterioration of deformity of the condylar head was observed following intra-articular injection.

Conclusion: The efficacy of intra-articular steroid injection into the TMJ is strongly related to the grade of successful intra-articular placement of the medication. We did not observe any negative effects on the condylar head following steroid injection, but the observation period may have been too short.

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Delayed Clinical Response in Great Part of Patients with Juvenile Idiopathic Arthritis Initially Not Responding to Etanercept. M.H. Otten[1], F.H.M. Prince[1], M. Twilt[1], M.A.J. van Rossum[2], W. Armbrust[3], E.P.A.H. Hoppenreijs[4], S.S.M. Kamphuis[1], Y. Koopman-Keemink[5], N.M Wulffraat[6], S.L. Gorter[7], R. ten Cate[8] and L.W.A. van Suijlekom-Smit[1], [1]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Academic Medical Center, Amsterdam, Netherlands, [3]University Medical Center Groningen, Groningen, Netherlands, [4]Radboud University Medical Center, Nijmegen, Netherlands, [5]Juliana Children's Hospital, The Hague, Netherlands, [6]University Medical Center Utrecht, Utrecht, Netherlands, [7]Academic Hospital Maastricht, Maastricht, Netherlands, [8]Leiden University Medical Center, Leiden, Netherlands

Purpose: To evaluate clinical response in Juvenile Idiopathic Arthritis (JIA) patients who initially failed to meet response criteria at 3 months of etanercept therapy.

Methods: This study is embedded in the Arthritis and Biologicals in Children (ABC) project, a prospective ongoing multicentre, observational study of all Dutch JIA patients using etanercept.[1] Response was assessed in all patients using the American College of Rheumatology (ACR) Pediatric 30 criteria at start, 3 and 15 months of therapy.

Results: In total 179 patients in the register had a minimum follow-up of 15 months (70% female, median age onset 5.8 years). Thirty-four patients did not respond after 3 months, of which 21 continued etanercept and 12 (57%) achieved an ACR 30 response thereafter. Overall, 7% of the 179 patients were delayed responders after 3 months of treatment and this was most likely in those with the oligoarticular, arthritis psoriatica and enthesitis related arthritis subtypes.

Conclusion: In JIA patients 57% of non-responders at 3 months who continue etanercept eventually respond. Therefore, we suggest extending the use of etanercept in non-responding patients beyond the commonly recommended 3 months therapy window to achieve higher response rates in JIA patients.

Reference:

1 Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis*. 2009;**68**:635-41.

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Growth in a UK Cohort of Juvenile Idiopathic Arthritis (JIA) Patients Treated with Etanercept and/or Methotrexate. Taunton R. Southwood[1], Carole Cummins[1], Kate Cotter[1] and British Society of Paediatric and Adolescent Rheumatology[2], [1]University of Birmingham and Birmingham Childrens Hospital, Birmingham, United Kingdom, [2]Liverpool, United Kingdom

Purpose: Since 2004, the British Society for Paediatric and Adolescent Rheumatology (BSPAR) Biologics and New Drug Register has enrolled and monitored JIA patients treated with etanercept and/or methotrexate. Here we report change in height standard deviation scores (SDS) after monitoring for 2 years.

Method: After informed consent, JIA patients treated with etanercept and/or methotrexate were enrolled and disease subtype/activity, growth parameters, co-morbidity, treatment efficacy and safety data were recorded at baseline, 3 and 6 months and annually thereafter. Height and weight SDS, BMI and International Obesity Taskforce cut-offs were calculated from British 1990 growth charts and Excel add-on program LMS Growth 2.64 (H Pan & T Cole). Patients with missing/erroneous measurements were excluded.

Results: 702 JIA patients were enrolled from 29 UK centres (67% female, 13% systemic arthritis). Height SDS for the cohort and treatment groups at baseline (table 1) were left skewed; there was a moderate correlation with disease duration ($r = -0.255$, $p<0.01$). 21% of the cohort were thin (23% of systemic arthritis patients had grade 3 thinness), 18% were overweight or obese.

Table 1 Height SDS at baseline

Treatment group at baseline	n	Age at baseline	Height SDS (mean ± SD)
Etanercept alone	221	11.0 ± 3.5	– 0.74 ± 1.35
Etanercept and Methotrexate	315	11.2 ± 4.37	– 0.86 ± 1.43
Methotrexate alone	166	8.0 ± 4.75	– 0.13 ± 1.38 (P<0.001)

Girls (– 0.83 ± 1.26) had a lower height SDS than boys (– 0.39 ± 1.55) ($p<0.001$). Patients with systemic arthritis were shorter than other forms of JIA (mean SDS -1.42 ± 1.47) and were more likely than others to be treated with both etanercept and methotrexate, $p<0.001$). Height monitoring data at 1 year follow up was available in 338 patients (table 2). The mean difference in height SDSs between baseline and 2 years for all patients with both measurements (n=201) was 0.278 (paired t test $p<0.001$).

Table 2 Change in Height SDS after monitoring for 1 and 2 years

Treatment group at baseline	1 year after baseline (n=338)		2 years after baseline (n=201)	
	n	mean ± SD	n	mean ± SD
Etanercept alone	107	0.54 ± 0.86	68	0.31 ± 0.94
Etanercept and Methotrexate	148	0.45 ± 0.71	96	0.35 ± 0.86
Methotrexate alone	83	0.12 ± 0.79	37	0.02 ± 1.43
		P = 0.001		NS

Conclusion: Children with JIA starting etanercept and/or methotrexate were shorter than expected and significant proportions were either thin or overweight/obese. After two years, there was an improvement in height SDS for the whole cohort. A statistically significant increase in height gain was seen in etanercept and combined etanercept / methotrexate treated patients compared with patients treated with methotrexate alone at one year but not at 2 years, possibly due to lower patient numbers. There is potential for confounding by pubertal

stage and associated growth spurts as final adult height has not yet been measured and children treated with methotrexate alone were younger than those on etanercept.

Disclosure: T. R. Southwood, Wyeth Pharmaceuticals, 2 ; **C. Cummins**, Wyeth Pharmaceuticals, 3 ; **K. Cotter**, Wyeth Pharmaceuticals, 3 .

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Risk of Relapse After Discontinuation of Medications in Patients with Polyarticular Course Juvenile Idiopathic Arthritis. Diana Milojevic[1], Megan L. Curran[1] and Beth S. Gottlieb[2], [1]UCSF, San Francisco, CA, [2]Schneider Childrens Hospital, New Hyde Park, NY

Purpose: Two goals of medical treatment in juvenile idiopathic arthritis (JIA) are to achieve remission of the disease and minimize medication toxicity. Discontinuation of medications during disease quiescence decreases cumulative toxicity. It is not known if the type of treatment used to achieve clinical remission on medications (CRM) affects the subsequent duration of inactive disease off medications in polyarticular JIA. In this study, we compare the risk of relapse during inactive disease off medications in polyarticular course JIA patients who achieved CRM with methotrexate versus methotrexate and etanercept.

Methods: This is a retrospective study of 64 JIA patients who achieved CRM and were subsequently taken off all medications. They belonged to one of the following four sub-types of JIA as defined by ILAR criteria: extended oligoarticular, psoriatic, polyarticular rheumatoid factor (RF) negative and polyarticular RF positive. Group 1 consisted of 26 patients treated with methotrexate and followed from 1995 to 2000, prior to the introduction of etanercept into clinical practice. Groups 2 and 3 were patients followed from 2003 to 2008, treated with methotrexate alone (22 patients, group 2) or with methotrexate and etanercept (16 patients, group 3). The Wallace Criteria were used to define CRM. All patients achieved CRM and were taken off all medications after one year of inactive disease. Relapse was defined as persistent arthritis in at least one joint for at least 6 weeks.

Results: Patients treated with the combination of methotrexate and etanercept (group 3) had significantly more active joints ($p < 0.001$) and significantly higher weekly and cumulative methotrexate dosages ($p = 0.02$ and $p = 0.009$, respectively). On average, prior to achieving CRM, patients in group 3 were treated with methotrexate for 23 months and etanercept for 6.2 months, while group 1 patients were treated with methotrexate for 8.7 months and group 2 patients for 16 months. Type of treatment did not significantly affect the risk of relapse in the three groups ($p = 0.56$), although compared to group 1, the risk in group 2 was 4% lower (HR 0.96, 95% CI 0.45, 2.04) and in group 3 was 49% higher (HR 1.49, 95% CI 0.66, 3.35). The risk of relapse did not significantly change after adjusting for age, gender, sub-type of JIA, number of affected joints, weekly and cumulative dosages of methotrexate, time from diagnosis to treatment and duration of methotrexate treatment.

Conclusion: Our results indicate that treatment with methotrexate and etanercept compared to treatment with methotrexate alone does not significantly affect the risk of relapse in patients with polyarticular course JIA who achieved CRM and were off all medications. However, patients treated with methotrexate and etanercept had more severe disease, indicated by more active joints and longer duration of methotrexate treatment prior to achieving remission.

Disclosure: D. Milojevic, None; **M. L. Curran**, None; **B. S. Gottlieb**, None.

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The Peripheral Blood Genes That Account for Predictability of Clinical Response to Tocilizumab (TCZ) Treatment, Corticosteroid Dose Reduction, and Serum IL-6 Normalization at Week 48 On Systemic Onset Juvenile Idiopathic Arthritis (sJIA) Patients. Norihiro Nishimoto[1], Yuichi Kawata[2], Hooi-Ming Lee[3], Chieko Aoki[1], Yasuo Adachi[1], Hidehiko Sugino[3], Tomoyuki Imagawa[4], Masaaki Mori[4], Minako Tomiita[5], Naomi Iwata[6], Takuji Murata[7], Mari Miyoshi[8], Syuji Takei[9], Yukoh Aihara[10], Takahiro Ochi[11] and Shumpei Yokota[4], [1]Wakayama Medical University, Osaka, Japan, [2]Chugai Pharmaceutical Co.,Ltd., Tokyo, Japan, [3]Osaka University, Osaka, Japan, [4]Yokohama City University, Yokohama, Japan, [5]Chiba University, Chiba, Japan, [6]Aichi Children's Health and Medical Center, Daifu, Japan, [7]Osaka Medical College, Takatsuki, Japan, [8]Kobe Children's hospital, Kobe, Japan, [9]Kagoshima University, Kagoshima City, [10]Yokohama City University Medical Center, Yokohama, Japan, [11]Osaka Police Hospital, Osaka, Japan

Purpose: TCZ, an anti-interleukin-6 receptor (IL-6R) antibody, has been demonstrated to improve the signs and symptoms of sJIA. In the phase 3 trial, 86% of the children achieved JIA70 (70% or more improvement of signs and symptoms of JIA) at week 48. Consequently, corticosteroid doses could be reduced to 5mg/day or less in 44% of the patients at week 48. Furthermore, serum IL-6 levels decreased to normal range (<35pg/ml) in 51% of the patients at the same time, suggesting that such patients can extend the treatment interval or discontinue TCZ treatment without acute flare. To identify the genes expressed in peripheral blood that account for predictability of the response to TCZ treatment, capability of corticosteroid dose reduction, and serum IL-6 normalization, at week 48 on sJIA patients.

Method: We have analysed peripheral blood mRNA expression of 29640 genes using DNAchip (AceGene Human 30K; DNA Chip Research Inc., Yokohama, Japan) in patients with sJIA treated with TCZ and selected the genes that could be used to distinguish (1) JIA70 achieved and not-achieved groups, (2) patients who could be reduced prednisolone dose to 5mg/day or less and those who could not be, and (3) attained and unattained groups of serum IL-6 normalisation (< 35pg/ml). Cross validation was performed by leave one out method.

Results: To distinguish JIA70 achievement, corticosteroid reduction, and IL-6 normalisation, 143 genes ($p<0.01$), 40 genes ($p<0.01$), and 86 genes ($p<0.05$) were selected, respectively. Cross validation revealed that the gene sets distinguished the patients with JIA70 response, corticosteroid reduction, and IL-6 normalisation at accuracy of 84, 84, and 72%. Specifically, the gene sets well predicted the corticosteroid dose reduction with sensitivity 79%, specificity 88%, positive predictive value 83%, and negative predictive value 84%. **Conclusion:** Gene expression profile in peripheral blood cells at baseline may be useful to predict the clinical response, corticosteroid dose reduction, and serum IL-6 normalization by TCZ therapy at week 48.

Disclosure: N. Nishimoto, Chugai, Roche, 5, Chugai, Wyeth., 2, Chugai, 7 ; **Y. Kawata**, Chugai, 3 ; **H. M. Lee**, None; **C. Aoki**, None; **Y. Adachi**, None; **H. Sugino**, None; **T. Imagawa**, None; **M. Mori**, None; **M. Tomiita**, None; **N. Iwata**, None; **T. Murata**, None; **M. Miyoshi**, None; **S. Takei**, None; **Y. Aihara**, None; **T. Ochi**, None; **S. Yokota**, None.

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Gene Expression Signatures in Polyarticular Juvenile Idiopathic Arthritis Predict Likelihood of Achieving Inactive Disease within Two Years of Treatment. Rachel Mason[1], Michael Barnes[2], Robert A. Colbert[3], Susan D. Thompson[2], David N. Glass[2] and Thomas A. Griffin[2], [1]Xavier University, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]NIAMS/NIH, Bethesda, MD

Purpose: We tested the ability of recently identified gene expression signatures in polyarticular juvenile idiopathic arthritis (JIA) (Griffin, *et al.*, *Arthritis Rheum*, 2009) to predict disease outcomes within two years of starting treatment with methotrexate and/or anti-tumor necrosis factor (TNF) medications. Signature I (S-I) contains monocyte-associated genes and correlates with more severe arthritis at baseline, while Signature III (S-III) is associated with reduced numbers of circulating T lymphocytes and is linked to milder arthritis at baseline.

Method: S-I and S-III were quantified in peripheral blood mononuclear cells (PBMC) from a cohort of 59 subjects with recent-onset polyarticular JIA prior to treatment with methotrexate and/or anti-TNF medications. Clinical data from this observational study were reviewed at baseline through 24 months to identify subjects achieving inactive disease (ID) and those treated with anti-TNF medications. ID was defined as no joints with active arthritis, erythrocyte sedimentation rate levels within normal limits, and physician's global assessment of disease activity score of zero. Outcomes were compared between subject groups defined by S-I and S-III. Statistically significant differences were determined by chi-square analysis.

Results: Fourteen subjects expressed only S-I, 12 subjects expressed only S-III, 12 subjects expressed both signatures, and 21 subjects expressed neither signature. ID was achieved at comparable rates for subjects with or without S-I (46% vs. 45 %). This contrasts with 58% of S-I subjects being treated with anti-TNF medications compared to only 30% of the other subjects ($p=0.03$). Conversely, ID was achieved by only 33% of S-III subjects compared to 54% of subjects lacking S-III ($p=0.11$), despite comparable rates of treatment with anti-TNF medications (46% vs. 40%). Notably, this difference in rate of achieving ID was quite pronounced when subjects expressing only S-III were compared to all other subjects (17% vs. 53% ($p=0.02$)).

Conclusion: Subjects expressing S-I, who clinically had more severe arthritis at baseline, were treated more often with anti-TNF medications, but achieved a similar rate of ID compared to other subjects. Conversely, subjects expressing S-III were treated with anti-TNF medications at comparable rates, but achieved a lower rate of ID. We speculate that S-III identifies a subset of polyarticular JIA patients with milder arthritis at baseline that is more difficult to control over time, warranting more aggressive early therapy than in current clinical practice. Thus, PBMC gene expression signatures may be useful tools for guiding therapy in polyarticular JIA.

Disclosure: R. Mason, Arthritis Foundation, 2, NIH/NIAMS, 2 ; **M. Barnes**, NIH/NIAMS, 2, Arthritis Foundation, 2 ; **R. A. Colbert**, Arthritis Foundation, 2, NIH/NIAMS, 2 ; **S. D. Thompson**, NIH/NIAMS, 2, Arthritis Foundation, 2 ; **D. N. Glass**, NIH/NIAMS, 2, Arthritis Foundation, 2 ; **T. A. Griffin**, NIH/NIAMS, 2, Arthritis Foundation, 2 .

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Enhanced Drug Safety Surveillance (EDSS) Pilot Project. Carol A. Wallace[1], Audrey F. Hendrickson[1] and Rachel E. Sobel[2], [1]Seattle Children's Hospital, Seattle, WA, [2]Pfizer, Inc., New York, NY

Purpose: Medication safety is of utmost importance for pediatric rheumatologists (PR), yet there is little to no information available regarding long-term safety in children or the occurrence of rare adverse events for most of the medications used to treat JRA/JIA (Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis), including nonsteroidal anti-inflammatory drugs. Additionally, there is currently no effective method to monitor potential long-term effects of the many medications used for the treatment of JRA/JIA. The FDA has a voluntary MedWatch reporting system in place (passive surveillance), however only a small proportion of physicians fill out these reports, even though their patients may experience significant events that might be related to medications. A long-term registry of all children with JRA/JIA in North America would foster the collection of this critical information. The objective of this project is to partner with Pfizer, Inc. to implement a pilot process that would facilitate capture of significant safety and medical events in children with JRA/JIA utilizing the CARRA (Childhood Arthritis and Rheumatology Research Alliance) physician network.

Method: The EDSS Pilot Project facilitates significant safety and medical event collection by monthly survey of treating PR for two years. The survey asks if any of their JRA/JIA patients had an SAE (Serious Adverse Event) or IME (Important Medical Event) during the preceding month. When an SAE or IME is identified, the CARRA coordinating center assists the CARRA physician in completing a MedWatch form, which is then submitted to Pfizer, the FDA, and other pharmaceutical companies as appropriate. Collection of the unduplicated number of JRA/JIA patients seen at each site every 6 months for 2 years gives a denominator for the SAE/IME events. If site databases allow, PR also provide denominator information on JRA/JIA by subtype as well as medications prescribed.

Results: As of 4/30/09, there were 73 PR responses to the initial survey from 30 CARRA sites. 68.1% of respondents indicated that they have never filed a MedWatch Report (or filed >5 yrs ago). 74 PR at 27 sites completed follow-up monthly surveys, with 328/439 surveys completed, a 74.7% response rate. Aggregate six-month site data reveals 4,372 patients seen at 19 sites by 57 PR with 56 SAEs/IMEs reported during these six-month time periods, or 2.14 SAE/IMEs per 100 patient-years of observation. Infection was the most common SAE/IME followed by flare of JIA, neurological adverse events, and elevated liver function tests.

Conclusion: More than two-thirds of participating PRs have never previously filed a MedWatch form. The EDSS is a simple and effective tool that is increasing SAE/IME reporting and has generated rates consistent with the Amgen Etanercept/Methotrexate JIA Registry.

Disclosure: C. A. Wallace, Pfizer Inc, 2, Centocor, 2, Amgen, 2 ; **A. F. Hendrickson**, None; **R. E. Sobel**, Pfizer Inc, 3 .

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Malignancy in Juvenile Idiopathic Arthritis. S. Bernatsky[1], A. Rosenberg[2], Kiem G. Oen[3], Rosalind Ramsey-Goldman[4], Y. St. Pierre[1], E. Turnbull[1] and A. E. Clarke[1], [1]MUHC, Montreal, QC, [2]Royal Univ Hosp, Saskatoon, [3]University of Manitoba, Winnipeg, MB, [4]Northwestern University, Chicago, IL

Purpose: There is considerable interest in the increased risk of malignancy in adult rheumatoid arthritis, particularly for lymphoma and lung cancer. However, to date there have been no assessments specifically in JIA Our objectives thus were to assess the observed malignancy incidence in JIA, and compare this to the expected incidence, based on general population cancer data.

Methods: We examined cancer occurrence within the JIA clinic registries maintained at two North American pediatric rheumatology centers. The subjects in the clinic registries were linked to regional tumor registries to determine the occurrence of cancers over the observational interval, which spanned the calendar years 1974-2006. In-situ cancers were excluded. The person-years of follow-up for each subject were calculated from the date first seen at the rheumatology clinic, and the first of three possible events: death, cancer, or the end of the study interval (December 31, 2006). Pooling the data, we determined the total number of observed cancers occurring over the total person-years of observation. The total number of cancers expected to occur over the observation interval was determined by multiplying the

person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years.

Results: The study sample was comprised of 1,168 patients. The proportion of females in the cohort was 67.3%, and the average age at cohort entry was 8.9 years (SD=5.1). The vast majority of cohort members were Caucasian (80.5%), with the second largest racial/ethnicity group being individuals of First Nations/Inuit origin (16.9%). Subjects were observed for a total of 16,396 patient-years, with an average follow-up of 14.0 years (SD=8.1). Within this observation interval, based on regional age- and sex-appropriate cancer rates, **six** invasive cancers would have been expected, however, **no** invasive cancers occurred in our subjects.

Conclusion: No invasive cancers were demonstrated in this large sample of individuals with JIA, observed for an average of 14 years each. These data suggest that, at least in the initial years following JIA diagnosis, the risk of invasive cancers is not markedly increased. A potential limitation is the small number of specific minorities (e.g. blacks, Asians, Hispanics, etc.). Hence, study of longer-term cancer outcomes, ideally in a multi-center, multi-ethnic cohort, is of further interest.

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Antibody against Mutated Citrullinated Vimentin (anti-MCV) as a Serological Marker for Juvenile Idiopathic Arthritis. Priscila Lora[1], Sandra Machado[2] and Ricardo M. Xavier[3], [1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, [3]Porto Alegre, Brazil

Background: RF, ANA and anti-CCP are some biomarkers that have been used in the diagnostic of JIA. Nevertheless none of them have demonstrated great predictive value for this use. It has been suggested that anti-MCV antibodies are more sensitive than anti-CCP antibodies to diagnose RA and also that it correlates with RA activity (DAS 28).

Purpose: To study the presence of anti-MCV antibodies in a group of patients with AIJ.

Methods: Anti-MCV antibodies were tested in serum from 33 patients with JIA and 7 control individuals without symptoms or signs of rheumatic diseases using an ELISA test (Orgentec, Grm). Anti-CCP antibodies were tested by ELISA test, second generation (DIASTAT, Scotland). The procedures were conducted according to the manufacturer's instructions. All measurements were performed by experienced operators who were blinded to clinical conditions. The study was approved by local ethics committee.

Results: Anti-MCV was observed in 30.3% of JIA patients (10/33), being absent in all controls (specificity= 100%). Besides, none of JIA patients presented anti-CCP antibodies. In clinical aspects, there was no difference in the age of onset ($p = 0.12$) and duration of the disease ($p = 0.37$) between those who were anti-MCV positive or negative. Polyarthritis was the most frequent subtype (39% 13/33) and showed the highest prevalence of anti-MCV (15.5%, 5/33). (table I).

Conclusion: In our cohort of patients with JIA, anti-MCV was highly specific when JIA patients were compared to a small group of controls, and the sensitivity of anti-MCV was superior to anti-CCP, since none of these patients presented anti-CCP antibodies. Further studies with larger sample sizes and including patients with others inflammatory diseases could help to better identify the clinical performance of anti-MCV in JIA.

Table I: JIA patients' demographic data and biomarkers frequency.

JIA subtype	Polyarthrits	Oligoarthritis	Systemic	Psoriatics
	(n=13)	(n =12)	(n = 5)	(n = 3)
Demographic data				
Age (in years, mean (SD))	9.1 (3.0)	12.6 (5.1)	8.7 (3.3)	11.9 (6.3)
Age of onset (in years, mean (SD))	4.5 (2.9)	6.0 (3.2)	5.5 (4.4)	4.7 (1.1)

during of the disease (in years, median (amplitude))	3.5 (2.4 – 7)	7.6 (2.6 – 9.6)	3.2 (1.5)	6.3 (1.3 – 9.6)
Biomarkers				
Anti-MCV (% (n))	38.5 (5)	8.3 (1)	40.0 (2)	66.7(2)
Anti-CCP(% (n))	0	0	0	0
RF(% (n))	30.8 (4)	11.1 (1)	0	0
ANA by IFI(% (n))	0	11.1 (1)	0	0

Disclosure: P. Lora, None; **S. Machado**, None; **R. M. Xavier**, None.

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What Should Medical Students Know about Pediatric Musculoskeletal (pMSK) Medicine? Sharmila Jandial[1], Jane Stewart[1], Lesley Kay[2] and Helen Foster[1], [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Newcastle Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom

Purpose: Children and adolescents with musculoskeletal (MSK) complaints commonly present to doctors working in primary and secondary care, rather than direct to sub-specialists. Appropriate triage relies on competent clinical skills and knowledge, yet many doctors report low confidence in their pMSK clinical assessment [Jandial 2008]; this may contribute to reported delay in access to care for children with chronic arthritis [Foster 2007]. pMSK medicine is not currently included in most medical schools in the UK [Jandial 2009] and North America [Oswald 2008]. Our aim was to derive consensus based pMSK learning outcomes, including rheumatology and orthopaedics, relevant to the graduating doctor and provide the basis for a pMSK curriculum.

Method: Participants were recruited from national professional bodies, including paediatric rheumatology and orthopaedics, general and sub-specialist paediatrics, family practice, allied health professionals and medical students with UK wide representation. Qualitative and quantitative methods and analysis were used; initially systematic review followed by focus groups and interviews to derive relevant pMSK themes, followed by a modified Delphi process to derive consensus with refinement by group nominal technique. The project had full ethical approval.

Results: The project resulted in 47 pMSK learning outcomes with broad themes of establishing interaction (with child/parent) [n=4], history taking and physical examination including assessment of pain [n=26], initial investigations and management [n=17]. Relevance to the graduating doctor, rather than subspecialist was deemed paramount; the inclusion of "core" presentations [n=8] and "core" conditions [n=14] were added to give context and covered knowledge of normal pMSK developments, "red flags" to suggest life threatening problems, common conditions encountered in family practice, medically significant (albeit less common) conditions, initial investigations and referral pathways to facilitate access to appropriate care. Core presentations included swollen joint(s), arthralgia and polyarthralgia, limping child, fracture, back pain, unexplained fever, loss of limb function and core conditions included juvenile idiopathic arthritis, bone and joint sepsis, Perthes disease, talipes, slipped capital femoral epiphysis, malignancy, scoliosis, common fractures, non-accidental injury, rickets, growing pains and normal variants.

Conclusion: This set of pMSK learning outcomes is relevant to all medical students to be acquired by the time of graduation from medical school and are consensus derived involving the breadth of stakeholders within pMSK medicine. They are useful to establish curricula, produce teaching resources and be incorporated into assessments.

Disclosure: S. Jandial, None; **J. Stewart**, None; **L. Kay**, None; **H. Foster**, None.

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An Evidence and Practice Based Regional Musculoskeletal Examination for School Aged Children – pREMS. Helen Foster[1], Tim Rapley[1], Ben Heaven[1], Lesley Kay[2] and Carl May[1], [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Newcastle Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom

Purpose: Competent examination of the paediatric musculoskeletal (pMSK) system is essential in the process of making a diagnosis in children presenting with MSK complaints. The aim of this project was to develop a regional examination for school-aged children that is evidence based, age appropriate and brings together primary research on clinical technique, systematic review, and expert consensus in a similar format to REMS [Coady 2004].

Method: Video observations of 89 MSK examinations by staff (doctors n=11; therapists n=8) of school-aged children attending outpatient clinics in 7 UK paediatric rheumatology centres, and 14 semi-structured review interviews with clinicians. Qualitative and quantitative analyses revealed descriptions, frequencies and variations in technique for joint regions in various clinical scenarios. Systematic literature review and data from clinical observation were combined to derive a proposed regional MSK examination with feedback from a further group of 37 pMSK experts through a web-based survey. All results were collated and discussed by consensus development groups to derive pREMS (paediatric Regional Examination of the MSK system).

Results: Systematic review revealed little evidence about pMSK examination. Video observation showed variation in examination techniques used between therapists and doctors between orthopaedics and rheumatology, especially at the hip and the knee in the context of mechanical and inflammatory clinical scenarios and with differences from those techniques used in adult REMS. pREMS is based on "look, feel, move" similar to adult REMS but with the addition of a "measure" option (e.g muscle strength) with reference given to age specific range of joint movement. Further manoeuvres were added based on the clinical scenario (such as suspected hypermobility, mechanical knee pain) and including specific tests as appropriate (e.g patella apprehension test). Where there was variation in technique the consensus group proposed a test based on the study results and, where available, the literature. The consensus group decided that pREMS in entirety was aimed at trainees in paediatric rheumatology although some components of pREMS (e.g hip abduction and adduction) are essential for medical students and others were aimed at paediatric orthopaedics (e.g foot and thigh angle).

Conclusion: pREMS is the first evidence and consensus based regional examination for school aged children based on clinical practice, and gives a series of clinical manoeuvres that are relevant to clinical scenarios. A structured approach with guidance on the level of skills required for undergraduate and postgraduate medicine is an important step towards improved pMSK clinical skills relevant to clinical training.

Disclosure: H. Foster, None; **T. Rapley**, None; **B. Heaven**, None; **L. Kay**, None; **C. May**, None.

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Assessment of Joint Cartilage Thickness by Ultrasound in Healthy Children: Age and Sex-Related Standard Reference Values. Anne Helene Spannow[1], Mogens Pfeiffer-Jensen[2], Niels Trolle Andersen[3], Elisabeth Stenbøg[1] and Troels Herlin[1], [1]Aarhus University Hospital Skejby, Aarhus N, Denmark, [2]Aarhus University Hospital Aarhus Sygehus, Aarhus C, Denmark, [3]Aarhus University, Aarhus C, Denmark

Purpose: Loss of joint cartilage may be an early feature of destructive disease in juvenile idiopathic arthritis (JIA). When using conventional radiography early inflammatory changes are generally not detected and only late changes such as joint space narrowing and bone erosions are visualized. Joint cartilage is easily visualized with high frequency ultrasonography (US) but before US measurements of cartilage thickness is implemented there is a need for age- and sex-related normal standard reference values. The aim of the study was to establish age- and sex-related normal standard reference values for cartilage thickness US measurements in JIA target joints

Methods: In 394 healthy Danish Caucasian children (215 boys/179 girls) we performed a cross-sectional study of bilateral greyscale US cartilage thickness measurements of the knee, ankle, wrist, and 2nd metacarpophalangeal (MCP) and 2nd proximal interphalangeal (PIP) joints making a total of 3940 joints investigated. Ultrasonographic settings: B-mode obtained on a real-time Hitachi EUB-6500 CFM scanner, equipped with a linear 6-13 MHz transducer (d-THI, frequency 14MHz, dynamic range 65), all measurements were obtained blinded and US images and cartilage thickness measurements for each child were stored on DVD. All statistics were performed with the STATA version 10 statistical package.

Results: There was a significant difference in cartilage thickness measurements between sexes, ($p<0.001$ for all joints), boys having thicker cartilage compared to girls. Our results showed a clear decrease in cartilage thickness with increasing age for both sexes. A formula for

calculating cartilage thickness for different ages and sexes in childhood was suggested. Given the estimate of the thickness y_8 for a 8-years old child, the slope β and the standard deviation of the residual sd_{line} an estimate of the thickness y_x for a x-years old child can be calculated by $y_x = y_8 + \beta*(x-8)$ and a 95% PI by $y_8 + \beta*(x-8)$ +/- 1.96 * $sd_{line.}$ No difference between the right and left side of the investigated joints was observed.

Difference in cartilage thickness between boys and girls age 7-16 years		
	Difference boys – girls (mm)	**95% CI**
Knee	0.471	0.383–0.559
Ankle	0.120	0.083–0.157
Wrist	0.257	0.185–0.328
MCP	0.256	0.221–0.291
PIP	0.124	0.098–0.149

Conclusion: We have been able to establish age- and sex-related normal reference intervals for cartilage thickness measurements in the knee, ankle, wrist, and MCP and PIP joints with US for children with the age between 7 – 16 years and established a formula for calculation of hyaline cartilage thickness measurements in all age-groups throughout childhood.

Disclosure: A. H. Spannow, None; **M. Pfeiffer-Jensen**, None; **N. T. Andersen**, None; **E. Stenbøg**, None; **T. Herlin**, None.

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Knee Joint in JIA: A Prospective Study-Ultrasound Is More Sensitive Than Both Clinical Examination and MRI in Detecting Disease Activity. Laura Pascoli[1], Noel Napier[1], Maria Wray[2], Maura McCarron[2], Catherine McAllister[1] and Madeleine E. Rooney[3], [1]Belfast Trust, Belfast, Northern Ireland, [2]Belfast trust, Belfast, Northern Ireland, [3]Queen's University Belfast, Belfast, Northern Ireland

Purpose: Since 2004 we have undertaken a prospective study of children with newly diagnosed JIA with knee involvement. At outset and at regular intervals for 2 years, clinical, ultrasound (US) and MRI scans of the knees were obtained. We noted that, not infrequently, knees deemed clinically normal had appreciable effusions on US. We therefore wished to assess the accuracy of clinical, US and MRI assessments of the knee joints in children with JIA.

Method: Clinical assessments and US images from children who were recruited to our prospective study were obtained on the same day and analysed in a blinded fashion. A subgroup of these children had MRI scans of the knee obtained within 0 to 14 days from clinical and US examinations. Clinical and US assessment of the knee were scored from 0-3, where 0 = normal; 1 = mild; 2 = moderate; 3 = marked. Effusion and SH, were scored according to our modified scoring system created utilizing the assessment of knee involvement in adults[1-3]. The scans were scored independently by a musculoskeletal radiologist (NN): E (0-3), SH (0-3). Ordinal regression analysis to compare clinical, US and MRI assessment was undertaken (SPSS version 15).

Results: One hundred an ninety four clinical assessments and matching US scans were analysed from 40 children over a two year period. Of these 40 had matching MRI scans. To date we have scored the first 19. Of the 194 clinical versus US assessments, 134 had clinically normal knees, however only 62 of these had normal US (46 had mild E on US, 21 moderate, and 5 marked E). Sixty had abnormal clinical examinations, and 59 matched US were abnormal. Thirty-two were deemed to have a mild E clinically, however only 4 US demonstrated mild E (23 moderate E, 4 marked E, and 1 no E). Finally, 11 knees had marked E on examination, and 10 US scans showed marked E (1 scan a mild E). Ordinal regression analysis confirmed that there was 7.7 units of difference between Clinical scores and US score ($p< 0.001$), confirming greater sensitivity with US. With 6 units = 1 point on the scoring system. Thus, US on average scored 1.3 point higher on the scoring system when compared to clinical examination. US and MRI scans were compared for E and SH scores. US gave a higher grading than MRI with 4.1 units of difference ($p<0.001$). Thus, US on average scored 0.7 point higher on the scoring system compared to MRI.

Conclusion: A significant number of knee joint effusions are missed on clinical examination. US was much more sensitive at identifying joint effusions and synovial hypertrophy when compared to clinical assessment and MRI. The finding that US, in this study, was more sensitive than MRI at detecting joint effusions, was may be due to: 1) the time delay between US and MRI; 2) lower sensitivity of MRI as T2 weighted images rather than contrast with gadolinium was used. There was good correlation between US and MRI in detecting pathology.

US of the knee is a simple, cheap, and effective method of detecting joint effusions and synovial hypertrophy in JIA and should be used as an adjunct to clinical examination, especially when joint injections are being considered.

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Ultrasound Abnormalities of Enthesitis in Juvenile Idiopathic Arthritis and Correlation with Clinical Examination. Sandrine Jousse-Joulin[1], Sylvain Breton[2], Claire Cangemi[2], Elisabeth Finel[3], Loic De Parscau[3], Alain Saraux[1] and Valerie Devauchelle-Pensec[1], [1]Rheumatology, Brest, France, [2]Radiology, Brest, France, [3]Paediatric, Brest, France

Purpose: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous condition including a subtype with enthesitis. The clinical assessment and quantification of peripheral enthesitis is quite difficult and lack of sensitivity. Ultrasonography is an attractive imaging technique that could permit the detection of enthesitis under clinical investigation. However, US aspect of enthesitis in children with JIA has never been described.

The aim of our study was to describe ultrasonography (US) in B mode with power Doppler abnormalities in peripheral enthesitis in JIA and to compare US findings with clinical examination.

Method: Patients with recent JIA in according to Durban criteria were included. US examination was performed by a rheumatologist experienced in musculoskeletal US (SJJ), and blinded to the diagnosis. Ultrasound in B mode and power Doppler was performed with an HDI 5000 ultrasonography system (IU-22 Philipps) using a 12, 5-MHz linear array. Five peripheral entheseal insertion sites were examined bilaterally: patella (two sites of insertions of the patellar tendons), quadricipital femoral tendon insertion, Achilles tendon and plantar fascia insertions on the calcaneus. Physical examination was performed by an experimented practitioner (VDP) who considered pain, tenderness and swelling. In absence of consensus, US enthesitis (USE) was considered as detection of vascularization at the site of the enthese and graded from 0 to 3.In absence of consensus, particular attention was given to the detection of vascularization at cortical bone insertion of entheses and junction with the cartilage; the thickness of body of tendon, and bursa

Results: Eighteen patients with JIA were included (10 females, median age 12.1 ± 3 years, range 3.6 to 16.9 years). 38.9% (7/18) had arthritis and enthesitis, 16.7% (3/18) had polyarthritis with rheumatoid factors and 33.3% (6/18) had oligoarthritis. 173 entheseal insertion sites were evaluated and 8.1% (14/173) had USE, among them 42.9% (6/14) were not diagnosed by clinical examination. Overall, USE and physical examination were significantly associated ($p<0.0001$) for pain only. However, inter-observer agreement between USE and clinical evaluation was moderate (kappa 0.43). It was also strongly associated with the diagnosis of arthritis/enthesitis ($p< 0.0001$) and the HLA-B27 status ($p= 0.002$). USE were preferentially located at proximal insertion of the patellar tendon.85.7% (12/14) of USE were graded 3. Thickness of the enthesitis was not associated to USE or clinical findings as bursitis. The cartilage vascularization rarely found (4%, 7/173) was not associated with USE or clinical findings and was also found in a cohort of healthy children.

Conclusion: USE was associated with clinical examination, however, enthesitis were frequently undiagnosed by clinical examination. USE can be defined by Doppler vascularization at cortical bone insertion of entheses. Tendon thickness is probably not a good diagnosis criteria for USE and the cartilage vascularization should be a normal aspect.

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Proposal for Outcome Measures for Juvenile Idiopathic Arthritis (JIA)–Associated Uveitis From the JIA-Uveitis Outcomes Working Group. Ivan Foeldvari[1], J. Anton[2], J. Deboer[3], C. Edelsten[4], E. Graham[5], K. Kotaniemi[6], F. Mackensen[7], S. Nielsen[8], C. E. Rabinovich[9], A. V. Ramanan[10], K. Minden[11], R. K. Saurenmann[12], Justine A. Smith[13] and A. Heiligenhaus[14], [1]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany, [2]Childrens Hosp, Barcelona, Spain, [3]Children Hosp, Utrecht, Netherlands, [4]GOS, London, United Kingdom, [5]St T. Hosp, London, United Kingdom, [6]Rheum Found Hosp, Heinola, Finland, [7]Uni. Heidelberg, Heidelberg, Germany, [8]Uni Child Hosp, Copenhagen, Denmark, [9]Duke Univ Med Ctr, Durham, NC, [10]Hosp Childr, Bristol, United Kingdom, [11]DRFG, Berlin, Germany, [12]Uni Child Hosp, Zurich, [13]Oregon Health & Science Univ, Portland, OR, [14]Ophth., Muenster, Germany

Purpose: Uveitis associated with JIA is a leading cause of vision loss in children in the Western world. To date no standardized criteria exist to evaluate the efficacy of treatment approaches. Our multidisciplinary group is focusing on the development of outcome measures.

Aim: To develop outcome measures for JIA-associated uveitis to facilitate the evaluation of the efficacy of a given treatment on the activity and complications of uveitis.

Methods: An expert group of paediatric rheumatologists and ophthalmologists specializing in uveitis was established. Three face-to-face meetings were conducted, using the Delphi process, in order to develop outcome measures.

Results: Proposed JIA-associated uveitis outcome measures

Domain	Item
Grade of flare /visit (SUN grading system)	□ Slit lamp examination □ (optional tool – flare meter)
Grade of uveitis activity (cells)/ visit (adapted from SUN grading system)	□ Slit lamp examination (record number of cells)
Number of visits with active uveitis	□ Records of the treating physician (require at least 4 visits/year)
Duration of activity (at least 3 monthly visits)	□ Slit lamp examination □ (optional tool- flare meter)
Visual acuity (as defined by WHO criteria, adapted for use in children)	□ Snellen visual acuity
Development of a new complication (SUN criteria except blindness)	□ Posterior synechiae – in quadrants – yes/no □ Glaucoma - yes /no □ Ocular hypertension > 24 mmHg) - yes /no □ Cataract (LOCS III criteria) □ Band keratopathy - yes/no □ Macular edema – assessed preferably by OCT – yes /no
Quality of life	□ Global assessment by parents - VAS score □ Global assessment by child – VAS score □ CHAQ □ CHQ □ (Pediatric uveitis specific quality of life instrument – does not yet exist - research tool)

	□ Number of missed school days
Global disease activity	□ assessment by parents - VAS score □ assessment by children – VAS score □ Uveitis activity /severity and overall uveitis related concerns by treating ophthalmologist □ Overall disease activity and uveitis activity assessment by treating paediatric rheumatologist □ CHAQ □ Pediatric ACR
Biomarkers	□ (Disease specific biomarkers – research tool)
Need for surgery	□ Yes /no according to patient's records

Conclusion: In the next step this proposed domains and items will be validated prospectively on consecutive patients, at the time that a change in treatment is made. The aim is to develop validated outcome measures in compliance with the OMERACT procedure.

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Determination of Response to Treatment of Anterior Uveitis with Juvenile Idiopathic Arthritis and Isolated Chronic Idiopathic Uveitis. S. Charuvanij[1], J. Guzman[1], C. Lyons[2] and R. Petty[1], [1]Division of Rheumatology, BC Children's Hospital, Vancouver, BC, [2]Department of Ophthalmology, BC Children's Hospital, Vancouver, BC

Purpose: Chronic Idiopathic Uveitis (CIU) and chronic anterior uveitis with Juvenile Idiopathic Arthritis (JIA+U) pose difficult therapeutic challenges. Topical corticosteroids are usual initial therapy. Non-responders are usually treated with oral or subcutaneous methotrexate (MTX). Non-response to the combination of MTX and topical corticosteroids therapy usually prompts addition of an anti -TNF agent, cyclosporine (CyA) or mycophenolate mofetil (MMF). This study evaluates treatment requirements in 71 children with chronic anterior uveitis.

Method: A retrospective chart review of children with JIA+U and CIU seen between January 1999 and June 2009 at British Columbia's Children's Hospital, Vancouver, Canada. Remission of uveitis was defined as ≤ 1 cell in the anterior chamber at the last slit-lamp examination.

Results: Of 71 patients with chronic uveitis 43 had JIA and 28 had isolated CIU. Of those with JIA, 25 had persistent oligoarticular JIA, 10 had extended oligoarticular JIA, 4 had enthesitis-related arthritis, 3 had rheumatoid factor negative polyarticular JIA and 1 had psoriatic arthritis. Mean age at diagnosis of JIA was 4.6 yrs. The mean of diagnosis uveitis in the JIA group was 6 yrs and in the CIU group was 8.7 yrs. Females and Caucasians were predominant in both groups. ANA was present in 21 JIA patients (48.8%) Bilateral uveitis was present in 20 (51%) JIA and 24 (85%) CIU patients. The most common complications were cataract, posterior synechiae and glaucoma. The mean follow up of JIA+U was 5.7 yrs and of CIU 3.9 yrs. All children received topical corticosteroids as initial therapy, which adequately controlled uveitis in 7 patients with JIA (16.2 %) and 8 (28.5%) with CIU. Twenty-one (48.8%) of those with JIA and 15 (53.6%) of those with CIU additionally required oral or subcutaneous MTX. Fourteen patients (9 with JIA and 5 with CIU) received infliximab, (4 – 10 mg/kg every 4 – 8 weeks), leading to remission in 8 patients, but failing to control uveitis in 6 after 38 to 945 days (median 624 days, IQR 178.8 - 795.7) of therapy. Three of these patients received CyA, and 1 received MMF. Age of the time diagnosis of uveitis, sex, ethnicity, JIA, JIA subtype, ANA, RF and HLA-B27 were not associated with the response to treatment.

Conclusion: Control of uveitis with topical corticosteroids was achieved in < 20% of children with JIA and < 30% of those with CIU. A combination of topical corticosteroids and MTX was effective in 48.8% of patients with JIA and 53.6 % of those with CIU. Initial treatment of uveitis with topical corticosteroids and MTX may minimize the toxicity of corticosteroids and should be prospectively evaluated. The failure of infliximab to promptly control disease in 42.8% of MTX-resistant patients, suggests that alternative therapy should be considered.

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Comparison Between Infliximab and Adalimumab for the Treatment of Refractory Chronic Uveitis in Childhood. Gabriele Simonini[1], Cecilia Bresci[1], Monica Lo Russo[1], Ilaria Pagnini[1], Cinzia De Libero[2], Roberto Caputo[2] and Rolando Cimaz[1], [1]University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [2]Ophtalmology Unit, Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy

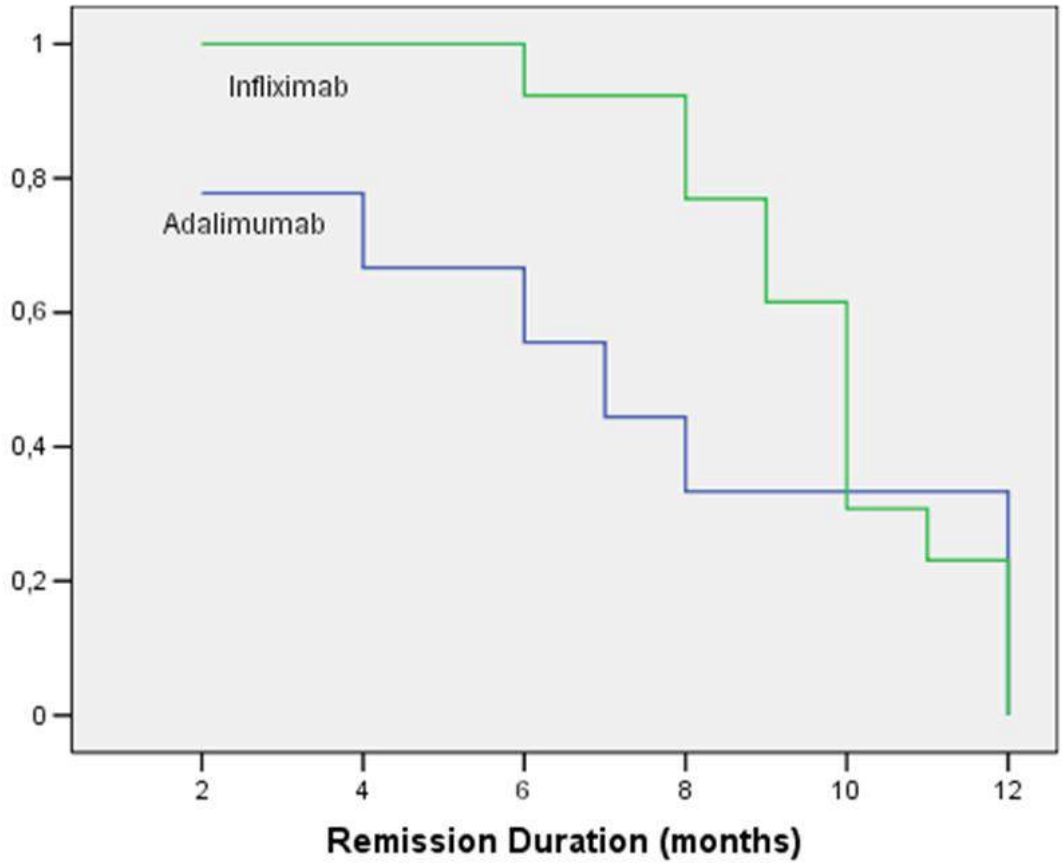
Purpose: we wanted to compare the efficacy of Infliximab (I) *vs* Adalimubab (A) in the treatment of childhood chronic uveitis during the first year of treatment.

Methods: Eighteen patients (median age 11 yrs, range 5–21) with chronic uveitis were enrolled. Before anti-TNF treatment, children had presented active uveitis despite Metothrexate and/or Cyclosporine A. All were also receiving oral prednisone (1–2 mg/kg/day) for at least 1 month. Nine children (5F 4M; diagnoses: JIA 4 pts, idiopathic uveitis 3, early-onset sarcoidosis 1, Behçet's 1) received I (6 mg/kg), administered at weeks 0, 2, 6, then every 6–8 weeks. Nine children (6F, 3M; JIA 7 pts, idiopathic uveitis 2) received A **(**24 mg/sq.mt., every 2 weeks). Absence or recurrence rate of uveitis up to the last visit, visual acuity pre- and post-biologics, and tapering of oral corticosteroids were recorded.

Results: In the Infliximab group, median follow-up time of treatment was 30 months (range 16–38 months) with a median number of infusions of 22 (range 11–30); in the Adalimumab group, median follow-up was 8 months (range 5-12) with a median number of administrations of 16 (range 9-24). The two groups did not differ as for age, gender, previous cumulative corticosteroid dose, previous treatments duration, active uveitis duration, number of previous flares.

During the first year of treatment after starting anti-TNF therapy, all children achieved a complete remission, on **I** over a median period of 10 weeks (range 6–16 weeks), on **A** over a median period of 8 weeks (range 8-14). Steroid administration was always discontinued during the first months (on **I** range 2–5 mo., on **A** range 3-5, p= NS). Survival Cox-regression analysis, limited to the first year of treatment and at mean of covariates (gender, age at uveitis onset, disease duration, underlying diagnosis, and concomitant medication), did not show statistical significant differences between the two treatment with regard to time to remission, time to steroid discontinuation, and remission duration (Figure).

Conclusion: Even if limited to a small group and in a short-term analysis, this comparative cohort-study suggests that Adalimubab is as efficacious as Infliximab in the treatment of sight-threatening childhood uveitis.



Disclosure: G. Simonini, None; **C. Bresci**, None; **M. Lo Russo**, None; **I. Pagnini**, None; **C. De Libero**, None; **R. Caputo**, None; **R. Cimaz**, None.

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Safety and Efficacy of Anti-TNF Agents in Refractory Uveitis in Juvenile Idiopathic Arthritis: The Italian REGISTRY. Maria Elisabetta Zannin[1], Giorgia Martini[2], Irene Pontikaki[3], Rolando Cimaz[4], Loredana Lepore[5], Claudia Bracaglia[6] and Francesco Zulian[7], [1]University of Padua, Padua, Italy, [2]Dpt of Pediatrics, University of Padua, Padua, Italy, [3]Gaetano Pini Institute, Milan, Italy, [4]University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [5]IRCCS Burlo Garofalo, Trieste, Italy, [6]Division of Rheumatology, Rome, Italy, [7]Dpt of Pediatrics, Rheumatology Unit, University of Padua, Padua, Italy

Purpose: Recently, tumour necrosis factor-alpha (TNF-α) blocking agents have been used to treat chronic and refractory uveitis, in adults as well as in children. Since 2007 an national registry, reporting all patients with Juvenile Idiopathic Arthritis (JIA)-related uveitis treated with anti-TNFα agents, have been established in Italy.

We report the results of two-year follow-up on safety and efficacy of anti-TNFα treatment in refractory uveitis, associated to JIA.

Methods: A cohort of children treated with anti-TNFα agents for refractory JIA-related uveitis between January 2007 and December 2008 were followed by a standardized protocol. Uveitis course, ocular complications, type and dosage of anti-TNF agents used, and side effects have been analysed.

Results: Fifty-three patients (45 female, 8 male) have been included in the registry, mean age 10.7 years and mean follow-up 10.4 months. All patients failed previous traditional immunosuppressive treatments (MTX, CyA, MMF). Twenty-eight patients were initially treated with adalimumab (ADM), 25 with infliximab (IFX). Five patients (9,4%) shifted from IFX to ADM due to infusion reactions (3) or inefficacy (2). The mean IFX dosage was 4.9 mg/kg (range 3.0-6.0), the mean ADM dosage was 0.9 mg/kg (range 0.5 -1.3 mg/kg). Side effects have been reported in 8/46 (17.4%) including, during IFX treatment, headache (3), infusion reactions (3), irritability (1), recurrent upper respiratory tract infections (1), and, during ADM treatment, urticarial rash (1), hypertransaminasemia (1) and menomethrorragia (1).

In 28/53 subjects with at least one year F/U, cataract was present at treatment start in 12 subjects (42.9%), vitreitis in 3 (10.7%), cystoid macular edema (CME) in 2 (7.1%) and ocular hypertension in one. After one year of treatment, no new ocular complications appeared and the pre-existing remained stable. All 15 patients with no ocular complications at the treatment start did not develop complications at the end of the one-year F/U.

Conclusion: Anti-TNF agents, IFX and ADM, appear to be effective and safe for the treatment of refractory JIA-related uveitis. The national registry represents an innovative instrument to improve the quality of the clinical research and to address the safety issues for the health regulatory agencies.

Disclosure: M. E. Zannin, None; **G. Martini**, None; **I. Pontikaki**, None; **R. Cimaz**, None; **L. Lepore**, None; **C. Bracaglia**, None; **F. Zulian**, None.

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Health-Related Quality of Life of Children with Cryopyrin-Associated Periodic Syndromes (CAPS) Before and After IL-1 Blockade.

Roberta Caorsi[1], Giulia Paloni[2], Maria Alessio[3], Francesco Zulian[4], Marco Cattalini[5], Donato Rigante[6], Nicola Ruperto[7], Alberto Martini[1], Loredana Lepore[2] and Marco Gattorno[1], [1]Istituto Giannina Gaslini, Genoa, Italy, [2]IRCCS Burlo Garofalo, Trieste, Italy, [3]Dpt of Pediatrics, Rheumatology Unit, University of Naples Federico II, Naples, Italy, [4]Dpt of Pediatrics, Rheumatology Unit, University of Padua, Padua, Italy, [5]Dept of Pediatrics, Spedali Civili e University of Brescia, Brescia, Italy, [6]Univ Cattolica Sacro Cuore, Rome, Italy, [7]IRCCS Istituto G. Gaslini, Universita' di Genova, Genova, Italy

Purpose: to evaluate the health quality of life in patients affected by cryopyrin-associated syndromes and its change after treatment with IL-1 beta receptor antagonist (Anakinra).

Method: 19 patients (F:M = 10:9, median age 12.4 years, range1.59-32) with a clinical diagnosis of Muckle-Wells syndrome (4 pts) or CINCA/NOMID (15 pts) were enrolled. 70% of them carried mutations of NALP3 gene. Patients were asked to evaluate their quality of life before treatment with Anakinra and at follow-up. The Child Health Questionaire (CHQ-PF 50) was used to access the health related quality of life; the results were compared with the ones obtained from an healty patients control group of 315 healthy children (52.2% female), with a mean (SD) age of 11.2 (3.8) years.

Results: At baseline the patients showed a poorer health-related quality of life than healthy children, with a major impact on physical concepts (PhS, mean 38.2, SD 3.9; controls 54.5, SD 3.1, $p < 0.001$) in respect to psychosocial concepts (PsS, mean 41.2, SD 8.9, controls 51.2 SD 7.4, $p < 0.01$) with a clear difference in the impact of the disease activity on HRQOL between CINCA/NOMID and MWS patients.

14 out of 19 patients were treated with IL-1 blockers (Anakinra) at the minimal dosage able to determine the complete control of the clinical and laboratory features (from 1 to 3.5 mg/kg/day). The mean duration of treatment 37.5 months (range 12-54 months). Independently from treatment duration, all treated patients displayed a significant improvement in all health concepts (PhS mean 52.2, SD 4.5; $p < 0.001$ Wilcoxon Pairs Test; PsS mean 47.8 SD 8.4; $p < 0.01$) at follow-up. Both CINCA and MWS patients showed significantly lower values than healthy controls in most of the CHQ health concepts, particularly those related to physical domains. The most impaired CHQ health concepts were global health (GGH), physical functioning (PF), role/social limitations–emotional/behavioural (REB), bodily pain/discomfort (BP), general health perception (GH) and parental impact emotional (PE).

Conclusion: Patients with CAPS present a severe limitation of health related quality of life. Long term IL-1 blockade produces a significant and persistent improvement not only in the clinical manifestations associated with the disease, but also on the overall quality of life.

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Mevalonate Kinase Deficiency: A French Multicenter Retrospective Study. B. Bader-Meunier[1], Benoit Florkin[2], L. Cuisset[3], D. Rabier[2], Mo Rolland[4], B. Neven[2], Anne Marie F. Prieur[5] and P. Quartier[1], [1]Hopital Necker-Enfants Malades, Paris, France, [2]Hôpital Necker, Paris, France, [3]Hôpital Cochin, Paris, France, [4]Hôpital de Lyon, Lyon, France, [5]Hopital Enfants-Malades, Paris

Purpose: To describe the wide spectrum of clinical and genetic manifestations of mevalonate kinase (MK) deficiency (MKD)

Method: A retrospective French study included patients who had clinically suspected MKD confirmed by at least one of the following criteria: i) mutated MVK gene, ii) decreased MK activity in lymphocytes or fibroblast, iii) elevated mevalonic acid in urine. Medical charts were reviewed or questionnaires were filled in by treating physician

Results: 40 patients (23 women and 17 men) belonging to 34 families were included. The median age at the onset of symptoms was 6 months. The median duration of the follow-up was 31 years. First symptoms occurred before age 2 years in 90% of patients Attacks of fever lasted from one to ten days. During the attacks, all the patients presented with at least two of the following features: arthralgia/arthritis (68%), lymphadenopathy (63%), abdominal pain (63%), diarrhea (63%), skin lesions (60%). Digestive symptoms were associated with rectitis and ulcerative colitis (1 patient each), anal ulcer and fistula (1 patient each), abdominal adhesions (3 patients). Less frequently, aphtous ulcers (38%), vomiting (32%), febrile seizures (7%), pericarditis (2%), hepatitis (2%), thrombocytopenia (7 %) and macrophage activation syndrome (7%) occurred. Additionally, 14 patients presented with severe lasting neurological, renal (including two patients with renal angiomyolipoma), pulmonary, ocular and/or endocrine involvements. During attacks, all patients had an increased C-reactive protein (median, 152 mg/L; range, 59-440), and leucocyte count (median, 20.8.109/L; range,7.5-59). Serum immunoglobulin (Ig) D concentration was > 100 IU/L in 20/24 patients, and median serum Ig A values 4 g/L (range, 1.1-20.9**).** Mevalonic aciduria tested during attacks was increased in the 20/20 tested patients. MK activity was decreased in comparison with controls in 33/33 tested patients. V377I mutation was the most prevalent mutation (21/34 families). MKD related-death occurred in two patients from staphylococcal sepsis associated with a macrophage activation syndrome, and from multiorgan failure secondary to the severe inflammatory response syndrome respectively. Non-steroid anti-inflammatory drugs, steroids, statin, colchicine, anti-tumor necrosis factor alpha, anti-interleukin-1 were tested to treat and prevent attacks, with variable success. One patient successfully received allogenic stem cell transplantation.

Conclusion: The present study emphasizes the clinical heterogeneity of MKD and underlines its severity in a subset of patients

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ACR Poster Session A

Systemic Lupus Erythematosus Treatment, Demographic and Environmental Effects, and Other Outcomes
Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Association of Adiponectin and Soluble Endothelial Protein C Receptor (sEPCR) with Longitudinal Assessments in the Induction Phase of a Randomized Multicenter Trial Comparing Mycophenalate Mofetil and Intravenous Cyclophosphamide. Robert M. Clancy[1], Ellen M. Ginzler[2], MMF/IVC Lupus Nephritis Induction Trial[3] and Mimi Kim[4], [1]NYU School of Medicine, New York, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY, [3]New York, NY, [4]Albert Einstein Coll Med, Bronx, NY

Purpose: A major barrier to understanding and treating lupus nephritis (LN) is the paucity of sensitive and validated biomarkers. Recent evidence has suggested that two markers found on the endothelium of LN biopsies merit focus. Adiponectin is expressed on the endothelium of all vessels in biopsies from patients with LN but decreased in areas of fibrosis and/or inflammation. Adiponectin knockout mice suggest that adiponectin may be a key regulator of proteinuria. Increased expression of membrane EPCR in LN biopsies predicts a poor response to therapy. Based on these vascular clues, this study leveraged the LN induction trial comparing intravenous cyclophosphamide (IVC) and mycophenolate mofetil (MMF) to evaluate the relationship between clinical response of LN and levels of adiponectin and sEPCR as a proxy for vascular “protective” molecules.

Methods: The endothelial markers, adiponectin, sEPCR, e-selectin, and nitric oxide were measured in 109 plasma from 48 patients enrolled in the LN induction trial. Response was evaluated based on reaching a primary endpoint with a prespecified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. The span of the induction period was 24 weeks. Sample collection included visits 4 (4wks), 7 (15 wks) and 9 (24 wks).

Results: There was a consistent trend toward increased levels of plasma adiponectin in responders vs nonresponders (19.2 ± 6.8 vs 16.4 ± 9.1 at visit 4; 13.0 ± 5.2 vs 11.7 ± 6.5 at visit 7; 13.7 ± 7.8 vs 10.9 ± 4.9 at visit 9). In patients with subnephrotic proteinuria (<3g/day urine protein; 63% of the total), plasma adiponectin was similarly increased in responders vs nonresponders at all visits. Moreover, when combining data across all visits nonreponders had significantly lower adiponectin (p=0.0032). There was a tendency of sEPCR to decrease in responders vs nonresponders (243 ± 164 vs 284 ± 167 at visit 4; 338± 271 vs 341 ± 197 at visit 7; 260 ± 104 vs 368 ± 216 at visit 9). In comparing MMF vs IVC, sEPCR, levels were significantly higher in the IVC group when data was combined over all visits (p=0.005). Consistent with evidence that therapy in the responder arm mobilizes vascular protective molecules, levels of nitric oxide changed in the predicted direction (62 ± 47 vs 68 ± 66 at visit 4; 39 ± 46 vs 52 ± 65 at visit 7; 27 ± 33 vs 92 ± 55 at visit 9; p=0.02). Combining data across all visits, nonresponders had significantly higher NO levels than responders (p=0.046). The differences in plasma NO were not accounted for by clearance as fractional excretion of NO did not differ between responders and nonresponders. Levels of sE selectin did not track with response.

Conclusion: These results demonstrate longitudinal associations between increased adiponectin and decreased sEPCR levels as a combined biomarker of renal response. Accordingly, vascular protection tracks with favorable outcomes.

Disclosure: R. M. Clancy, NIH, R01 AR055088-01, 2 ; **E. M. Ginzler**, Aspreva, 6 ; **M. Kim**, None.

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Mycophenolate Mofetil (MMF) Is Effective for Systemic Lupus (SLE) Arthritis, Final Results of An Organ-Specific, Double-Blind, Placebo-Controlled Trial. Joan T. Merrill[1], Molina Mhatre[2], Fredonna Carthen[3], Sandra K. Wilson[4], Stan Kamp[2], Joy G. Hutcheson[1], Joseph Rawdon[2], Eric Finley[2], Ewa Olech[2], Robert M. Clancy[5] and Jill Buyon[5], [1]OMRF, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma City, OK, [4]OK Med Resch Foundation, Oklahoma City, OK, [5]NYU School of Medicine, New York, NY

Purpose: Design of clinical trials for SLE is challenging, possibly due to the clinical and biologic heterogeneity of the disease, compounded by variable background treatments. This focused, proof of concept study of MMF combined an arthritis-specific primary outcome with simplification of background medications and a biomarker-linked responder analysis. We previously reported 3 month results (ACR 2008), and now submit final, six month data after crossover of placebo patients to MMF.

Methods: MMF or placebo (PBO) was dispensed in ascending dose with clinic visits and blood draws at 2, 4, 8, 12, 16, 20 and 24 weeks. 160 mg Depomedrol was given at baseline. Prednisone </= 10 mg/d and hydroxychloroquine were continued, but background immune suppressants were withdrawn.

Results: There was no difference in PBO (n=14) vs MMF (n=13) groups at baseline in age, gender, ethnicity, or # ACR criteria. Mean BILAG scores were 9.5 vs 9.0 at entry, with no difference in swollen or tender joint counts (jts). The pre-specified primary outcome (complete response: BILAG “C” arthritis at wk 12 with </= 25% baseline jts) was met in 0/14 placebo pts vs 4/13 MMF-treated, p=0.041. Major response (MR): BILAG C with </= 50% baseline jts, was met in 0 PBO vs 5 MMF, p=0.016. 4 PBO vs 9 MMF, p=NS, met partial response (PR) at 12 weeks (A to B or B to C in BILAG arthritis or </= 50% baseline jts). MMF, but not PBO, improved composite BILAG scores from mean 9.6 to 5.3 in 12 weeks (p=0.007) From week 12-24 all pts received MMF. 11 PBO-MMF pts completed 8-12 weeks of MMF with 3 MR and 5 PR (p=0.07 for MR and MR+PR vs PBO period). Combining all pts with at least 8 wks MMF, there were 9/24 MR (p=0.014 vs PBO), 19/24 MR+PR (p<0.001) and improved BILAG from median 9 to 2 (Day 0 vs wk 24 scores, p<0.001). Adverse events were minor, primarily URI or GI. Exploratory studies aimed to distinguish the baseline biology or MMR effects on responders vs non-responders. MMF decreased neutrophil CR3 at week 12 vs placebo (p =0.031) and dramatically decreased CR3 of those pts high at entry (>1,000 MFU). These pts had greater decrease in BILAG (p=0.063) and SLEDAI (p=0.015) vs pts with low baseline CR3 (<300 MFU). Other results included:

Baseline Marker	MR n=9	NR n=5	p value
GMCSF pg/ml	4.000	33.22	0.016
IL10 pg/ml	1.89	3.313	ns
IL4 pg/ml	0.132	1.652	0.032
IL1RA pg/ml	71.335	263.59	0.046
IP10 pg/ml	28.7	69.1	ns
Marker after Rx	MR	NR	p value
GMCSF pg/ml	2.584	41.611	0.016
IL10 pg/ml	1.37	2.84	0.045
IL2 pg/ml	0	1.546	ns
IL1RA pg/ml	127.99	223.95	ns
IP10 pg/ml	50.3	68.4	ns
Adiponectin ug/ml	19.8	27.6	ns
NO	11.0	15.9	ns
sE Selectin ng/ml	25.24	35.76	ns

Conclusion: MMF is effective in the treatment of arthritis in patients with SLE. A potential benefit on the vasculature and the possibility that vascular markers could predict or guide optimal treatment is also suggested.

Disclosure: J. T. Merrill, Galencia, 2, Galencia, 5 ; **M. Mhatre**, Galenica, 2 ; **F. Carthen**, Galenica, 2 ; **S. K. Wilson**, Galenica, 2 ; **S. Kamp**, Galenica, 2 ; **J. G. Hutcheson**, Galenica, 2 ; **J. Rawdon**, Galenica, 2 ; **E. Finley**, Galenica, 2 ; **E. Olech**, Galenica, 2 ; **R. M. Clancy**, Galenica, 5 ; **J. Buyon**, Galenica, 5 .

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Long-Term Outcomes-Mycophenolate Mofetil Treatment for Lupus Nephritis with Addition of Tacrolimus for Resistant Cases. J. Cortés-Hernández[1], M. Torres-Salido[1], A. Segarra-Medrano[2], M. Vilardell-Tarres[1] and Josep Ordi-Ros[3], [1]Systemic Autoimmune disease Research Unit. Hospital Vall d'Hebron., Barcelona, Spain, [2]Vall d'Hebron Hospital, Barcelona, Spain, [3]Hospital Vall d'Hebron, Barcelona, Spain

Purpose: Although mycophenolate mofetil (MMF) is increasingly used to manage lupus nephritis (LN), little is known about its long-term benefits and the role of anti-calcineurin agents for MMF-resistant nephritis. The aim is to report our long-term experience with MMF therapy as continuous induction-maintenance treatment in a cohort of 70 patients with LN followed during 5 years. We also report the efficacy of adding tacrolimus as a rescue therapy for resistant cases

Method: Seventy patients with LN were included (84% with type III/IV GMN and 40% with relapsing disease) and followed up to a mean of 60±23 months. Patients received 3 pulses methylprednisolone and MMF (2g/d) for induction and tapering doses of MMF for maintenance therapy. Tacrolimus (0.075 mg/kg/day into divided doses) was added for resistant cases. Primary end-point was the achivement of complete remission (presence of an inactive sediment, proteinuria <0.3 g/day and estable renal function) at 6, 24 and 60 months. Secondary end-points included partial remission, treatment failure, relapse and side effects.

Results: Forty-eight patients (69%) already met criteria for an early response at 12 weeks. See Table 1 for treatment outcomes. Long-term complete response was higher in patients with newly diagnosed glomerulonephritis than those with relapsed nephritis (64% vs. 32%, p=0.014). Renal function was permanently impaired at last follow-up in fourteen patients (20%), six of them had their creatinine level

doubled (9%) and two of them reached ESRD. Time to treatment failure was associated with persistent hypoalbuminemia and higher proteinuria (HR=0.87; 95%CI 0.81-0.95, p=0.001, and HR=1.29; 95%CI 1.03-1.62, p=0,030, respectively) and fewer early responses (HR 0.28, 95%CI 0.10-0.77, p=0.014). Twenty-six (37%) patients suffered a renal relapse. Time to flare was associated to persistent anti-dsDNA titres and younger age at renal flare (HR=1.001; 95%CI 1.001-1.003, p=0.005, and HR=0.36; 95%CI 0.14-0.90, p=0.29, respectively). Tacrolimus was added to MMF in seventeen (24%) patients. After a mean follow-up period of 23±3 months, twelve (70%) patients achieved response (6 CR and 6 PR). Proteinuria levels were significantly reduced by 3 months (p=0.0018). GI side effects (23%) were the most common reported. Three patients developed herpes Zoster and one developed pulmonary tuberculosis in the tacrolimus-combined therapy.

Table 1.

	6m	24m	60m
	N % (95%CI)	N % (95%CI)	N % (95%CI)
Response to therapy	13 19% (0-30%)	32 46% (34-58%)	36 51% (39-64%)
Complete response	48 69% (56-79%)	19 27% (17-39%)	12 17% (9-28%)
Partial Response	61 87% (77-94%)9 13% (6-23%)	51 73% (61-83%) 19 27% (17-39%)	48 69% (56-79%)
CombinedResponse Treatment Failure			22 31% (21-44%)
Relapse	6 (9)%	17 (24%)	26 (37%)
Initiation of Tacrolimus	5 (7)%	13 (19%)	17 (24%)
Death	0	0	1

Conclusion: MMF is an effective treatment for induction-maintenance of remission for LN. Combination therapy with tacrolimus is an effective and safe alternative for MMF-resistant patients.

Disclosure: J. Cortés-Hernández, None; **M. Torres-Salido**, None; **A. Segarra-Medrano**, None; **M. Vilardell-Tarres**, None; **J. Ordi-Ros**, None.

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Clinical Audit of the Therapeutic Efficacy of Mycophenolate Mofetil for the Treatment of Systemic Lupus Erythematosus (SLE).

Richard A. Hickman[1], B.H. Chaudhry[1], C.-S. Yee[1], S. Ghazali[1], V. Toescu[1], C.J. Day[2], C. Osafo[2], D. Adu[2] and C. Gordon[1], [1]University of Birmingham, Birmingham, United Kingdom, [2]University Hospital Birmingham NHS Foundation Trust, Birmingham, United Kingdom

Purpose: Mycophenolate mofetil (MMF) is a novel, steroid-sparing agent that can induce remission in lupus nephritis but is not licensed for use in SLE and there have been no clinical trials in non-renal SLE. We performed an audit to determine whether 70% or more patients who were prescribed MMF, achieved improvement in their disease activity within one year of starting MMF and what proportion of patients had a reduction in their daily steroid dose.

Method: SLE patients attending specialised SLE clinics who were prescribed MMF for ≥ 1 year were studied (n=70). Five patients were not analysed because they were being managed by another centre or MMF was stopped because of increased disease activity before the target dose was achieved. There were 29 (45%) patients of Caucasian origin, 21 (32%) Afro-Caribbeans, 12 (18%) South Asians, 1 (2%) Chinese and 2 (3%) were of other origin. The mean ± sd age at diagnosis of SLE was 31 ± 12.5 years. The mean ± sd age for starting MMF was 31 ± 13.7 years. Disease activity on the date that MMF started and one year later was assessed by the BILAG index score (BIS). A standard was set such that 70% of patients should i) reduce their BIS by >1 category (eg. A to B, B to C etc.), ii) reduce their steroid dose to ≤10 mg, and iii) improve disease activity markers as determined by complement 3 (C3) and complement 4 (C4) levels.

Results: Of 49 (75%) patients that could improve their non-renal BIS (as they had BILAG A or B scores at baseline), 84% (n=41) demonstrated overall improvement in their non-renal BIS. Of 25 (38%) patients that could improve their renal BIS (n=25), 19 (76%) showed improvement in their renal BIS. 72% of patients (n=47) reduced their prednisolone dose. Overall, there was a non-significant reduction (p=0.24) in mean + steroid dose after one year of MMF therapy (mean steroid dose at baseline 20 ± 12.3 mg; mean steroid dose one year

later = 13.1 ± 6.0 mg). Of patients with prednisolone doses >10mg/day at MMF start (n=50), 19 (38%) had a reduction of their steroid dose by ≥10mg/day, whilst another 25 (50%) had a reduction of <10 mg/day; 24 (48%) of these patients with prednisolone doses >10mg/day had a steroid dose after one year of ≤10 mg/day. C3 and C4 significantly improved in those patients who initially had low values for C3 (n= 18) and for C4 (n=22): mean ± sd C3 at start= 0.58 ± 0.13 g/l, mean ± sd C3 after 1 year= 0.76 ± 0.26 g/l, p=0.03; mean ± sd C4 at start= 0.08 ± 0.024 g/l, mean ± sd C4 after 1 year= 0.14 ± 0.098 g/l, p=0.007. C3 values were normalized in 11 of 18 (61%) patients; C4 values were normalized in 8 of 22 (36%) patients.

Conclusion: MMF in conjunction with prednisolone appears beneficial in reducing disease activity in renal and non-renal disease in SLE. A randomised controlled trial assessing non-renal efficacy of MMF is needed.

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Tolerability and Efficacy of Mycophenolate Mofetil in An Ethnically Diverse, University Based Cohort. Samantha Bell and Maria Dall'Era, UCSF, San Francisco, CA

Purpose: Mycophenolate Mofetil (MMF), an inhibitor of de novo purine biosynthesis, is increasingly used to treat a variety of manifestations of systemic lupus erythematosus (SLE). Data from several controlled clinical trials in lupus nephritis and from small case series in non-renal SLE have suggested that MMF is efficacious and well tolerated. Our aim was to assess the tolerability and efficacy of MMF in an unselected, "real world" cohort of ethnically diverse SLE patients who were prescribed MMF for renal and non-renal indications.

Methods: We retrospectively studied 100 SLE patients treated with MMF while being followed in the UCSF Lupus Clinic from October 1997 to June 2008. The mean disease duration for all patients was 11.18 years. All patients were included in the tolerability analysis. The efficacy analysis included those 28 patients (15 with lupus nephritis, 13 with non-renal lupus) who initiated MMF while in the UCSF Lupus Clinic and who were on MMF for at least two months. As part of the efficacy analysis, patients were further designated as switchers or controls. Switchers were patients who switched from another immunosuppressive agent to MMF, and controls were patients who started MMF as their first immunosuppressive agent. Efficacy was assessed by changes in prednisone dose, SLEDAI, complement C3, and anti-dsDNA. In renal patients, serum creatinine, proteinuria, and hematuria were also measured.

Results: 100 patients were included in the tolerability analysis: 16% African American, 28% Caucasian, 33% Asian/Pacific Islander, 16% Hispanic. 28 patients were included in the efficacy analysis. Indication for treatment with MMF varied: 74 patients for nephritis, 8 patients arthritis, 9 patients skin disease, 8 patients hematological, 1 hearing loss, 4 serositis, 2 vasculitis, 1 transverse myelitis, and 3 neuropathy. In the overall population, MMF was well tolerated. Kaplan-Meier analysis indicated 60% of patients continued MMF for > 4 years (75% of lupus nephritis patients, 25% non-renal patients). Fourteen patients discontinued MMF due to an adverse event: epigastric discomfort/nausea in 6 patients, diarrhea in 3 patients, herpes zoster in 1 patient, pruritis in 2 patients, serositis in 1 patient, and self-discontinuation in 1 patient. No patient discontinued MMF because of leukopenia.

In both lupus nephritis and non-renal lupus patients, we found a statistically significant reduction in prednisone dose and SLEDAI over the course of follow-up. Within the lupus nephritis group, we observed that serum creatinine, protein to creatinine ratio, anti-dsDNA, and urine red blood cells increased in the switcher group but decreased in the control group.

Conclusion: Our study demonstrates that MMF is well tolerated in a "real world" SLE population. Discontinuation due to an adverse event occurred in only 15% of patients treated with MMF, most commonly due to epigastric discomfort or diarrhea. Our data also suggest that MMF is efficacious for the treatment of lupus nephritis and non-renal lupus.

Disclosure: S. Bell, None; **M. Dall'Era**, None.

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Mycophenolate Mofetil Dosing and Renal Relapse or Renal Endpoint in Lupus Nephritis. Mary Katherine Farmer-Boatwright, Keisha L. Gibson, Susan L. Hogan, Yichun Hu, Caroline E. Jennette and Mary Anne Dooley, Univ of NC at Chapel Hill, Chapel Hill, NC

Purpose: To examine the relationship between mycophenolate mofetil (MMF) dosing and renal endpoints in a SE US renal-biopsy based cohort. Endpoints included renal relapse, sustained doubling of creatinine, end-stage renal disease (ESRD) and death.

Methods: We performed a retrospective chart review of consented patients with proliferative or membranous nephritis from this registry. Data were examined using descriptive statistics and Wilcoxon two-sample test.

Results: Sixty-two subjects with a median age of 28.5 years (range 8.4-60.7) were included. Baseline estimated GFR (eGFR) and eGFR at last follow up were similar (84.3+/- 40.4 cc/min; 83.7 (+/- 47.9) cc/min). Median follow up was 36 months (range 6-114 months). The median maximum daily dose of MMF was 2000 mg (range 750-3000 mg). Seven patients (11%) reached a renal endpoint. They had an average daily maximum dose of 1607 mg MMF (+/- 453 mg), compared to those with no renal endpoint (2273 +/- 632 mg [$p = 0.013$]). We characterized 33 relapses in 25 patients at an average of 20.3 months (+/- 10.9) into treatment. The average maximum daily dose of MMF among relapsers was 2096 mg (+/- 637 mg) compared to 2400 mg (+/- 548 mg) in non-relapsers ($p = 0.069$). The average MMF dose at the time of first relapse was 1481 mg (+/- 790 mg), versus non-relapsers at 2400 mg (+/- 548 mg; $p<0.0001$). Two deaths occurred, both in patients who were non-relapsers: one due to CNS lymphoma, and the other to non-accidental trauma.

Conclusion: Our results suggest that lower doses of MMF are associated with renal relapse, doubling of serum creatinine, ESRD or death. Further studies are necessary to define the interaction between patient factors and dosing.

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Systematic Review and Meta-Analysis of Randomized Trials of Mycophenolic Acid/ Mycophenolate Mofetil for Induction Treatment of Lupus Nephritis. Zahi Touma, M.B. Urowitz and Dafna Gladman, University of Toronto, Toronto Western Hospital, Toronto, ON

Background: Mycophenolic Acid (MPA, Myfortic) and Mycophenolate Mofetil (MMF, Cellcept) have emerged as a treatment modality for induction treatment of Lupus nephritis (LN) while the use of Cyclophosphamide has been accepted as the standard of care for many years.

Purpose: We conducted a systematic review and meta-analysis to assess the effectiveness and safety of MMF and MPA in the induction treatment of LN.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Library for relevant articles without language restriction up to June 25, 2009. We also searched the bibliographies of selected articles. The primary outcome was renal remission (complete, partial and overall); secondary outcomes were adverse events (infections, leucopenia, gastrointestinal symptoms, herpes zoster, amenorrhea and alopecia) at end of original study, death and end stage renal disease (ESRD) using reported extended follow-up data. For binary outcome variables (renal remission and adverse events), we calculated the relative risks (RRs), as well as respective 95% confidence intervals (CIs).The Mantel-Haenszel fixed-effects model was used to determine the pooled RR along with its 95% CI for renal remission and adverse events for MMF versus Cyclophosphamide using data from all eligible randomized clinical trials (RCTs). We assessed statistical heterogeneity among RCTs using Cochran Q test and by calculating I2 values. We incorporated the random-effects model to deal with heterogeneity among studies. The Cochrane collaboration's software program, RevMan 5 was used to prepare and complete this review.

Results: The literature search resulted in 1551 citations. Abstracts of potentially relevant citations were reviewed. 76 citations were retrieved for detailed evaluation. We included RCTs comparing MMF/MPA versus Cyclophosphamide for induction therapy in patients with biopsy-proven LN with no restriction to age. We identified 4 RCTs with 618 patients for inclusions in the meta-analysis comparing MMF versus Cyclophosphamide. In 4 RCTs MMF (maximum dose used ranged from 2 to 3 g/d given for 6 months) was compared to intravenous Cyclophosphamide (according to the National Institutes of Health protocol 0.75-1g/m2 monthly for 6 months but in one study where it was administered orally as 2.5mg/day for 6 months). In all 4 RCTs patients were treated simultaneously with prednisone at 1mg/kg and tapered thereafter. We observed no significant difference for renal remission (partial, complete, and overall) comparing MMF with Cyclophosphamide. There was no significant difference for infections, leucopenia, gastrointestinal symptoms, herpes zoster and amenorrhea. There was a significant reduction in alopecia (relative risk [RR] 0.27, 95% CI 0.17-0.43) when MMF was compared with Cyclophosphamide.

The analysis of the extended follow-up data showed no significant reduction in ESRD and death when MMF was compared to Cyclophosphamide.

Conclusion: There was no significant difference for the induction treatment of LN when comparing MMF to Cyclophosphamide. Patients treated with MMF showed reduced risk for alopecia.

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Gladman**, None.

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Identification of Factors Influencing Mycophenolic Acid Area Under the Curve in Systemic Lupus Erythematosus. Laurent Arnaud[1], Noël Zahr[2], Julien Haroche[1], Jean-Sébastien Hulot[2], Pierre Marquet[3], Christian Funck-Brentano[2], Jean-Charles Piette[1] and Zahir Amoura[1], [1]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [2]Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France, [3]INSERM U850, Limoges, France

Purpose: Mycophenolate Mofetil (MMF) is widely used for the treatment of Systemic Lupus Erythematosus (SLE). Mycophenolic Acid (MPA) is the active metabolite of MMF. We have shown that MPA Area Under the plasma Concentration-time Curve from 0 to 12 hours (MPA $AUC_{0\text{-}12}$) > 35µg.ml/h is strongly associated with lower SLE disease activity. In this study, we sought to identify factors significantly influencing MPA $AUC_{0\text{-}12}$.

Method: MPA $AUC_{0\text{-}12}$ was determined in 71 consecutive SLE patients (61 women and 10 men, mean (± SD) age at sampling 34 ± 10 years) with stable MMF dose, using a Bayesian estimator developed for SLE. We performed a multiple linear regression built by the *Least Squares method* to identify factors significantly influencing the MPA $AUC_{0\text{-}12}$.

Results: Multivariate analysis including the following parameters: sex, age at sampling, ethnicity, Body Mass Index, daily doses of MMF, daily doses of steroids, hydroxychloroquine blood levels, creatinine clearance (MDRD), and albumin plasma level revealed that daily doses of MMF (p=0.03), albumin plasma level (p=0.04), and MDRD creatinine clearance (p=0.03) were the only 3 independent parameters associated with MPA $AUC_{0\text{-}12}$.

Conclusion: Not only daily doses of MMF but also albumin plasma level and MDRD creatinine clearance are significant parameters influencing MPA $AUC_{0\text{-}12}$. These findings argues strongly for individualized dosing regimen of MMF. Lupus nephritis patients with low albumin plasma level should receive a higher daily dose of MMF to ensure proper exposure to MMF.

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Effect of Rituximab (RTX) On Anti-dsDNA and C3 Levels and Relationship to Response: Results From the LUNAR Trial. R. Furie[1], B. Rovin[2], G. Appel[3], D.L. Kamen[4], F.C. Fervenza[5], A. Spindler[6], R. Maciuca[7] and J. Garg[7], [1]NSLIJHS, Lake Success, NM, [2]Ohio State University Medical Center, Columbus, OH, [3]Columbia, New York, NY, [4]MUSC PO Box 250637, Charleston, SC, [5]Mayo Clinic, Rochester, MN, [6]Universidad Nacional Tucumán, Tucuman, Argentina, [7]Genentech, Inc., South San Francisco, CA

Purpose: Previous studies have suggested that improvements in anti-dsDNA titers and complement C3 levels are associated with remissions in lupus nephritis (LN). Changes in these serologic markers and relationship to renal response were assessed in the LUNAR trial.

Method: Pts with a diagnosis of active class III/IV LN and urine protein to creatinine ratio > 1 were randomized 1:1 to receive RTX (1000mg) or placebo (PLA) on days 1, 15, 168, and 182. Changes in anti-dsDNA titers and complement C3 levels were assessed at Week 52 and correlated to renal responses.

Results: 144 randomized pts (72 to each arm) comprised the intent-to-treat population. Mean daily MMF dose was 2.4±0.63g in PLA and 2.7±0.41g in RTX. Overall, there was no signficant difference in achieving a renal response between the PLA and RTX groups (p=0.55). Baseline median anti-dsDNA and mean C3 were 168.5 IU/mL and 74.1 mg/dL in the placebo group, respectively, and 122.5 IU/mL and 73.6 mg/dL in the RTX group. At Wk 52, there was a greater decrease in anti-dsDNA (p=.007) and greater increase in C3 (p=.025) in the RTX group compared to PLA. Changes by response status are presented in the table. Spearman's correlation coefficient between improvement in C3 and renal response was 0.55 (p<0.001) in PLA and 0.03 (p=0.8) in RTX. Correlation of change in anti-dsDNA to response was not statistically signfificant in either PLA or RTX.

Conclusion: RTX statistically significantly lowered anti-dsDNA titers and increased C3 levels compared to PLA. However, these changes did not translate into a significant clinical benefit for achievement of renal responses. There was a similar level of improvement in anti-dsDNA titers and absolute C3 levels in both RTX responders and RTX non-responders, suggesting that changes in these serologic markers at one year do not correlate with renal response in RTX-treated pts.

	PLA				RTX			
	All (n=72)	Resp (n=33)	NR (n=39)	Diff est* 95% CI	All (n=72)	Resp (n=41)	NR (n=31)	Diff est* 95% CI
Median % reduction in log (anti-dsDNA)	15.2	17.6	12.3	7.3 (-2.3, 17.6)	22.1	24.8	19.4	3.8 (-3.8, 11.1)
% Pts with anti-dsDNA<30	33.3	39.4	28.2	11.2 (-11.4, 33.8)	41.7	43.9	38.7	5.2 (-18.5, 28.9)
Mean increase C3	25.9	44	10.6	33.5 (20.3, 46.7)	37.5	40.9	33.1	7.8 (-5.8, 21.4)
% Pts with C3≥90	63.9	81.8	48.7	33.1 (12.0, 54.2)	80.6	80.5	80.6	0.16 (-19.2, 18.9)

*Difference estimate between responders and non-responders. Hodges-Lehmann estimates of shift, and corresponding 95% CI are calculated for the anti-dsDNA row.

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Tolerance and Efficacy of Rituximab (RTX) in Systemic Lupus Erythematosus (SLE): Data of 104 Patients From the AIR (« Auto-immunity and Rituximab ») Registry. Benjamin Terrier[1], Eric Hachulla[2], Béatrice Pallot-Prades[3], Jean Léone[4], Pierre Quartier[5], Olivier Fain[6], Jean Sibilia[7], Bernard Combe[8], Philippe Gaudin[9], Olivier Meyer[10], Arnaud Hot[11], Bertrand Godeau[12], Eric Vignon[13], Patrice Cacoub[14], Christine Bonnet[15], Claire Larroche[16], Xavier Mariette[1] and J.-E. Gottenberg[7], [1]Bicêtre, Kremlin Bicêtre, France, [2]Claude Hurier, Lille, France, [3]CHU Bellevue, Saint-Etienne, France, [4]CHU, Reims, France, [5]Necker-Enfants Malades, Paris, France, [6]Jean Verdier, Bondy, France, [7]Hautepierre, Strasbourg, France, [8]Lapeyronie, Montpellier, France, [9]CHU, Grenoble, [10]Bichat, Paris, France, [11]Edouard Herriot, Lyon, France, [12]Henri Mondor, Créteil, France, [13]Claude Bernard, Lyon, France, [14]Pitié-Salpétrière, Paris, France, [15]CHU, Limoges, France, [16]Avicenne, Bobigny, France

Purpose: To study safety and efficacy of RTX in 104 SLE patients included in the AIR registry.

Method: The French Society of Rheumatology and the Club Rhumatismes et Inflammation set up the AIR registry which includes patients treated with RTX for rheumatoid arthritis (RA) and other refractory autoimmune diseases.

Results: Epidemiological features: Among the 2235 patients in the registry, 104 SLE patients were included. 86 patients, who had at least 1 follow-up visit, were analyzed (women 80%, mean age 39±16 years, mean disease duration 8±7 years). Mean number of previous immunosuppressants (IS) was 2.4±1.4. 37% and 22% of patients had previously received mycophenolate mofetil (MMF) and cyclophosphamide (CYC), respectively. Indication of RTX: cutaneous and/or articular involvement in 43 patients (41%), renal involvement in 31 (30%, histological class IV: 19, III: 7, V: 4, and II:2 patients), autoimmune cytopenia in 24 (23%), other indications in 6 (6%). Disease activity before RTX: mean SLEDAI 10.5±9.5, mean BILAG 15.1±7.8 (all patients had BILAG A in >/= 1 organ domain), prednisone in 95 (91%) patients (mean: 28.2±20.5 mg/day). RTX administration: monotherapy in 26 patients (25%) and concomitant IS in 78 (75%) [hydroxychloroquine (n=49), MMF (n=19), CYC (n=10)]. Follow-up: Mean follow-up: 15.3±11.7 months = 96.4 patients-years (py). Tolerance: 1 severe infusion reaction, 5 delayed serum sickness-like reactions and 10 severe infections (8.9/100 py) were observed. 1 patient died due to infectious endocarditis. Outcome: Overall efficacy according to the clinician was observed in 63/86 patients (73%). Improvement of cutaneous and/or articular involvement was observed in 38/54 patients (70%), of renal involvement in 15/24 (63%), and of autoimmune

cytopenia in 14/19 (74%). In the 86 patients, mean SLEDAI, mean BILAG and mean prednisone dosage decreased from 10.7±9.4 to 3.3±4.7 ($p<0.0001$), 15.0±8.1 to 4.4±6.1 ($p<0.0001$) and from 26.2±17.5 to 12.6±9.7 mg/d ($p<0.0001$), respectively. RTX was effective in re-treated patients.

Conclusion: In patients with SLE, data from the AIR registry show short-term efficacy as well as a corticosteroid sparing effect of RTX. Tolerance was rather good but the rate of serious infections was higher than in RA (4.9/100 py) in the same AIR registry.

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Combined Rituximab and Cyclophosphamide Therapy in Systemic Lupus Erythematosus. Anusha Ramanathan, Risa Alperin, Emma J. MacDermott, Alexa B. Adams and Thomas J. A. Lehman, Hospital for Special Surgery, New York, NY

Purpose: Although cyclophosphamide and mycophenolate mofetil have been used extensively as steroid sparing agents in systemic lupus erythematosus, their prolonged use caries increased risks of infection, infertility and future malignancy. Newer regimens are needed which minimize the duration of cytotoxic therapy while providing better disease control. In this study, we propose that a systematic regimen of cyclophosphamide plus rituximab achieves this goal.

Method: Fourteen patients (11 female, 3 male) with SLE who received combined rituximab and cyclophosphamide infusions at our institution between 2004 and 2008 were evaluated for clinical and laboratory parameters by prospective data collection. 10 patients had renal biopsy proven nephritis and 4 were treated for non-renal manifestations of SLE. Rituximab was administered at 750mg/m^2 on day 0 followed by cyclophosphamide at 750mg/m^2 on day 1, and this was repeated at days 14 and 15 for each course of therapy. Courses of therapy were separated by an interval of 6 months between the first and second course, and by 1 year between the second and third course. Mean number of treatments with rituximab and cyclophosphamide was 5.9 (SD 2.5) and 8 patients received at least 3 courses of therapy.

Results: From baseline to 1 year follow-up (6 months from last treatment), there was significant improvement in mean prednisone dose from 33.3 ± 19.7 to 11.9 ± 4.7 mg/day ($p = 0.0002$), and improvement in complement level (C3) from 70.3 ± 26.6 to 118.1 ± 30.3 mg/dl ($p = 0.0023$) with a decrease in ESR from 26.4 ± 15.2 to 14.8 ± 12.8 mm/hr ($p = 0.0134$) and decrease in SLEDAI score from 9.79 ± 5.99 to 1.43 ± 1.83 ($p = 0.0009$). Among 7 patients with proteinuria prior to treatment, mean 24 hour urine protein decreased from 1204 ± 833 to 147 ± 255 mg/day ($p=0.0156$). Two patients had hematuria prior to treatment which resolved. Hemoglobin (11.9 ± 2 vs 12.6 ± 1 gm/dl, $p=0.3575$) and WBC (7.9 ± 3 vs 8.2 ± 4/nl, $p=0.8077$) remained stable and there was no significant change in serum creatinine (0.7 ± 0.22 vs 0.69 ± 0.12 mg/dl, $p=0.8438$). Immunoglobulin levels were significantly lower at 1 year follow-up, with IgG going from 1191 ± 326 to 910 ± 289 mg/dl ($p=0.0039$) and IgM falling from 98 ± 54 to 41 ± 16 mg/dl ($p=0.0059$). There were no serious adverse events during the follow-up time, and minor infections occurred in four patients, all of whom responded promptly to antibiotic or antiviral treatment.

Conclusion: Combined therapy with Rituximab and Cyclophosphamide administered in a systemic manner is both well tolerated and effective as an alternative in the management of systemic lupus erythematosus. Long term, prospective studies are needed to determine optimal treatment protocol and late side effects.

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Rituximab Therapy Induces Durable Remissions in Hispanic and African American Patients with Refractory Systemic Lupus Erythematosus (SLE). George A. Karpouzas[1], Maneesh Gogia[1], Rosalinda C. Moran[1] and Bevra H. Hahn[2], [1]Harbor-UCLA Medical Center, Torrance, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: Autoreactive B cells produce pathogenic autoantibodies (Ab) that deposit in tissues and cause injury in patients (pts) with SLE. While combinations of antimalarials, corticosteroids and immunosuppressives may control disease activity in most pts, about 10% suffer recalcitrant disease. Rituximab is a chimeric monoclonal Ab that eliminates B cells through binding of CD20 surface antigen. We evaluated the ability of Rituximab (RTX) to induce sustained remission in minority pts with refractory SLE.

Methods: We studied 35 pts with refractory SLE between 1/1/06 and 6/30/08. Subjects were given 4 weekly infusions of RTX monotherapy at 375mg/m^2. All had regular follow-up in a single academic center. Disease activity was measured with SLEDAI-2k every 3 months. Responses were reported in quarterly intervals and analyzed with paired t-tests.

Results: Thirty five pts received 1 cycle and 7 received a 2nd cycle within 9±2.4 months (mo) after the 1st infusion. Depletion of $CD19^+$ cells was observed in all ($p<0.001$-table). Baseline SLEDAI-2k was 8.5±0.8, significantly decreased in the 1st quarter (4.4±0.5, $p<0.0001$), and remained so to the end of the observation period. This was associated with a significant increase in serum complements. Sixteen pts with arthritis were followed over 15.2±5.1 mo: 75% had initial complete resolution, and 56% had sustained response (SR≥6 mo). Time to SR was 3.6±1.9 mo and SR lasted 13.2±1.3 mo. Primary and 2dary efficacy failures were seen in 19% and 25% of pts respectively. All (100%) achieved 2dary SR within 3.6± 1.3 mo of rechallenge. Among 13 pts with nephritis and baseline proteinuria of 4.5±1.5 g/24h followed over 11.5±5.7 mo, 92.3% had >50% improvement within 5±3.7 mo, and 53.8% achieved SR with proteinuria <500 mg/24 h within 6.8±3.7 mo.

Conclusion: In this open study, RTX therapy induced global durable responses in the majority of our cohort of Hispanic and AA pts with refractory SLE, and should, therefore, be considered as a therapeutic alternative in that context.

Table 1: Patient Characteristics

Total n	35									
Hispanic /AA/A	23/11/1									
Females (%)	80									
Age (yrs, M±SD)	41±12									
Duration (yrs)	5.5±3.4									
n-criteria @ Dx	4.7±0.9									
n-prednisone (%)	31 (89)									
Pred dose (mg)	28±20									
n-DMARD	2.1±0.6									
CD19+ before	194±46									
CD19+ after	29±9*									
Quarters (mo)	0	1	2	3	4	5	6	7	8	
SLEDAI-2k (M±SEM)	8.5±0.8	4.4±0.5*	4±0.5*	3.6±0.6*	3±0.6*	2.2±0.4*	2.9±0.9*	3±1.3µ	3.3±0.7	
SLEDAI-2k≤4 (%)	20	63	66	73	83	94	82	75	100	
4<SLEDAI-2k≤10 (%)	54	34	31	27	13	6	18	25	0	
SLEDAI-2k>10 (%)	26	3	3	0	4	0	0	0	0	
Arthritis-remission	0	75	56	80	86	92	100	100	100	
Proteinuria (gr/24h)	4.5±1.5	1.6±0.6µ	0.6±0.2†	1±0.5µ	0.6±0.3µ	0.6±0.2	0.6±0.3	0.14		
C3 (mg/dl)	89±6	103±7†	105±5†	107±7*	100±6†	118±7*	121±12†	107±13	114±11	

C4 (mg/dl)	14±2	18±2*	19±2µ	18±2†	16±2µ	19±2†	17±2µ	15±2	16±1
Log10 a-dsDNA	0.6±0.2	0.5±0.2	0.8±0.2	0.5±0.1	0.3±0.2µ	0.3±0.2	0.2±0.1	0.3±0.3	0.4±0.4

*<0.001, †<0.01, µ<0.05

Disclosure: G. A. Karpouzas, Centocor, Inc., 8, Abbott Immunology Pharmaceuticals, 8, Actelion Pharmaceuticals US, 8, Actelion Pharmaceuticals, 2 ; **M. Gogia**, None; **R. C. Moran**, None; **B. H. Hahn**, None.

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Rituximab in Cutaneous Lupus: Responsiveness Depends On Pattern of Skin Involvement. Edward M. Vital[1], Shouvik Dass[1], Maya H. Buch[1], Colin T. Pease[2], Michael F. Martin[2], Andrew C. Rawstron[2], Mark Goodfield[2] and Paul Emery[1], [1]University of Leeds, Leeds, United Kingdom, [2]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Purpose: Rituximab in SLE has been described in >200 published cases; positive responses were seen in all systems. However, cutaneous pathology in lupus is heterogeneous, including some lesions that occur in patients without autoantibodies. Responses to targeted B cell therapies therefore warrant more detailed assessment.

Method: 35 SLE patients were treated with 2 x rituximab 1000mg + methylprednisolone 100mg. Patients with skin involvement were reviewed in a combined rheumatology/dermatology clinic. B cells were monitored using highly sensitive flow cytometry.

Results: 14 patients had significant cutaneous disease. Antimalarials (5/14) or other immunosuppressants (7/14) were continued. The skin was the primary indication for treatment in 3 patients.

Non-cutaneous disease: 12 had significant (BILAG A/B) non-cutaneous disease including renal(2), cerebral(3), haematological(3) and arthritis(3). Responses were good with reduction of BILAG A/B to C/D in 11/12.

Discoid LE: 4 patients had discoid disease. None showed significant change after treatment.
Cutaneous vasculitis: 2 patients had cutaneous vasculitis with purpura; both responded completely.

Changing pattern of lupoid cutaneous disease: 1 patient with papulosquamous subacute LE responded well for 11 months then relapsed with the same rash. In 3 other patients, acute photoaggravated LE responded, but they then developed disseminated discoid LE. In these patients B cell depletion was incomplete, transient improvement occurred during depletion, and change in pattern of skin disease occurred during repopulation.

Developing non-lupoid cutaneous disease: 3 patients developed non lupoid rashes. 2 patients were treated for arthritis with initial good response. Following a second cycle of rituximab 1 developed Sweet's syndrome and 1 pemphigus erythematosus. 1 patient was treated for thrombocytopenia and cerebral vasculitis but developed psoriasis. These rashes occurred while B cell depleted. All were biopsy-proven.

Conclusion: Responsiveness of cutaneous lupus to rituximab is complex. Discoid lesions did not respond. Acute non-discoid LE and vasculitis in patients with active systemic disease initially improved along with other manifestations. However, some patients switched to a disseminated discoid pattern following B cell repopulation. This may be explained by expansion of a T cell population during B cell depletion that becomes activated during repopulation. Alternatively transient and incomplete B cell depletion may alter the pathological B cell repertoire. Some patients develop other cutaneous diseases, but the mechanism for this is unclear. The role of B cells may vary between different patterns of skin disease in SLE and rituximab may not be the most appropriate therapy for all patients. Careful monitoring of the skin is needed when using rituximab in SLE. These results may have implications for the design and interpretation of clinical trials of B cell therapies in SLE.

Disclosure: E. M. Vital, Roche Pharmaceuticals ; **S. Dass**, Roche Pharmaceuticals ; **M. H. Buch**, Roche Pharmaceuticals ; **C. T. Pease**, None; **M. F. Martin**, None; **A. C. Rawstron**, None; **M. Goodfield**, None; **P. Emery**, Roche Pharmaceuticals, 8, Wyeth Pharmaceuticals, 8, Abbott Laboratories, 8, Schering, 8 .

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Prolonged Immunoadsorption (IAS) Leads to Sustained Stabilization of Disease Activity in Lupus Nephritis. Georg H. Stummvoll[1], Peter Biesenbach[2], Sabine Schmaldienst[1], Josef S. Smolen[1] and Kurt Derfler[2], [1]Medical University of Vienna, Vienna, Austria, [2]Medical Uiversity of Vienna, Vienna, Austria

Purpose: SLE is characterized by pathogenic autoantibodies and immune complexes, which can effectively be removed by extracorporeal procedures such as IAS. After up to one year of IAS, we had previously observed a reduction of proteinuria, disease activity and autoantibody levels in highly active SLE with renal involvement with contraindication or refractoriness to cyclophosphamide (Cx). Antibody removal, however, does not block the formation of autoantibodies; thus, a large proportion of these patients underwent prolonged IAS (>1 yr for up to 10yrs) and are the focus of this report.

We evaluated patients under prolonged IAS for sustainability or further improvement of the primary response to IAS (proteinuria, disease activity, anti-dsDNA-Abs) and for the number of flares, infections, adverse events and tumors.

Methods: Highly active SLE patients with lupus nephritis (proteinuria 7.1±4.8 g/day, SLEDAI 20±8, anti-dsDNA 394±712 IU/ml) underwent IAS therapy if i.v. Cx was contraindicated or not effective enough to control disease activity. 13 patients responding to initial IAS therapy were included into the prolonged program, showing moderate disease activity at the start of the extension period (proteinuria 2.0±2.4, SLEDAI 3±2, anti-dsDNA 47±36 IU/ml). We defined the end of observation (EoO) upon either completion of 10 yrs of IAS therapy or the end of 2008. During IAS, oral immunosuppression and ACE/ATII-inhibitors were kept constant, steroids were tapered as clinically feasible. IAS was performed with high affinity columns using either sheep-IgG or Protein A as ligand. The effective removal of serum Ig was monitored. Severe infections were defined as requiring i.v. therapy or hospitalization, flares according to the SELENA protocol.

Results: Under prolonged IAS (mean observation period of 6.7±3.5 years), proteinuria further decreased from 2.0±2.4 g/d to 0.9±1.7g/d, $p<0.05$. Complete remission (proteinuria<0.5g/d) was achieved in 9 (69%) patients. One patient flared and was discontinued. Nine (69%) patients are still under IAS therapy at the EoO. In 4 patients IAS was stopped because of a sustained response. Disease activity and anti-dsDNA levels could be stabilized at low levels (SLEDAI 3±4, anti-dsDNA 26±24 IU/ml at EoO).

Severe infections (0.1±0.3 per patient year) and severe flares (0.1±0.2 per patient year) were uncommon. Tumors, anaphylactic or orthostatic adverse events were not observed.

Conclusion: Prolonged IAS can lead to sustained stabilization of disease activity in moderately active SLE patients and has an acceptable safety profile.

Disclosure: G. H. Stummvoll, None; **P. Biesenbach**, None; **S. Schmaldienst**, None; **J. S. Smolen**, None; **K. Derfler**, None.

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The Efficacy of Intravenous Immunoglobulin Therapy for Immune Thrombocytopenia Associated with Systemic Lupus Erythematosus. Eun Joo Song[1], Ji Hun Kim, Jin Young Kang[1], Kyung Hoon Kim[1], Jae Seok Seo[1], Eon Jeong Nam[2] and Young Mo Kang[1], [1]Kyungpook National University School of Medicine, Daegu, South Korea, [2]Kyungpook National Univ Hosp, Daegu, South Korea

Purpose: Severe immune thrombocytopenia (IT) usually occurs in the context of active systemic lupus erythematosus (SLE) and is conventionally treated by high-dose corticosteroid (HDCS) as the first-line therapy. In IT associated with SLE, intravenous immunoglobulin (IVIG) has been empirically used in cases refractory to or dependent on HDCS. However, the clinical efficacy of IVIG for treatment of IT associated with SLE remains undetermined. We sought to investigate the clinical efficacy of IVIG therapy for IT associated with SLE.

Method: We reviewed medical records of 350 admitted patients with SLE according to the American College of Rheumatology 1997 revised criteria, among whom 126 patients were identified to have IT. A retrospective analysis was made for 35 patients, who had platelet count $< 50 \times 10^9$/L and had been regularly followed for clinical examinations. Of these patients, 20 patients received IVIG (2 g/kg for 5 days) combined with HDCS (the combination therapy group), and 15 patients were treated with HDCS alone (the monotherapy group). Efficacy was evaluated on the basis of platelet count change by therapeutic regimens, cumulative doses of corticosteroid and numbers of days, which were required until the platelet count exceeded 50×10^9/L or 100×10^9/L, and the amount of transfusion which was needed for the prevention of bleeding in case of severe IT.

Results: At the baseline, there was no significant difference in clinical and demographic features between the combination therapy and monotherapy groups, although the mean platelet count was lower in the combination therapy group. The platelet counts on day 5 and day 14

after treatment were significantly higher in the combination therapy group than in the monotherapy group (96.9 ± 9.9 vs. 56.1 ± 8.8 $\times 10^9$/L at day 5, p=0.001; 162.8 ± 16.3 vs. 95.2 ± 15.3 $\times$ 10^9/L at day 14, p=0.003). The cumulative dose of corticosteroid and number of days, which were required until the platelet count exceeded 100 $\times$ 10^9/L, were statistically lower in the combination therapy group than in the monotherapy group respectively (482.8 ± 158.5 vs. 1033.3 ± 266.0 mg, p<0.001; 6.8 ± 0.7 vs. 12.3 ± 1.7 days, p=0.001). The amount of transfusion in each group was not significantly different.

Conclusion: Our results suggest that IVIG therapy has the advantage of faster restoration of normal platelet count with a lower cumulative dose of steroid, thus being warranted as an effective first-line treatment for severe IT associated with SLE.

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Efficacy and Safety of Long-Term Use of Thalidomide for Refractory Cutaneous Lupus. J. Cortés-Hernández, M. Torres-Salido, S. Buján, M. Vilardell-Tarres and J. Ordi-Ros, Systemic Autoimmune disease Research Unit. Hospital Vall d'Hebron., Barcelona, Spain

Purpose: Cutaneous manifestations of lupus erythematosus are characterized by a great heterogeneity of clinical manifestations that usually have a chronic and relapsing course. Although is not a life-threatening condition, the lack of a rapid improvement can lead to a significant permanent scarring and disfigurating lesions. Thalidomide is increasingly being shown to be effective for the treatment cutaneous disease refractory to conventional management. The aim is to prospectively evaluate the clinical efficacy and safety of long-term treatment with low-dose of thalidomide in a cohort of 50 patients with refractory cutaneous lupus disease.

Methods: From 1992 to 2009, fifty consecutive patients with refractory disease (23 with discoid lupus erythematosus (DLE), 12 with subacute cutaneous lupus (SCLE), 4 with profundus lupus, 7 with acute cutaneous lupus, 1 with lupus tumidus, and 3 with a non-specific rash) were treated with thalidomide. Initial treatment was started at 100 mg daily. If the cutaneous lesions vanished, the dose was lowered to 50-25 mg daily as maintenance therapy. Patients were follow-up for a mean of 82±63 months (12-204). Complete response was defined as a total resolution of the cutaneous lesions. Partial response was considered when at least >50% of the improvement was achieved. Patients were followed up periodically and were assessed for the development of neuropathy and other adverse effects. Contraception was initiated in women of childbearing age.

Results: Forty-seven patients (94%) achieved complete or partial response with thalidomide therapy. Complete response occurred in forty-one patients (82%). Time to remission was as quick as to 10.7±5.30 weeks (4-28). There was an elevated rate of relapses (65.8%), usually 8-16 weeks after thalidomide's withdrawal or reduction. All patients achieved complete response after the drug was reintroduced. No response occurred in 3 patients (6%). The duration of thalidomide therapy was of 21±19.74 months (2-76). The most common adverse effects were sedation, constipation and weight gain. Five women developed amenorrhea during the treatment, but menses returned after its withdrawal. Seven patients (14%) reported symptoms of paresthesia, but only in three of them polyneuropathy was confirmed by EMG. One patient, heavy smoker and without antiphospholipid antibodies, had a stroke. None of the three patients with antiphospholipid antibodies developed a thrombotic event. Thalidomide did not improve the systemic disease or the scarring alopecia.

Conclusion: Low dose thalidomide is a safe and an effective treatment for the different manifestations of cutaneous lupus refractory to conventional therapy. In view of the high rate of relapses after treatment discontinuation, a long-term maintenance dose might be required. The rapid response achieved and the safe profile support that thalidomide, alone or in combination, might be used as initial therapy to avoid sequelae.

Disclosure: J. Cortés-Hernández, None; **M. Torres-Salido**, Public Health Services, 3 ; **S. Buján**, None; **M. Vilardell-Tarres**, None; **J. Ordi-Ros**, None.

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The Effects of Hydroxychloroquine On Antiphospholipid Antibodies in SLE Patients. Anna Broder and Chaim Putterman, Division of Rheumatology, Albert Einstein College of Med, Bronx, NY

Purpose: Treatment with hydroxychloroquine (HCQ) is associated with a decreased risk of thrombosis in antiphospholipid (APL) syndrome. In vitro, HCQ decreases the binding of APL-beta2 glycoprotein complexes to phospholipid bilayers and reduces clinical APL assays. The time-dependent effects of HCQ on APL antibodies in SLE patients have not been studied extensively. We investigated a potential association between changes in APL antibody (Ab) titers over time and HCQ therapy.

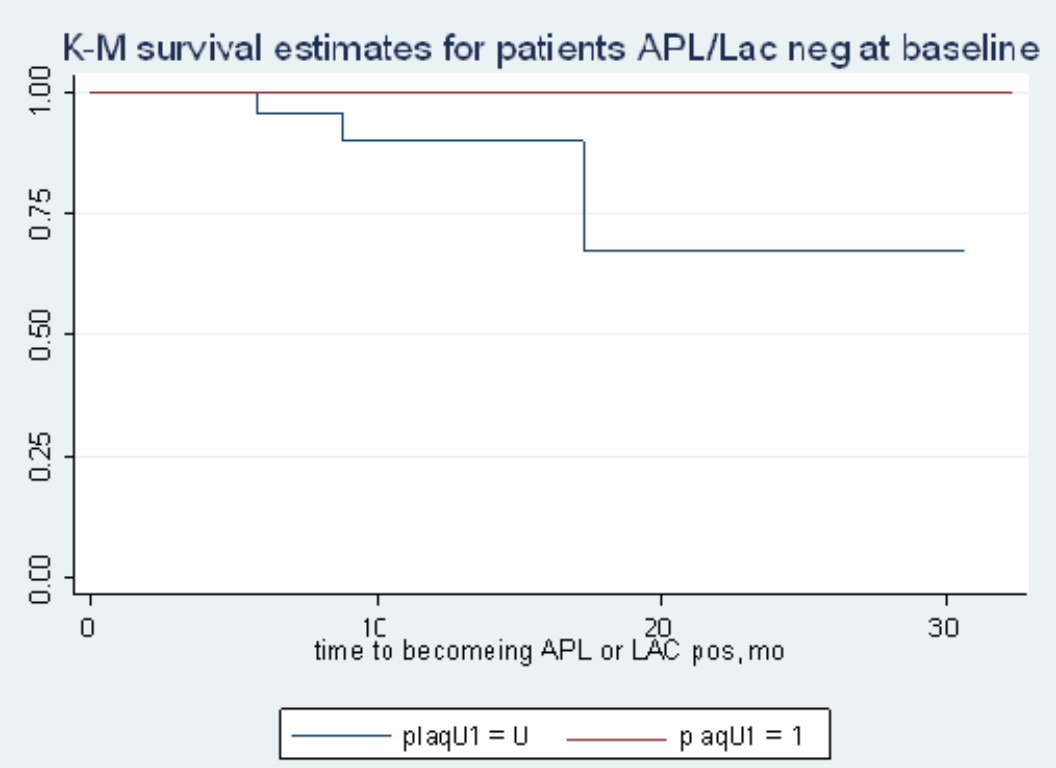
Method: We identified all SLE patients followed at a tertiary care center who had APL Abs or lupus anticoagulant (Lac) checked at least twice between 2002 and 2009. At baseline, patients were defined as APL/Lac- if all APL Abs and Lac were negative. Similarly, patients were defined as APL/Lac+ if at least one APL Ab or Lac was positive at baseline. We used the standard laboratory cut-offs for the above definitions. In the APL/Lac+ group an "event" was defined as APL Ab and/or Lac conversion from positive to negative. In the APL/Lac- group an "event" was defined as APL or Lac conversion from negative to positive. "Time to event" was defined as the number of months to censoring or conversion. Patients were defined as HCQ+ if they were on HCQ at the event time, and HCQ- if they were not on HCQ at the event time.

Kaplan-Meier graphs were generated separately for the APL/Lac+ and APL/Lac- groups.

Results: Eighty four patients met the above inclusion criteria. The median age was 31.5, IQR (21, 40.8) years. Seventy eight (93%) were women; 63 (75%) were African-American or Hispanic. HCQ data was available for 58 (69%) patients: 31 (64%) were HCQ-, 27 (46%) were HCQ+. At the event time the HCQ+ and HCQ- groups were similar in age (median 26, IQR (20,30) years), race (76% Hispanic or African American), gender (91% women), and had similar duration of follow-up (median 10.6, IQR (3.5, 17.2) months), platelet counts (median 237, IQR (183, 299) 10^9/l), serum creatinine levels (median 0.8, IQR (0.6-1.0) mg/dl), and complement levels. The frequency of elevated anti-DsDNA titers (≥99 IU/ml) was 39% (n=9) HCQ+ vs. 23% (n=5) HCQ-, p=0.3. HCQ+ patients had a lower frequency of Warfarin therapy, 33% (n=9) in HCQ+ vs. 64% (n=20) in HCQ- group, p=0.02. HCQ+ patients more likely to use Prednisone: 100% (n=27) HCQ+ vs. 74% (n=24), p=0.004. HCQ+ patients were more likely to use disease modifying drugs such as Azathioprine, Mycophenolate Mofetil, or Cyclophosphamide: 81% (n=22) HCQ+ vs. 52% (n=16) HCQ-, p=0.02.

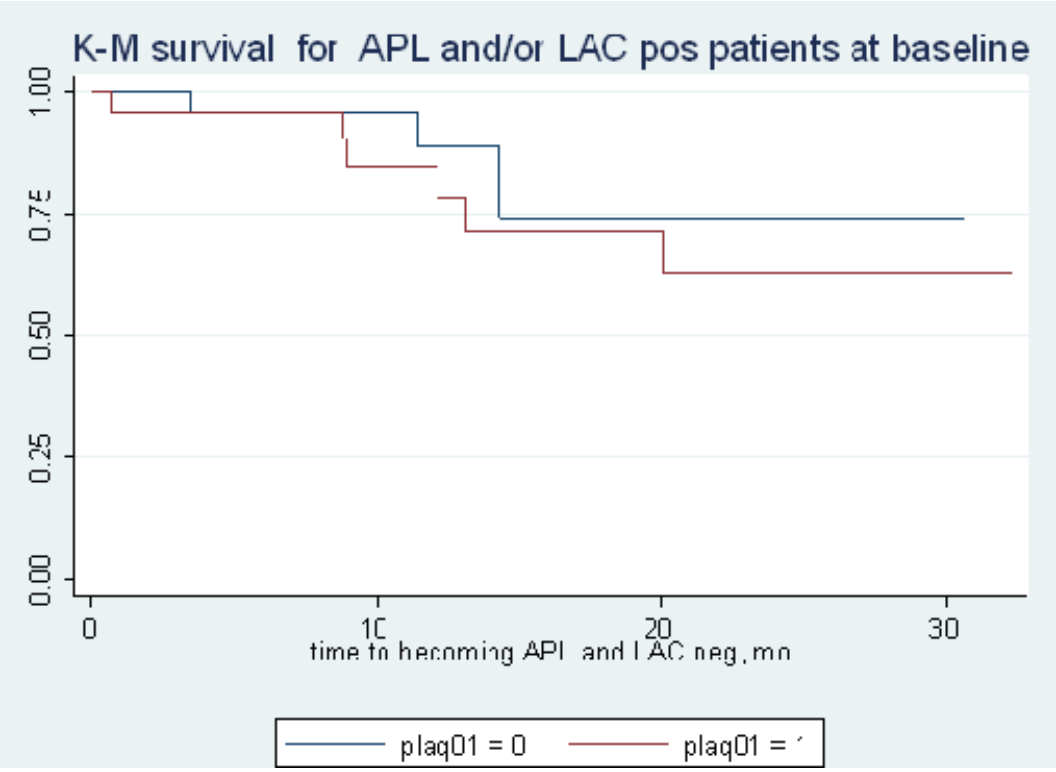
Thirty two patients, 16 (50%) HCQ+ and 16 (50%) HCQ-, were APL/Lac- at baseline. Three (9%) patients became APL/Lac+. All 3 were in the HCQ- group.

The differences were statistically significant by the log-rank test (p=0.0026)



Twenty six patients, 11 (42%) HCQ+ and 15 (58%) HCQ-, had at least one APL/Lac+ at baseline. Six(55%) were on HCQ and 3(20%) were not on HCQ at the time of conversion to all APL/Lac-.

The differences were statistically significant by the log-rank test (p=0.0009)



Conclusion: In our study cohort HCQ therapy in APL Abs/Lac+ patients is associated with an increased rate of conversion to APL Abs/Lac-HCQ may play a role in decreasing APL antibody levels in APL-positive patients and maintaining low APL levels in APL-negative patients.

Disclosure: A. Broder, None; **C. Putterman**, None.

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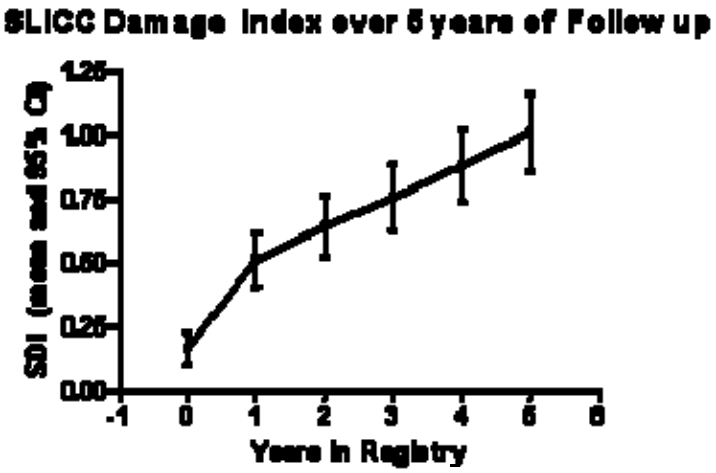
Damage Due to Glucocorticoids in a Multicentre SLE Inception Cohort. Murray Urowitz[1], Dafna Gladman[1], Dominique Ibañez[1] and Systemic Lupus International Collaborating Clinic (SLICC), [1]University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: As survival has increased in patients with SLE, organ damage has been shown to accumulate over time as a result of both the disease and its treatment especially corticosteroids. We determined the contribution of corticosteroids to the pattern of damage accumulation in a multicentre, inception cohort of SLE patients followed for 5 years.

Method: An international consortium comprising 27 centres from 11 countries has established an inception cohort followed yearly according to a standardized protocol between 2000 and 2009. Of these, 298 patients have been followed for a minimum of 5 years and constitute the study population. Accrued damage was measured using the SLICC/ACR Damage Index (SDI). Organ damage was categorized into the following groups: definitely related to steroids (cataracts, osteonecrosis, osteoporosis); possibly related (cardiovascular, peripheral vascular, neuropsychiatric, diabetes); independent of steroids (renal, pulmonary, gastrointestinal, skin, gonadal failure and malignancy). Descriptive statistics were used.

Results: Of the 298 patients followed for at least 5 years, 86.6% were female, 55.4% % were Caucasian, 12.1% were Black, 14.4% were Asian, 16.1% Hispanic and 2.0% Other. 41.9% were married and 60.4% had at least College education. Their age at enrolment was 35.3 yrs and SLEDAI-2K at enrolment was 5.9. The duration from diagnosis to enrolment was 5.5 months. Glucocorticoids were taken by 66.1% of the patients at enrolment, 72.8% at year 1 and persistently in 76% of the patients thereafter. The mean SDI increased from 0.16 to 1.01 over 5 years.



Damage definitely due to glucocorticoids increased over 5 years whereas damage independent of glucocorticoids remained stable over 5 years (table)

Year	Definitely glucocorticoid (%)	Possibly glucocorticoid (%)	Independent of glucocorticoids
0	11.3	43.4	45.3
1	12.9	42.6	44.5
2	15.6	40.2	44.3
3	18.3	37.6	44.1
4	21.8	36.7	41.6
5	25.5	32.1	42.1

Conclusion: With improving survival patients with SLE accrue organ damage a significant portion of which is glucocorticoids related. In this study 25.5% of accrued damage in the first 5 years of disease is definitely related to glucocorticoids therapy.

Disclosure: M. Urowitz, None; **D. Gladman**, None; **D. Ibañez**, None.

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BILAG Versus SELENA-SLEDAI Scoring in Systemic Lupus Erythematosus (SLE) Patients in EXPLORER. C. Gordon[1], Joan T. Merrill[2], D.J. Wallace[3], H. Hsieh[4] and P. Brunetta[4], [1]University of Birmingham, Birmingham, United Kingdom, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Cedars-Sinai Medical Center/UCLA, West Hollywood, CA, [4]Genentech, Inc., South San Francisco, CA

Purpose: SLE is a heterogenous autoimmune disease affecting multiple organ systems. B cells may play a central role in SLE, but measurement of efficacy is complex due to heterogenous manifestations of disease activity. Rituximab (RTX) induces peripheral CD20+ B

cell depletion. The EXPLORER trial assessed the efficacy and safety of RTX vs placebo (PLA) over 52 weeks in moderate to severely active extrarenal SLE. Our objectives were to report and assess the correlation of BILAG index vs SELENA-SLEDAI (S-S) scoring of disease activity in SLE in the EXPLORER trial.

Methods: The BILAG and the S-S indices measure disease activity either in the previous month, or within the prior 10 days, respectively. S-S is a global composite index that includes 24 clinical and laboratory variables weighted by the type of manifestation but not by severity. The BILAG is an index measuring 8 organ systems weighted by severity. It was devised to provide separate letter scores (ordered from A-E with A indicating the most severe disease) for each domain. Two systems of global scores were applied. System 1 was derived by summing 8 domains scores and assigning 9, 3, 1, 0, 0, to letter scores A, B, C, D, and E, respectively. System 2 summed 8 domains scores and assigned 12, 5, 1, 0, and 0, to A, B, C, D, and E, respectively. In EXPLORER pts, BILAG was assessed monthly and S-S was assessed on alternate months from baseline through 12 months. The correlations of S-S and BILAG were assessed by the global scores, and specifically in the musculoskeletal (MUS) and mucocutaneous (MUC) domains, the most prevalent systems involved in EXPLORER pts.

Results: The intent to treat (ITT) population included 88 and 169 patients in the PLA and RTX groups. A total of 1877 patient visits were assessed by both S-S and BILAG. S-S is positively correlated with BILAG in global scores with a Pearson correlation coefficient of 0.57 and 0.58 using BILAG scoring system 1 and 2, respectively. There were 383 and 645 patient-visits indicated as severe disease by S-S ($\geq$ 11) and BILAG ($\geq$ 1A or $\geq$ 3B), respectively. There were 689 and 1005 patient-visits indicated as mild disease by S-S (1-5) and BILAG ($\leq$ 1B). In the MUC domain, the concordance rate of presenting or not presenting activities by both S-S and BILAG was 88.55% (Kappa=0.73), In the MUS domain, the concordance rate was 68.83% (Kappa=0.4). Most of the discordance (8.84%) in the MUS domain resulted from a C score being present in BILAG without concomitant presence in the S-S.

Conclusion: Disease activity assessed by either the BILAG index or the S-S correlated well in describing disease status in a cross-sectional analysis. Overall, the BILAG index discriminated severe and mild disease activity more than the S-S did in this cohort. Implementing an alternative scoring system for the BILAG didn't alter the correlation with S-S activity when evaluating global scores in this study population.

Disclosure: C. Gordon, Roche and Genentech, 5 ; **J. T. Merrill**, Genentech , 5, Genentech , 2 ; **D. J. Wallace**, None; **H. Hsieh**, Genentech , 3 ; **P. Brunetta**, Genentech , 3 .

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Immunosuppressive Drugs in SLE Differ in Their Hematologic Side-Effects. Waleed Bolad[1], Laurence Magder[2] and Michelle Petri[3], [1]Johns Hopkins University, Baltimore, MD, [2]University of MD, Baltimore, MD, [3]Johns Hopkins Univ, Baltimore, MD

Purpose: The adverse reactions of mycophenolate mofetil (MMF) have been long studied in the renal transplant patient population. Bone marrow suppression leading to cytopenias is a major potential concern, and requires regular monitoring. The reported incidence of leukopenia in these trials ranges from 23% to 46%, hypochromic anemia 26% to 43%, and thrombocytopenia 24% to 36%. The safety of MMF in patients with severe renal impairment and in SLE has yet to be established. Azathioprine (AZA) and methotrexate (MTX) are both known to have dose related bone marrow suppression, particularly in the renally impaired, that results in leukopenia in up to 27% of patients and thrombocytopenia in up to 5%. **Method:** 456 SLE patients in a prospective cohort were included: 245 on mycophenolate (MMF), 199 on azathioprine (AZA), 102 on methotrexate (MTX), and 85 on one or more. We compared the times that the patients were on immunosuppressants with the times they were not on immunosuppressants with respect to platelet, hematocrit and white blood cell counts. Mixed effects models were used to control for sex, ethnicity, age and account for repeated measures in the same patient.

Results: The median number of quarterly visits on medication was 16 (MMF), 19 (AZA) and 16 (MTX). The patients were 89% female (MMF), 91% (AZA) and 94% (MTX). The ethnicity was African-American in 49% (MMF), 53% (AZA), 44% (MTX) and Caucasian in 42% (MMF), 40% (AZA) and 49% (MTX). The average age was 38.6 (MMF), 39.0 (AZA) and 44.9 (MTX). Comparison was made of off the immunosuppressive versus on the immunosuppressive, controlling for sex, ethnicity, age and accounting for repeated measures in the same patient.

	PLT		WBC		HCT	
	Estimated Effect (95% CI)[2]	P-value[1]	Estimated Effect (95% CI)[3]	P-value[1]	Estimated Effect (95% CI)[4]	P-value[1]

MMF	16.1 (12.9, 19.2)	<.0001	0.85 (0.67, 1.03)	<.0001	0.29 (0.17, 0.42)	<.0001
AZA	9.6 (6.5, 12.6)	<.0001	-0.41 (-0.58, -0.23)	<.0001	-0.61 (-0.74, -0.49)	<.0001
MTX	0.3 (-4.2, 4.8)	.90	-0.38 (-0.64, -0.12)	.0037	-0.06 (-0.23, 0.12)	.53

Conclusion: MMF is the safest immunosuppressive in SLE for the hematologic system and actually significantly increases all blood counts. AZA is safer than MTX in terms of platelets but MTX is safer than AZA in terms of hematocrit. These results have important clinical ramifications in terms of choosing an immunosuppressive, especially in SLE patients with baseline cytopenias. Furthermore, these data suggest that cytopenias on MMF should not be ascribed to MMF, but to lupus or other processes.

Disclosure: W. Bolad, None; **L. Magder**, None; **M. Petri**, None.

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Comorbidity in SLE Compared with Rheumatoid Arthritis and Non-Inflammatory Rheumatic Disorders. Frederick Wolfe[1], KD Michaud[2], Tracy Li[3] and RS Katz[4], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]U Neb Med Cntr and NDB, Omaha, NE, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Rheumatology Associates, Chicago, IL

Purpose: Although comorbidity is well described in SLE, there have been no head-to-head comparisons of comorbidity prevalence in SLE and other rheumatic conditions. We used self-report comorbidity from patients participating in a longitudinal study of rheumatic disease outcomes to evaluate comparative comorbidity and the potential contribution of fibromyalgia; to describe the prevalence of comorbid condition in SLE,; to determine the relative risk (RR) of comorbidity in SLE compared with other rheumatic conditions; and to evaluate the effect of FM.

Methods: We evaluated 1,316 community SLE patients, 14,252 with rheumatoid arthritis (RA), and 3,768 with non-inflammatory rheumatic disorders (NIRD), excluding FM, and a comorbidity index was calculated (Michaud 2007). The presence of FM was determined using survey FM criteria (Katz 2006). We determined damage by the newly developed Lupus Damage Index Questionnaire (LDIQ), a self-report version of the ACR/Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI).

Results: The comorbidity index score was significantly increased in SLE 2.6 (95% CI 2.5, 2.7) compared with RA 1.7 (1.7, 1.7) and NIRD 1.9 (1.8, 1.9), and this increase was observed at all age levels and remained significant after non-linear adjustment for age and sex. To test the potential effect of simultaneous fibromyalgia, we examined differences between the comorbidity index before and after adjusting for the presence of FM using survey FM criteria. The presence of FM was associated with a 1-unit increase in the comorbidity index, but did not change the comorbidity scores in the 3 disorders. Survey FM was present in 24.4% with SLE, 17.0% with RA and 14.4% with NIRD.

Hypertension (37.4%) and depression (33.8%) were the most common current comorbid conditions among those with SLE. SLE patients differed most from those with RA in RR of current comorbid renal disease (RR 5.7), neurologic disorder (3.7), myocardial infarction (RR 2.8), pulmonary disease (RR 2.3), and stroke (RR 2.0). Patterns were very similar when SLE was compared with NIRD, and in comparisons utilizing lifetime rather than current comorbidity.

Comorbidities in SLE, as measured by the comorbidity index, were most strongly associated with the LDIQ damage score (r=.502) and with SF-36 PCS (r=.383), SF-36 pain (r=.359), and with the Symptom Intensity Scale (FM scale) (r=.331). Associations with correlation coefficients <0.300 included fatigue, patient global, SF-36 mental health, and HAQ disability.

Conclusion: Comorbidity is increased generally in SLE compared with RA and NIRD, including expected cardiovascular and renal conditions. Although more patients with SLE satisfied survey FM criteria, the presence of FM did not alter the increase in comorbidity in SLE. Increase in comorbid conditions is consistent with known increased mortality in SLE.

References: Michaud, K. Best Prac Clin Rheum 21:85-06; Katz, R. Arth Rheum 54:2006, 169-76.

Disclosure: F. Wolfe, Bristol-Myers Squibb, 2 ; **K. Michaud**, None; **T. Li**, Bristol-Myers Squibb, 3 ; **R. Katz**, None.

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Multiorgan Dysfunction, High SLEDAI Scores, and Markedly Elevated Ferritin Levels Correlate with Macrophage Activation Syndrome in Adult Patients with SLE. B. Shakoory[1], R. D. Sanders[2], Vishnu Reddy[2], G. S. Alarcon[1], R. Q. Cron[3] and W. W. Chatham[1], [1]UAB Rheumatology, Birmingham, AL, [2]UAB Pathology, Birmingham, [3]UAB Pediatric Rheumatology, Birmingham, AL

Purpose and Background: SLE is the 2nd autoimmune disease recognized to be complicated by MAS. However, clinical similarities between underlying disease activity, sepsis syndromes and malignancies and MAS can delay its diagnosis resulting in increased mortality. Aggressive immunosuppression of MAS requires its accurate and timely diagnosis. We demonstrate the clinical correlates of MAS in SLE patients and compare the accuracy of the clinical assessment with other diagnostic tools in correctly identifying MAS.

Methods: Patients with SLE (≥ 4 ACR criteria) between 2006 and 2008 with available bone marrow specimens were identified. The specimens were examined by hemopathologists and graded from 0-4 based on presence of CD-163+ histiocytes. Abstraction of clinical, laboratory and radiographic features within 30 days of bone marrow biopsies took place independently and blinded from the pathology data. The likelihood of MAS was determined by a rheumatologist based on clinical parameters including organ systems involved, and changes in the blood cell counts, blood levels of LDH, ALT, AST, D-dimer, ferritin, and CRP. The "Clinical" decision was denoted as a weighted score of 1= low, 2= maybe, 3= probable, 4= highly likely. The suggested 2004 criteria for MAS in systemic juvenile idiopathic arthritis (MAS-04) and the weighted clinical parameters were compared with the validated 2004 diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH-04) to determine the respective sensitivity, specificity and positive (P) and negative (N) predictive values (PV) and overall accuracy. Clinical features, severity and length of hospital stay of SLE patients with and without HLH-04 defined MAS were compared using Student's t test (SAS 9.1).

Results: The group consisted of 18 adults with SLE with mean age of 45.3; 88.9% were women and 66.7% were African American. Four patients (22%) had MAS per HLH-04 criteria. Both "Clinical" and MAS-04 scores were highly correlated with the HLH-04 score (Clinical: $r=0.88$, $p<0.0001$ and MAS-2004 $r=0.74$, $p<0.0005$). For diagnosis of MAS by HLH-04, the Clinical score had a sensitivity= 100%, specificity=92%, PPV= 80%, NPV=100% and accuracy= 94%) as compared to 100%, 0%, 22%, 0% and 94% for the MAS-04 criteria. MAS patients experienced longer hospital stay (27.5 vs.11.2 days; $p<0.0001$), longer intubation (17.2 vs. 0.07 days; $p<0.05$), higher SLE disease activity by SLEDAI (18.0 vs. 5.4; $p<0.05$) and higher ferritin levels (20659, vs. 1083; $P<0.0005$).

Conclusion: and clinical implications: The clinical diagnosis of MAS has adequate metric properties when compared with the HLH-04 criteria. Readily available clinical data may allow the diagnosis and prompt treatment of MAS in SLE patients with high levels of disease activity (SLEDAI) even in the absence of bone marrow histopathologic data. This will result in its earlier diagnosis and prevent undue morbidity and mortality. Moreover, the MAS-04 score is not appropriate in the setting of SLE.

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Pancreatitis in Systemic Lupus Erythematosus. Ashima Makol[1] and Michelle A. Petri[2], [1]Michigan State University, East Lansing, MI, [2]Johns Hopkins University, Baltimore, MD

Purpose: Pancreatitis is a rare but potentially life threatening complication of systemic lupus erythematosus (SLE). Its incidence and etio-pathogenesis in lupus is unclear, but vasculitis of the gastrointestinal tract is the most commonly proposed mechanism. We determined the frequency and associated factors of SLE-related pancreatitis.

Method: A large prospective cohort was reviewed to identify patients who developed episodes of acute pancreatitis since the diagnosis of SLE. Clinical and laboratory parameters of SLE patients who developed pancreatitis were compared to SLE patients who did not develop pancreatitis. Statistical analysis was done using chi-square test or Fischer's exact test for dichotomous variables and Student's t-test for continuous variables. For demographic, physical and laboratory variables that were found to be different between patients with and without pancreatitis, multiple logistic regression analysis was used to identify the variables that independently predicted pancreatitis. A two tailed P value of <0.05 was considered statistically significant in all comparisons in the study.

Results: 76 of 1811 patients developed one or more episodes of pancreatitis. Five patients were excluded due to non availability of records or based on exclusion criteria. 71 remaining SLE patients developed 152 episodes of pancreatitis, with a mean of 2.1 episodes/person and an

average frequency of 0.10 episodes/person/year. The etiology was found to be related to SLE, in 63 patients (Prevalence 3.5%). 12 (19%) patients had elevated triglycerides, 29 (46%) had antiphospholipid antibodies (aPL) and 11 (17%) were on an immunosuppressive drug during their episode of pancreatitis. 73% patients showed complete resolution of pancreatitis, 14% developed chronicity and 3% died. Pancreatitis attributed to SLE was associated with lower household income, less private insurance, more disability and smoking. Associated clinical conditions included fever, vasculitis, pleurisy, psychosis, organic brain syndrome, cognitive impairment, anemia, Sjogren's syndrome, anti-La, hypertension, diabetes mellitus, venous thrombosis, stroke and myocardial infarction. SLE patients with pancreatitis accrued more permanent organ damage, including pancreatic insufficiency, renal and neuropsychiatric damage. No association was found with any aPL, immunosuppressant medication or steroids.

Conclusion: Our series found that SLE-attributable pancreatitis, although rare, identified a subset of SLE patients with much higher organ damage and mortality. Antiphospholipid antibodies were not associated, but a history of thrombosis, cutaneous vasculitis, secondary Sjogren's and triglyceridemia were all suggested as potential mechanisms. Only triglyceridemia remained in the multiple regression model in terms of a causative variable.

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Comparison of Quantiferon-TB Gold Test and Tuberculin Skin Test for Identification of Latent Mycobacterium Tuberculosis Infection in Lupus Patients. Neslihan Yilmaz, Sibel Aydin, Nevsun Inanc, Haner Direskeneli and Sule Yavuz, Marmara University Faculty of Medicine, Rheumatology, Istanbul, Turkey

Purpose: The tuberculin skin test (TST) might have a low sensitivity for making the diagnosis of tuberculosis (TB) in immunosuppressed patients ,such as connective tissue disease. Quantiferon-TB Gold(QFT-G) is an IFN-gamma-release assay that measures the release of interferon after stimulation in vitro by Mycobacterium tuberculosis antigens using ELISA. The main advantage of this assay with respect to TST is a lack of cross-reaction with bacillus Calmette-Guérin(BCG) and most non-tuberculous mycobacteria. The aim of our study is to compare QTF-G with TST for the detection of latent tuberculosis infection (LTBI) among patients with systemic lupus erythematosus (SLE).

Method: Fifty patients with SLE who fulfilled the ACR criteria and 49 healthy subjects were enrolled. All patients and controls were investigated for a history of tuberculosis, BCG vaccinations and chest x-ray for the presence of any signs of TB infections. QTF-G and TST were performed on both patients and controls. QTF-G results were recorded as positive, negative or indeterminate. A positive TST for SLE was defined as ≥5 mm.

Results: Forty seven of SLE patients (95,9%) had been BCG vaccinated.Thirteen of 50 (26%) patients had positive QTF-G with a similar result to controls (28,5%). One patient had an indeterminate result. The agreement between QTF-G and TST was observed to be 32/48 (66,6%)(κ=0.36). There were fewer positive QFT-G test results than positive TST results (26% vs 56%; $p<0,001$).Fifteen (31%) patients were TST(+)/QTF-G(-) while only 1(2%) patient was TST(-)/QTF-G (+). If 10 mm induration diameter was chosen as the TST cut-off value, the agreement between two tests was 41/48 (85,4%) with a kappa value of 0.65.

Conclusion: In a TB-endemic and BCG vaccinated population, the Quantiferon-TB Gold assay seemed to be a more accurate test for detection of LTBI in SLE patients compared with the TST. Although 5 mm is usually accepted to be the standart cut-off for TST in immunosupressed patients such as SLE, level of agreement between QTF-G and TST was better with a 10 mm cut-off in our population.

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Impact of Serious Infections in the Morbi-Mortality of a Cohort of Spanish Patients with Systemic Lupus Erythematosus. L. Castro, J. Cortés-Hernández, M. Torres-Salido, S. Buján, M. Vilardell-Tarrés and J. Ordi-Ros, Systemic Autoimmune disease Research Unit. Hospital Vall d'Hebron., Barcelona, Spain

Purpose: Infections remain a serious and important cause of morbidity and mortality in patients with SLE. Despite an early detection and aggressive treatment, severe infections still account for 20-55% of the SLE-related deaths. With the introduction of new immunosuppressant/biological drugs more studies are needed to establish whether there has been a change in the infectious pattern and their

impact in mortality/morbidity. The aim of this retrospective study is to determine the prevalence of infections in our cohort of SLE patients and to establish the impact on mortality and hospitalization as well as to evaluate the risk factors associated to the development of infection

Methods: Database information from the 570 patients attending our specialized SLE clinic between 1969-2009 was reviewed retrospectively to evaluate the incidence and characteristics of the infection, the clinical, treatment received and laboratory of the patients at the time of infection as well as the impact in hospitalization and mortality. Only serious infections were evaluated. Minor infections like urinary and respiratory upper tract infections were not included. Prognostic factors associated to infection development were assessed.

Results: One-hundred thirty-five patients had a serious infection (24%). Ten patients had more than one infection. The mean age at infection was 44±12 years. At the time of the infection the mean disease duration was 30±6 years. Fifty-two patients were receiving immunosuppressive treatment at the time of the infection (38%). Seventy-eight (58%) of them were serious enough to result in hospitalization. Sixteen of those required intensive care admission (16%). Most cases had a community acquired infection (83%). In 25 cases no causative agent was found. Of the rest of 135 infective episodes, 112 (83%) were due to a bacterial infection, 20 (15%) viral and 3 (2%) fungical. Of the bacterial infections, pyelonephritis was the most frequent bacterial infection (27%) being by E Coli in more than 50% of cases, pneumonia occurred in 23% of cases, being the Streptococcus pneumonia antigen positive in 13% of cases. None of those patients had been vaccinated against pneumococcus. Other bacterial infections were soft tissue infection (8%), Tuberculosis (6%), gastroenteritis (4%), meningitis (3%), endocarditis (3%) and osteomyelitis (3%). Of the viral infections, VZH infection was the most frequent (80%). Infection-related mortality occurred in 7 patients (5%), two of them due to miliar tuberculosis. When compared with patients who did not developed infection, the use of high dose of prednisone or other immunosuppressants, disease activity, hypocomplementaemia or hypogammaglobulinaemia did not increased the risk of infection.

Conclusion: Infection is still a problem in patients with SLE. In our series of patients 24% of patients had a serious infection. Infection-related mortality occurred in 7 patients (5%). A major risk factor of infection was not detected.

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Reticulocytes Bearing C4d in Patients Hospitalized for Acute Infections. Surabhi Agarwal, Harish Jasti, Susan Manzi, Abdus Sattar, Barbara Paul, Shane Lavin, Joseph M. Ahearn and Amy H. Kao, Lupus Center of Excellence, University of Pittsburgh Schools of the Health Sciences, Pittsburgh, PA

Purpose: Previous studies have shown that complement activation product C4d bound to the surface of reticulocytes (R-C4d) may serve as a biomarker of disease activity in patients with systemic lupus erythematosus (SLE). The goal of this pilot study was to begin to determine if R-C4d levels might be capable of distinguishing flare vs. infection in patients with SLE.

Method: R-C4d levels were measured using flow cytometry in non-SLE and SLE patients who were hospitalized for acute infections. SLE subjects with concurrent active disease defined by SLEDAI >=4 or BILAG A or B were excluded. Both groups were followed longitudinally if baseline levels of R-C4d > 1.9 (0.75 SD of levels in healthy controls). R-C4d levels were compared with historical controls (70 non-SLE and 49 SLE without infection respectively). The historical SLE controls did not have active disease as defined by SLEDAI <4.

Results: The acute infections of 24 non-SLE and 6 SLE subjects included urinary tract infection, pneumonia, Clostridium difficile colitis, cellulitis, peritonitis, pyelonephritis, sepsis, septic joint, impetigo, psoas abscess, osteomyelitis, ascending cholangitis and line infection. R-C4d remained low although slightly increased in non-SLE patients with infection compared to historical non-SLE controls without infection (median: 0.86 vs. 0.53, $p<0.01$ respectively). No significant difference was found in the levels of R-C4d in SLE patients with acute infection compared with historical SLE controls without infection (median: 2.22 vs. 2.65, $p= 0.14$ respectively). In the three non-SLE patients with acute infection that were followed longitudinally, R-C4d levels decreased as the infection cleared. No consistent pattern was observed in the three SLE patients with acute infection.

Conclusion: R-C4d levels are slightly increased in non-SLE patients in setting of acute infection; however, these levels remain below those observed in patients with SLE. There was no significant change in RC4d in the setting of infection in patients with SLE. These initial observations support the potential for RC4d to serve as a biomarker of disease activity in SLE and to facilitate distinction of flare versus infection in lupus patients.

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The Size, but Not the Number, of CD-163+ Histiocytes in the Bone Marrow Predicts Macrophage Activation Syndrome in Adults with Systemic Lupus Erythematosus. B. Shakoory[1], R. D. Sanders[2], V. Reddy[2], N. Mccollum[2], G. S. Alarcon[1], W. W. Chatham[1] and R. Q. Cron[3], [1]UAB Rheumatology, Birmingham, AL, [2]UAB Pathology, Birmingham, [3]UAB Pediatric Rheumatology, Birmingham, AL

Purpose and Background: Distinguishing macrophage activation syndrome (MAS) in the setting of active systemic lupus erythematosus (SLE) presents a challenge. The impact of early diagnosis and treatment of MAS on the outcome emphasizes the importance of markers for quick and unequivocal diagnosis. We explored a role for CD-163 staining in identification of bone marrow hemophagocytosis and examined the correlation of number and size of hemophagocytes with diagnosed MAS in patients with SLE.

Methods: Bone marrow biopsy specimens from 18 patients with confirmed SLE (4 ACR criteria) obtained between 2001 and 2008 were evaluated by hematopathologists after conventional staining and re-evaluated after staining for CD-163, a surface marker for activated macrophages (histiocytes). The degree of hemophagocytosis was graded from 0-4 as compared with 6 negative and 9 positive controls. The number and average surface area of the stained macrophages were established using Image J, 1.40 software. The available clinical, radiographic and laboratory data from the charts were reviewed and abstracted. All CD-163 evaluations were independent and blinded to the prior pathology assessments and the clinical and radiographic data. Correlations between CD-163 counts and cell size and clinical/radiographic data were assessed. The association between the number and size of hemophagocytes and the presence of MAS was examined with standard descriptive statistical tests; p was set at <0.05.

Results: The patients were all above 18 years with a mean age of 45.3 years, with 88.9% women and 66.7% African-Americans. Four of the patients (22%) had 5 of the 2004 hemophagocytic lymphohistiocytosis (HLH) criteria required for the diagnosis of hemophagocytic syndrome. The average CD-163 count was 55.5 (95% CI: 48-62) per 40x objective, 285.7 x 214.2 μm field with an average histiocyte size of 75.3 microns (95% CI: 64.5-86.1). The sensitivity of identifying hemophagocytosis increased from 14% in the initial general evaluation using routine H&E staining to 81% in a targeted search by a trained hematopathologists using CD-163 immunostaining. Interestingly, the mean size but not the number of the hemophagocytes was correlated with the presence of MAS in SLE (p=0.02).

Conclusion: CD-163 staining of bone marrow biopsies from patients with SLE allows for detailed characterization and significantly increases the sensitivity of detecting hemophagocytic macrophages in the bone marrow. The size, and not the number, of the hemophagocytic cells is associated with the presence of overt MAS in patients with SLE. Hence, CD-163 bone marrow immunostaining can be used for confirmation of clinically suspected MAS in adults with SLE.

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The Relationship of Physical Activity to Lupus Activity and Damage. Stacy D. Kennedy[1], Megan E. B. Clowse[1], Lisa G. Criscione-Schreiber[1], Martin Tochacek[1], Stacy P. Ardoin[2] and Kim M. Huffman[1], [1]Duke University, Durham, NC, [2]Ohio State University Medical Center, Columbus, OH

Purpose: Systemic lupus erythematosus (SLE) places patients at increased risk for cardiovascular disease. Studies have shown exercise lowers cardiovascular risk. U.S. guidelines recommend 30 minutes per day of moderate activity 5 days weekly for optimal health. We aimed 1) to measure the physical activity of women with SLE with a self-report tool, the Stanford Brief Activity Survey (SBAS), 2) to correlate SBAS scores with objectively measured physical activity in this population, and 3) to evaluate relationships between SBAS scores and SLE disease activity and organ damage.

Method: The SBAS was administered to 45 women with SLE between October 2008 and February 2009. Self-reported physical activity on-the-job and during leisure time was determined using the SBAS. Participants were separated into groups based on activity level from inactive

to hard intensity. In 23 participants, physical activity was measured with 7 days of accelerometry. Current disease activity was assessed with the Systemic Lupus Erythematosus-Disease Activity Index (SLEDAI) and overall disease damage was assessed with the Systemic Lupus International Collaboration Clinics (SLICC). Spearman correlation coefficients and one-way frequencies were determined.

Results: Mean age of participants was 36 (SD 11.5) years. A full 76% of participants did not meet recommended physical activity guidelines. SBAS scores were related to the accelerometer data (r=0.45, p=0.03). SBAS scores inversely correlated with organ damage (SLICC r=-0.40, p=0.01), but did not correlate with current SLE disease activity (SLEDAI r=0.12, p=0.45).

Conclusion: The majority of women in this study do not engage in regular exercise. The lack of physical activity was not related to current disease activity, but was related to morbidity associated with SLE. The SBAS appears to be a useful tool to gauge physical activity in this population. Given the increased cardiovascular risk in women with SLE, it is critical to better understand why these individuals do not meet recommended guidelines for physical activity.

Table Objectively Measured Physical Activity, SLE Disease Activity and SLE Disease Damage by SBAS Category (n= 45).

SBAS Categories	Inactive N=17 (37.8%)	Light Intensity N=17 (37.8%)	Moderate Intensity N=6 (13.2%)	Hard Intensity N=5 (11.1%)	r	P values
Accelerometer exercise (min/day)	9.77	14.27	18.86	38.33	0.45	0.03
SLEDAI	1.75	3.44	4.00	0.75	0.12	0.45
SLICC	1.88	1.38	0.20	0.25	-0.40	0.01
ESR (mm/hr)	46.31	49.60	35.29	8.50	-0.35	0.02
Body mass index, (kg/m2)	31.16	36.01	30.33	24.98	-0.13	0.38

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Quality of Life in Cutaneous Lupus Erythematosus. Rachel Klein[1], Siamak Moghadam-Kia[1], Jonathan LoMonico[1], Joyce Okawa[1], Katherine Chilek[1], Elizabeth Gaines[1], Chris Coley[1], Lynne Taylor[1], Mary-Margaret Chren[2] and Victoria P. Werth[1], [1]University of Pennsylvania, Philadelphia, PA, [2]University of California San Francisco, San Francisco, CA

Purpose: Cutaneous lupus erythematosus (CLE) is a chronic autoimmune disease that can cause significant disfigurement and often requires lifelong treatment with toxic medications. The purpose of this study was to assess the relationship between CLE and quality of life (QOL). We specifically sought to compare QOL in CLE to other diseases and to determine which independent variables are associated with poor QOL.

Method: All patients with CLE or SLE were invited to participate in the study. Subjects were asked to complete the Skindex-29, which assesses QOL in terms of symptoms, emotions, and functioning, with higher scores indicating worse QOL. They were also asked to provide demographic and basic medical history information. Disease severity was assessed with the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). Mean Skindex-29 scores in CLE were compared to norms for other diseases. Mean scores within the CLE population were compared between different genders, ethnicities, and disease subtypes. Pearson's correlation coefficients were calculated for Skindex-29 scores and disease severity, age, and age at diagnosis.

Results: 157 subjects were included in the analysis. Overall, patients with lupus were most affected in the emotions domain (m=48, SD=28) relative to symptoms (m=40, SD=23) and functioning (m=28, SD=25). The subscales were highly intercorrelated, such that a high score in one tended to be associated with high scores in the others (Pearson's r range 0.65-0.78, all $p<0.0001$). Compared to 8 other diseases, QOL in lupus was significantly impaired across all three domains; with respect to symptoms, only vulvodynia (m=50, SD=17) and eczema (m=48, SD=23) had higher scores than CLE (all $p<0.0001$). In the emotions domain, lupus was comparable to dermatomyositis (mean=45, SD=27) and vulvodynia (m=50, SD=20), and the other diseases were all less affected (all $p<0.0009$). For functioning, only patients with vulvodynia

(m=44, SD=22) were more impaired than patients with lupus (p<0.0001). Female gender was associated with poor quality of life in all three domains (all p<0.006), however there was no significant difference in QOL amongst different ethnicities or disease subtypes. There was a correlation between increased disease severity and worse QOL across all three subscales (Pearson's r range 0.27-0.38, all p<0.0006). There was a small correlation between younger age and worse symptoms (Pearson's r -0.16, p=0.04) and emotions scores (Pearson's r -0.22, p=0.005). There was also a small correlation between younger age at diagnosis and worse symptoms scores (Pearson's r -0.19, p=0.04).

Conclusion: CLE has a profoundly negative impact on QOL, particularly in women and individuals with severe disease. Poor QOL has been linked to psychiatric comorbidity (Sampogna et al, Psychosom Med 2004), therefore it is important to acknowledge and address this issue with patients.

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Comparison of Psychometric Properties of Health Related Quality of Life (HRQoL) Measures Employed in Adults with Systemic Lupus Erythematosus (SLE) - Review of the Literature. Madhura Castelino[1], Janice Abbott[2], Kathleen McElhone[3] and Lee-Suan Teh[4], [1]SpR, Blackburn, United Kingdom, [2]Psychologist, Preston, United Kingdom, [3]Research Associate, Blackburn, United Kingdom, [4]Rheumatologist, Blackburn, United Kingdom

Purpose: Patients with SLE have impaired HRQoL and thus well validated and reliable measures are needed to determine patient-based outcomes. A systematic review of the literature was carried out to evaluate validation studies of HRQoL measures in adults with SLE.

Methods: Full original papers in English were located with key words 'Lupus' and 'Quality of Life' as search strategy in the following databases; MEDLINE, EMBASE, Web of Science, CINAHL, PsycINFO and Health and Psychosocial Instruments. The psychometric properties of the HRQoL measures identified were evaluated using the checklist published by Bot et al[1].

Results: In total 13 papers were relevant. Six were validation studies for generic instruments and used the Short Form-36 (SF-36) (n=4), Quality of Life Scale (QOLS), EuroQoL-5D (EQ-5D) or the Short Form-6D (SF-6D). The remaining seven papers employed one of the disease-specific measures: SLEQOL, L-QOL, SLE Symptom Check List (SSC), LupusQoL (UK) and LupusQoL (US). Some of the psychometric properties are tabulated.

Measure	Construct Validity	Internal Consistency	Floor and ceiling effects	Test-retest reliability	Responsiveness	Interpretability
Chinese SF-36	+	+	[ ]	+	[ ]	[ ]
SF-36 (Singapore)	+	+	[ ]	+	[ ]	+
SF-36 (UK)	+	+	[ ]	[ ]	[ ]	+
EQ-5D	+	[ ]	+	+	+	+
SF-6D	+	[ ]	+	+	+	+
QOLS	+	+	[ ]	+	[ ]	+
SLEQOL	+	+	-	+	+	+
SSC	+	+	[ ]	+	+	+
L-QoL	+	+	+	+	[ ]	+
LupusQoL (UK)	+	+	+	+	[ ]	+
LupusQoL (US)	+	+	[ ]	+	[ ]	+

+: adequate property

[ ]: no information found

-: inadequate property

Using this checklist, the SF-36 and all the disease-specific measures had good internal consistency. All the measures demonstrated good construct validity, test-retest reliability and interpretability. Floor and ceiling effects and responsiveness (sensitivity to change) were only examined in five instruments. Measures varied in their ease of scoring. All the disease-specific measures had acceptable administration time, comprehensibility and content validity. The minimum clinically important difference was only determined in one paper (SLEQOL).

Conclusion: Generally, the psychometric properties of HRQoL measures employed in SLE are adequate. However, the checklist used in this work may not identify the most appropriate criteria for the evaluation of psychometric quality. It is notable that some properties such as responsiveness, floor and ceiling effects have not been evaluated for some of these measures. Full psychometric evaluation is essential before these instruments can be recommended as patient-based outcome measures in adult SLE patients.

1. Bot SD et al, Psychometric evaluation of self-report questionnaires: the development of a checklist. Proceedings of the second workshop on research methodology 25-27 Jun 2003. Amsterdam: VU University Amsterdam; 2003.p.161-8

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Hydroxy-Chloroquine Use and Disease Specific Health Related Quality of Life in Systemic Lupus Erythematosus. Meenakshi Jolly, Diana Segalite Sandler, Winston Sequeira and Joel A. Block, Rush University Medical Center, Chicago, IL

Purpose: Treatment of Systemic Lupus Erythematosus (SLE) with hydroxy-chloroquine (HCQ) has many known benefits, but its benefits on patient reported health outcomes such as Health Related Quality of Life (HRQOL) has not been previously studied. We have found SLE patients on HCQ to have better HRQOL using generic measures of HRQOL. Hence we hypothesized that HRQOL among SLE patients on HCQ will be better than non HCQ users, utilizing disease specific HRQOL tool (LupusQoL-US) as the outcome measure.

Method: We used a previously established data base on health outcomes in SLE to compare demographics, disease characteristics, and HRQOL among HCQ users and non-users. All patients met the American College of Rheumatology Classification Criteria for SLE. Data were available on 230 SLE patients cross-sectionally, collected using chart reviews, history, physical exam, and HRQOL. HCQ use was determined by patient self-report and confirmed by medical chart review. HRQOL was estimated using generic measures LupusQoL-US which has eight domains: Physical health, Pain, Planning, Intimate Relationships, Burden to Others, Emotional Health, Body Image, and Fatigue. We used chi square test to compare categorical data and Non Parametric Tests (Mann Whitney) compared continuous data not normally distributed. A p value of ≤ 0.05 on two tailed test was considered significant.

Results: Mean subject age was 42 ± 13 years. 60% of subjects were African American, 20% Caucasian, 14% Hispanic, and 6% Asian. Both groups were similar in age and ethnicity. Disease activity was similar in the two groups, however disease damage was lower (Mean ± SD, Median) in the HCQ users: SLEDAI Score (5.7±5.2, 5.0 vs 5.2±5.9, 4.4; p=0.10,) SLICC total score (1.1±1.5, 1.0 vs 1.5±1.6, 1.0; p=0.02.) HRQOL was similar among HCQ users (72% of patients) and non users, using the LupusQoL-US: HCQ users did not have better HRQOL (Mean ± SD, Median) vs. non users: Physical health (50.7±1.9, 53.1 vs 47.7±3.5, 46.4; p=0.8), Pain (48.4±2.4, 50.0 vs 44.6±3.9, 45.8; p=0.4), Planning (56.4±2.3, 58.3 vs 53.2±4.3, 58.3; p=0.8), Intimate Relationships (58.8±2.8, 62.5 vs 65.4±4.5, 75.0; p=0.9), Burden to Others (48.5±2.4, 50.0 vs 43.1±4.6, 45.8; p=0.09), Emotional Health (55.8±2.0, 58.3 vs 58.4±4.1, 66.7; p=0.7), Body Image (56.6±2.4, 56.3 vs 61.3±4.2, 70.0; p=0.8), and Fatigue (42.0±2.3, 43.8 vs 47.9± 4.2, 50.0; p= 0.9.)

Conclusion: Though HCQ use is associated with decreased disease damage accrual, it does not translate into a better HRQOL status on the LupusQoL-US measure. Similar results were seen when LupusPRO (another disease specific measure for HRQOL) was used (Data not included). Larger studies are needed to obtain better insight into this lack of correlation.

Disclosure: M. Jolly, None; **D. S. Sandler**, None; **W. Sequeira**, None; **J. A. Block**, None.

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Is Cigarette Smoking An Independent Correlate of Health Related Quality of Life in Patients with Systemic Lupus Erythematosus?
Meenakshi Jolly, Ravikumar Patel, Rohit Aggarwal, Winston Sequeira and Joel A. Block, Rush University Medical Center, Chicago, IL

Purpose: To determine if cigarette smoking is an independent determinant of health related quality of life (HRQOL), irrespective of its association with disease activity and damage in patients with systemic lupus erythematosus (SLE).

Methods: The data were extracted from an ongoing study on HRQOL in SLE. Consecutive consenting adult SLE patients seen in the rheumatology clinic at an academic hospital were enrolled from September 2006 to April 2008 and detailed clinical and demographic variables were collected from 216 SLE patients. The HRQOL was assessed by MOS-SF-36 and EuroQol-5D (EQ-5D). The SF-36 has 8 domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health and Role Emotional. It also provides two summary scores: Physical Component Score (PCS) and Mental Component Score (MCS). The EQ-5D is composed of the following domains: Mobility, Self care, Usual Activities, Pain/Discomfort and Anxiety/Depression. In addition, it includes a Visual Analog Scale (VAS) and an EQ-5D Summary Index. Smoking was defined as present if the subject reported smoking at the time of the study. Chi-Square test and Mann Whitney test were used to make comparisons between the cases 'smoker' and controls 'non-smoker'. Hierarchical linear regression analysis was performed using HRQOL as the dependent variable. In first model, the predictor variable was disease activity (SLEDAI). In second model, disease damage (SLICC) was added to first model. In final model, we added smoking status to second model. R square change for each model was noted. $P < 0.05$ was considered significant on one tailed test.

Results: The mean (±SD) age of participants was 42 ± 13 years and 93 % were females. The ethnic composition was: African American 60%, Caucasian 20%, Hispanic 14% and Asian 6%. Fifteen percent of subjects reported "currently smoking" status at the time of the study. Smokers had worse HRQOL than non smokers: specifically, differences were noted for physical function, bodily pain and vitality domains of SF-36 as well as on PCS (mean ± S.D, median) : physical functioning (45.6 ± 28.3, 50 vs. 56 ± 28.8, 55; p 0.047), bodily pain (38.2 ± 18.5, 41 vs. 54.6 ± 27.6, 51; p 0.001), vitality (38.2 ± 21.4, 45 vs. 49.1 ± 21.6, 50; p 0.012) and PCS (31.1 ± 9.4, 31 vs. 36.1 ± 11.2, 36.6; p 0.017). On EQ5D, smokers had worse functioning on anxiety/depression and visual analog scale: anxiety/depression for extreme problems (10 % vs. 4.5 %, p 0.049), anxiety/depression for some problems (56.6 % vs. 42.3 %, p 0.049) and visual analog scale (61.5 ± 22.4, 60 vs. 68.9 ±20, 70; p 0.048).

On hierarchical regression analysis, disease activity alone explained 3% of the variance in PCS (R square 0.027); disease activity and damage explained similar variance in PCS (R square change 0.028) and addition of smoking variable, increased the variance explained in PCS to 5% (R square change 0.049).

Conclusion: Cigarette smoking is independently associated with worse health outcomes in SLE, although it explains a relatively minor component of variance. Patients with SLE should be screened aggressively and counseled for their smoking history.

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What Does Patient-Reported Systemic Lupus Activity Questionnaire (SLAQ) Measure?
Meenakshi Jolly[1], Mariko L. Ishimori[2], Ioana Moldovan[3], Emmanuel P. Katsaros[4], Karina D. Torralba[5], Dilrukshie Cooray[6], Shuntaro Shinada[5], Joel A. Block[1], Daniel J. Wallace[7], Michael H. Weisman[8] and Perry Nicassio[9], [1]Rush University Medical Center, Chicago, IL, [2]Cedars-Sinai Medical Center, LA, CA, [3]Loma Linda Univ Med Ctr, Loma Linda, CA, [4]Loma Linda Univ, Loma Linda, CA, [5]Keck School of Medicine, University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [6]Harbor-UCLA Medical Center, Torrance, CA, [7]Cedars-Sinai Medical Center, West Hollywood, CA, [8]David Geffen School of Medicine at UCLA, Los Angeles, CA, [9]UCLA, LA, CA

Purpose: Systemic Lupus Activity Questionnaire (SLAQ) is a validated 24-item weighted lupus symptom index based on the physician-reported systemic lupus activity measure (SLAM), developed to track disease activity in an economical way for large groups of systemic lupus erythematosus (SLE) patients in clinical studies. It has been validated against SLAM, but its validity against Physician Global Assessment (PGA) and SLE Disease Activity Index (SELENA-SLEDAI) is not known. The objective of this study was to determine the correlation of SLAQ with PGA, SLEDAI and adjusted SLEDAI. The latter is derived by excluding the laboratory based SLEDAI assessment criteria. Also, correlation of SLAQ, PGA and SLEDAI with subject demographics was sought.

Method: Cross sectional Data from 98 SLE subjects collected from the PATROL (Patient-Reported Outcomes in Lupus) study was analyzed. PGA data was available for only 32 subjects. Descriptive, Spearman correlation coefficients were obtained between a) the three

disease activity measures, b) Demographics (Age, ethnicity, education, insurance, marital status, socio-economic status) with the three disease activity measures. Multiple linear regression with SLAQ as the dependent and significant demographic variables as the independent variables was performed. P value of ≤ 0.05 on two tailed tests was considered significant.

Results: 96% of SLE patients were women**.** 48% were Caucasians and 52% were Hispanics. Mean (SD) age was 44.2 (13.4) yrs. Median (IQR) disease activity scores were: SLAQ 12 (17.3), PGA 0.50 (1), SLEDAI 2.0 (4), adj SLEDAI 0 (2). Correlation between SLAQ and SLEDAI, adj SLEDAI and PGA were 0.06 (p=0.6), 0.19 (p=0.08) and 0.19 (p=0.30) respectively. SLEDAI and adj SLEDAI did not correlate with demographics. PGA correlated with age (-0.35, p=0.05) and ethnic minority (-0.40, p-0.02). SLAQ correlated with ethnic minority (-0.51, p=0.000), home ownership (-0.34, p=0.001), income (-0.29, p=0.007), annual household income (0.36, p=0.001), highest grade achieved (0.46, p=0.000) and insurance type (-0.62, p=0.000). These variables collectively explained 46% of the variance observed in the SLAQ score on regression analysis.

Conclusion: Patient reported SLAQ measure does not correlate with SLEDAI or PGA. Furthermore SLAQ scores are significantly influenced by socio-economic variables, especially insurance type and ethnic minority status.

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Validation of the SF-36 in Patients with Systemic Lupus Erythematosus (SLE). Jennifer L. Beaumont[1], Jin-Shei Lai[1], David Cella[1], P. Brunetta[2] and Sarika Ogale[2], [1]Northwestern University, Chicago, IL, [2]Genentech, Inc, South San Francisco, CA

Purpose: Systemic lupus erythematosus (SLE) is a multiple organ system autoimmune disease that has an impact on patients' health-related quality of life (HRQOL). The purpose of this study was to validate the SF-36, a widely used measure of HRQOL, for use in moderately-severely active extra-renal SLE patients.

Method: 254 SLE patients, who were participating in a clinical trial of rituximab (the EXPLORER trial), completed the following scales at baseline and weeks 12, 24, and 52: the SF-36, Brief Pain Inventory (BPI), and Patient Global Assessment Visual Analog Scale (PGA). Physicians completed the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the British Isles Lupus Assessment Group (BILAG) disease activity index at the same time points. We used changes in the BILAG General and Musculoskeletal domains as anchors to evaluate responsiveness and MID of the SF-36 Physical Component Score (PCS). A change in BILAG domain scores from A to B or better, or B to C or better, was classified as improved, and the reverse as worsened. A change from C to D/E or vice-versa was not considered clinically significant and classified as unchanged. PGA scores were categorized as improved or worsened if there was a >30% decrease or increase from baseline respectively, and used as anchors for the PCS and Mental Component Summary (MCS) scores.

Results: All SF-36 scores were 1-2 standard deviations (SD) lower than the US general population at baseline. Internal consistency of most of the SF-36 subscales was supported by Cronbach's alpha > 0.80 at all time points. In cross-sectional analyses, PCS scores successfully differentiated between groups defined by BILAG General and Musculoskeletal domain ratings at most visits. SF-36 had moderate (r = 0.40-0.65) correlations with BPI and PGA scores. Correlations with BILAG and SLEDAI total scores were low (r = 0.12-0.29). Mean changes from baseline in the eight SF-36 domain scores, PCS and MCS, were generally in agreement with improved, unchanged and worsened PGA scores. Patients with improved or unchanged BILAG General and Musculoskeletal status compared to baseline experienced a statistically significant improvement in most SF-36 PCS scores with effect sizes (mean change / SD) in the range of 0.3 to 0.7. Scores remained stable for patients with worsened BILAG ratings compared to baseline with effect sizes generally less than 0.3. Distribution and anchor-based estimates of the minimally important differences (MID) suggested MIDs of approximately 3-6 points.

Conclusion: The SF-36 is a valid and responsive measure of HRQOL in patients with SLE. MIDs in SLE patients are similar to those derived previously in other populations. Since few patients experienced worsening of BILAG General and Musculoskeletal domains and PGA in this study, further research is warranted to evaluate responsiveness of the SF-36 to worsening in this population.

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EQ-5D and SF-36 Quality of Life Measures in Systemic Lupus Erythematosus: Comparisons with RA, Non-Inflammatory Rheumatic Disorders (NIRD), and Fibromyalgia (FM). Frederick Wolfe[1], KD Michaud[2], Tracy Li[3] and RS Katz[4], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]U Neb Med Cntr and NDB, Omaha, NE, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Rheumatology Associates, Chicago, IL

Purpose: The SF-36 provides numerical measurement of patient health, but does not include preferences for health states and cannot be used in cost-effectiveness analyses. By contrast the EQ-5D is based on preferences and produces utility scores. However, EQ-5D has not been used before in SLE. In this project we describe the comparative HRQOL of the four groups of rheumatic disease patients according to SF-36 and EQ-5D - EQ-5D VAS results, examine predictors of HRQOL in SLE, and characterize results in term of patients' satisfaction with health.

Methods: We studied 1,316 patients with SLE, 13,722 with RA, 3,623 with NIRD, and 2,733 with FM. We determined SLE damage by the newly developed Lupus Damage Index Questionnaire (LDIQ), a self-report version of the ACR/Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI).

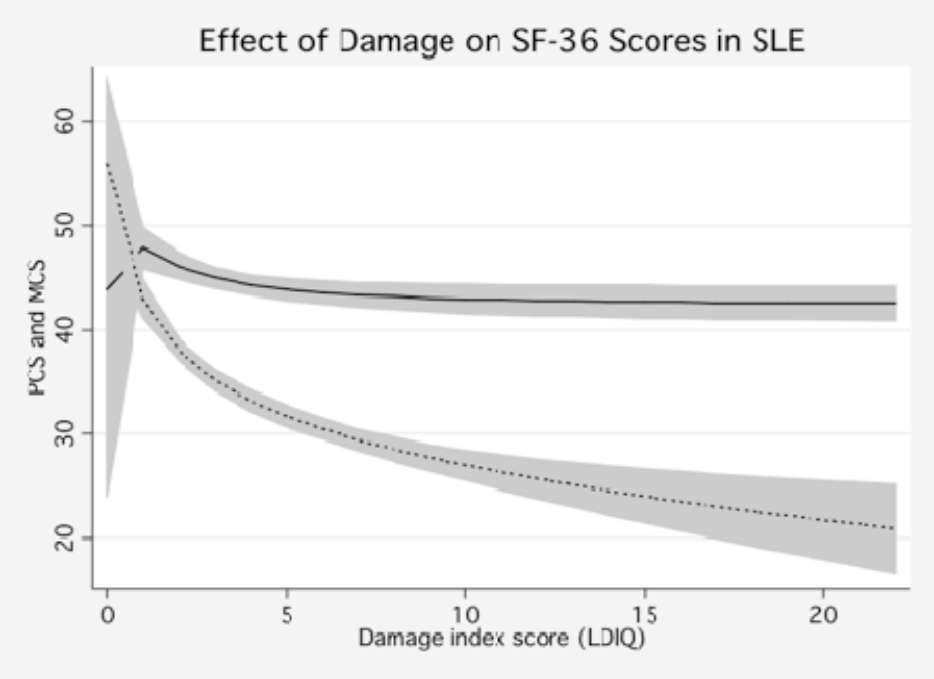
Results: The mean EQ-5D, PCS and MCS scores were 0.72, 36.3, and 44.3 in SLE (Table 1). There was essentially no difference among EQ-5D and PCS scores for patients with SLE, RA, or NIRD. MCS was lower in SLE compared with RA and NIRD (44.3, 49.1, 50.8). All scores were much more abnormal in FM (0.61, 31.9, 41.9). Within SF-36 domains, function was better, but general health, vitality, social function, emotional role, and mental health were more impaired in SLE compared with RA and NIRD. In SLE, QOL was predicted by damage (Figure 1), comorbidity, household income, education, and age. 15% of patients with SLE were very satisfied with their health, and their QOL scores (0.84, 45.4, 50.1) were the similar to those as found in the population for EQ-5D and MCS, but slightly reduced for PCS.

Conclusion: HRQOL in SLE, RA, and NIRD is similar with respect to SF-36 PCS and EQ-5D. SLE patients have the lowest MCS scores of the 3 disorders. Patients with fibromyalgia have the lowest HRQOL scores, regardless of measure. HRQOL in SLE is predicted by damage, comorbidity, age, household income, and educational attainment. About 47% of SLE patients are somewhat (22.1%) or very satisfied (15.1%) with their health.

Table 1. SF-36 and utility scores in SLE, RA, NIRD, and FM.

Health Status Variables	*SLE (N=1,316)*	*RA (N=13,722)*	*NIRD (N=3,623)*	*Fibromyalgia (N=2,733)*
SF-36 domains	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Physical function	52.7 (30.6)	49.5 (29.5)	47.6 (28.1)	40.7 (26.3)
Physical role	36.3 (41.5)	39.9 (42.0)	39.5 (41.6)	19.2 (32.3)
Pain total	48.5 (24.1)	50.1 (23.1)	48.3 (21.6)	34.3 (19.5)
General health	37.5 (23.0)	49.4 (23.3)	55.8 (22.5)	39.2 (22.1)
Vitality	35.9 (23.1)	43.4 (23.4)	46.1 (23.1)	27.1 (21.1)
Social function	62.0 (27.9)	69.7 (27.5)	71.6 (26.9)	51.8 (28.2)
Emotional role	54.5 (43.9)	63.5 (42.4)	65.6 (41.4)	43.9 (43.9)
Mental health	67.1 (20.3)	72.9 (18.9)	75.0 (18.2)	62.5 (21.8)
SF-36 Summary Scores				
Physical component score	36.3 (11.5)	36.7 (11.3)	36.4 (10.8)	31.9 (9.6)
Mental component score	44.3 (11.8)	49.1 (11.4)	50.8 (11.4)	41.9 (12.5)

Utilities				
EQ-5D VAS (0-1)	0.64 (0.21)	0.66 (0.21)	0.68 (0.20)	0.57 (0.22)
EQ-5D (US) (0-1)	0.72 (0.21)	0.73 (0.19)	0.73 (0.18)	0.61 (0.22)



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Predictors of Osteoporotic Fracture in SLE. Monthida Fangtham[1] and Michelle Petri[2], [1]Good Samaratan Hospital, Baltimore, MD, [2]Johns Hopkins Univ, Baltimore, MD

Purpose: Osteoporosis and osteoporotic fractures are the most frequent organ damage in systemic lupus erythematosus (SLE). We assessed the association between osteoporotic fractures and SLE clinical features, other organ damage and the impact of treatment, especially corticosteroids.

Method: In this large prospective cohort study of 1799 SLE patients, there were 340 osteoporotic fractures. Variables evaluated were sociodemographic data, disease variables, clinical features, organ damage, the use of corticosteroids and other complications. Clinical associates of fractures were determined by univariate and multivariate analyses.

Results:

Factor	Fracture Positive	Fracture Negative	P-value	Odds Ratio (95% CI)
African-American	32%	42%	0.0021	0.67 (0.52, 0.86)
Smoking ever	45%	37%	0.0092	1.38 (1.09, 1.76)
Raynaud's syndrome	65%	49%	<0.0001	1.93 (1.51, 2.47)
Renal insufficiency	23%	16%	0.0051	1.54 (1.15, 2.06)

Factor	Fracture Positive	Fracture Negative	P-value	Odds Ratio (95% CI)
Lupus anticoagulant	32%	24%	0.0052	1.46 (1.13, 1.90)
Prednisone ever	91%	83%	0.0001	2.15 (1.43, 3.22)
Prednisone use currently	64%	53%	0.0004	1.54 (1.21, 1.97)
Pulse steroid ever	47%	33%	<0.0001	1.79 (1.41, 2.28)
Obesity	50%	38%	<0.0001	1.66 (1.30, 2.10)

In the best multivariable model, African-American ethnicity, smoking ever, Raynaud's syndrome, lupus anticoagulant, prednisone ever, pulse steroid ever and obesity remained significant.

Conclusion: This study identified multiple risk factors for osteoporotic fracture in SLE. Corticosteroid use (ever, current, pulse) was a strong risk factor. For the first time, smoking, Raynauds', renal insufficiency, and antiphospholipid antibodies have been identified as additional risk factors.

Disclosure: M. Fangtham, None; **M. Petri**, None.

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Serum Concentrations of 25-OH Vitamin D in SLE Patients Are Inversely Related to Disease Activity- Is It Time to Routinely Supplement SLE Patients with Vitamin D? Howard Amital[1], Zoltá Szekanecz[2], Gabriella Szücs[3], Katalin Dankó[3], Endre Nagy[4], Tünde Csépány[3], Emese Kiss[5], Andrea Doria[6], Nadia Corocher[6], Nancy Agmon-Levin[7], Hedi C. Orbach[8], Gisele Z. Goddard[8] and Yehuda Shoenfeld[9], [1]Sackler Faculty of Medicine, Tel-Aviv University, Kfar-Saba, Israel, [2]University of Debrecen medical and Health Sciences Center, Debrecen, Hungary, [3]University of Debrecen Med Ctr, Debrecen, Hungary, [4]University of Debrecen Medical and Health Science Center, Debrecen, Hungary, [5]5Division of Rheumatology, University of Debrecen Medical and Health Science Center, Debrecen, H-4012, Hungary, Debrecen, Hungary, [6]University of Padova, Padova, Italy, [7]Center for Autoimmune Diseases, Sheba Medical Center, Israel, Ramat Gan, Israel, [8]Wolfson Medical Ctr, Holon, [9]Sheba Medical Center, Ramat Gan, Israel

Purpose: Low serum vitamin D concentrations were reported in several autoimmune disorders. The purpose of this study was to assess whether low serum vitamin D concentrations are related to disease activity of SLE patients.

Method: 378 patients were pooled from several European and Israeli cohorts and their disease activity was measured by two different methods; 278 patients had SLE disease activity-2000 (SLEDAI-2K) scores and 100 patients had European Consensus Lupus Activity Measurement (ECLAM) scores. The disease activity scores were measured on the day their serum samples were drawn. In order to combine the two systems we converted the scores into standardized values (z-scores), this manner enabled univariate summary statistics for the two variables (SLEDAI-2K and ECLAM).

We used the commercial kit, LIAISON® 25 OH Vitamin D Assay (310900-Diasorin) in order to measure serum concentration of 25 OH Vitamin D in 378 patients with SLE. The method for quantitative determination of 25 OH Vitamin D is a direct, competitive chemiluminescence immunoassay.

Results: In this cohort there were 31 male and 347 females patients, vitamin D levels did not differ between genders; the vitamin D serum concentration was 21.7±13.2 vs. 20.5±14.4 ng/ml in males vs. females respectively (p value not significant, p=0.67). A significant negative correlation was demonstrated between the serum concentration of vitamin D and the standardized values (z-scores) of disease activity scores as measured by the SLE-DAI2k and ECLAM scales (Pearson's correlation coefficient of -0.12, p=0.018).

As a comparator we analyzed serum anti-DNA antibodies in these two categories of patients and observed a higher titer according to the chemiluminescence immunoassay units (113.5±212.9 vs. 22.3±38.7, p<0.001). However anti-DNA antibody titers did not correlate with disease activity (Pearson's correlation coefficient of 0.05, p=0.54).

Conclusion: In a cohort of SLE patients originating from Israel and Europe vitamin D serum concentrations were found to be inversely related to disease activity.

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Prevalence and Clinical Predictors of Osteonecrosis in Systemic Lupus Erythematosus. Ashima Makol[1] and Michelle A. Petri[2], [1]Michigan State University, East Lansing, MI, [2]Johns Hopkins University, Baltimore, MD

Purpose: Osteonecrosis (ON) is a devastating complication often leading to rapid joint destruction and disability in young women with systemic lupus erythematosus (SLE). We aimed to determine the prevalence, clinical and laboratory predictors of ON in SLE patients from a large prospective cohort to identify patients at risk who could potentially benefit from early therapeutic intervention.

Method: A large prospective cohort was reviewed to identify SLE patients who developed ON at one or more sites. Clinical and laboratory parameters of SLE patients who developed ON were compared versus those who did not. Statistical analysis was done using chi-square test or Fisher's exact test for dichotomous variables and Student's t-test for continuous variables. A P value of less than 0.05 was considered statistically significant in all comparisons in the study. **Results:**

Factor	ON Positive	ON Negative	P-value	Odds Ratio (95% CI)
African-American	63%	37%	<0.0001	2.84 (2.05, 3.92)
Smoking (current)	23%	16%	0.0383	1.50 (1.04, 2.17)
Raynaud's	60%	51%	0.0241	1.43 (1.05, 1.96)
Vasculitis	30%	13%	<0.0001	2.79 (1.97, 3.94)
Lupus anticoagulant	33%	25%	0.0228	1.49 (1.06, 2.08)
Anti-dsDNA positive	66%	56%	0.0095	1.54 (1.12, 2.12)
Low C3	70%	52%	<0.0001	2.15 (1.55, 2.99)
LowC4	61%	46%	0.0001	1.83 (1.34, 2.50)
Deep venous thrombosis	18%	12%	0.0352	1.58 (1.05, 2.36)
Stroke	14%	7%	0.0064	1.95 (1.23, 3.08)
Myocardial Infarction	8%	4%	0.0349	1.96 (1.08, 3.56)
Digital Gangrene	5%	1%	0.0008	4.17 (1.95, 8.91)
Other Venous thrombosis	9%	4%	0.0064	2.23 (1.28, 3.86)
Any Venous thrombosis	28%	17%	0.0002	1.96 (1.39, 2.77)
Any Arterial thrombosis	25%	14%	0.0003	2.03 (1.41, 2.92)
Prednisone (ever)	99%	83%	<0.0001	18.4 (4.54, 74.6)
Pulse steroid	66%	32%	<0.0001	4.19 (3.03, 5.79)
Prednisone highest dose	71.9 ± 40.5	41.3 ± 39.8	<0.0001	

In the multiple variable model, African-American ethnicity, smoking, Raynaud's, vasculitis, lupus anticoagulant, low C3, and venous thrombosis all remained significant.

Conclusion: The association of corticosteroids with ON in SLE is well known. This prospective study also identified other potential mechanisms, including smoking, Raynaud's, low C3 and vasculitis – all of which damage vessels. We found an association with the lupus anticoagulant and with thrombosis. Corticosteroids, smoking, low C3, Raynaud's, and antiphospholipid antibodies are all potentially modifiable risk factors. Whether an antiplatelet therapy would be helpful must be determined in larger databases.

Disclosure: A. Makol, None; **M. A. Petri**, None.

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Lupus in Asian Canadians: The 1000 Canadian Faces of Lupus Study. C. A. Peschken[1], Janet E. Pope[2], Earl D. Silverman[3], P. R. Fortin[4], Christian A. Pineau[5], Michel Zummer[6], Murray Urowitz[7], Dafna Gladman[4], M. Hudson[5], Lori B. Tucker[8], G. Chedeville[5], A. Huber[9], S. Bernatsky[10], Ann E. Clarke[11], C. Douglas Smith[12], H. Arbillaga[13], SE. Ramsey[14] and CaNIOS Investigators, [1]Univ of Manitoba, Winnipeg, MB, [2]St Joseph Health Care London, London, ON, [3]Hosp for Sick Children, Toronto, ON, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]McGill University, Montreal, QC, [6]Ch Maisonneuve-Rosemont, Montreal, [7]U of Toronto, Toronto Western Hospital, Toronto, ON, [8]BC Childrens Hospital, Vancouver, BC, [9]IWK Health Centre, Halifax, NS, [10]MUHC, Montreal, QC, [11]McGill University Health Center, Montreal, QC, [12]TOH Riverside Campus, Ottawa, [13]CaNIOS, ON, [14]IWK Health Ctr, Halifax

Purpose: There are few reports of systemic lupus erythematosus (SLE) in North American Asians. We describe differences in disease expression, disease activity and damage between Asian (ASN) and Caucasian (CAU) SLE patients in a large multicentre cohort.

Method: SLE patients were enrolled in a multi-centre cohort and followed annually. Sociodemographic factors, diagnostic criteria, disease activity, treatment, damage, and self-reported disease activity and health were collected using standardized tools. Patients reporting ASN or CAU ethnic origin were abstracted, and results were compared between the two groups. Data from the last annual visit were analyzed, testing for differences in sociodemographic and clinical factors and patient reported measures between the two ethnic groups in univariate analyses; significant variables from univariate analyses were included in multivariate regression models.

Results: 1388 patients were studied, including 1113 CAU and 275 ASN. 330 patients reporting other ethnic backgrounds were excluded. Disease onset was at an earlier age (ASN= 22±12 yrs, CAU 33±15 yrs; $p<0.001$) and disease duration (ASN= 9±8 yrs, CAU 14±11 yrs; $p<0.001$) and age (ASN= 32±15 yrs, CAU 47±16 yrs; $p<0.001$) were lower in ASN compared to CAU. Income was similar, high school completion was higher in ASN (ASN 92%, CAU 84%; $p=0.001$). SLEDAI scores and number of ACR criteria met were similar. ASN had more frequent renal criteria (ASN 60%, CAU 34%; $p<0.001$), less frequent arthritis criteria (ASN 64%, CAU 80%; $p<0.001$). ASN were more frequently treated with prednisone (ASN 80%, CAU 64%; $p<0.001$), cyclophosphamide (ASN 18%, CAU 12%; $p=0.007$) and mycophenolate (ASN 22%, CAU 10%; $p<0.001$). Mean damage scores were higher in CAU but this was no longer significant after controlling for age and disease duration. SLAM scores were higher in CAU (ASN= 5.0±4.2, CAU 6.5±4.7; $p<0.001$). Self-reported flares, fatigue, disease activity and symptom scores (SLAQ) were lower in ASN. SF-36 physical (PCS) and mental (MCS) component scores were higher in ASN. In multivariate analyses, Asian ethnicity remained a significant predictor of better PCS ($\beta=3.3$, 95% CI 0.5,6.1;$p=0.02$) and MCS ($\beta=-2.9$, 95% CI 0.3,5.5;$p=0.03$) and lower SLAQ ($\beta=-5.0$, 95% CI -6.1,0.1; $p=0.01$) when age, disease duration, damage, immunosuppressives, ACR criteria met, education, and SLEDAI were included.

Conclusion: Although lupus was at least as severe in ASN Canadians, (younger age of onset, more renal involvement, and more exposure to immunosuppressives), ASN patients reported fewer disease flares, lower levels of disease activity and fatigue, and better physical and mental health compared to CAU. Cultural attitudes may influence patient perceptions of disease activity and overall health.

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Michigan Lupus Epidemiology & Surveillance Program (MILES): Increased Proportion of Target-Organ Threatening Involvement Among Male Versus Female SLE Patients. Emily C. Somers[1], Wendy Marder[1], Emily E. Lewis[1], Sheeja Francis[1], Patricia C. Cagnoli[1], Peter DeGuire[2], Caroline Gordon[3], Charles G. Helmick[4], James C. Leisen[5], J. Patricia Dhar[6], W. Joseph McCune[1] and MILES Group, [1]University of Michigan, Ann Arbor, MI, [2]Michigan Department of Community Health, Lansing, MI, [3]University of Birmingham, Birmingham, United Kingdom, [4]Centers for Disease Control and Prevention, Atlanta, GA, [5]Henry Ford Health System, Detroit, MI, [6]Wayne State University, Bloomfield Hills, MI

Purpose: Although SLE disproportionately affects women (female to male ratio ~9:1), anecdotal evidence suggests males with SLE have particularly aggressive disease. We compare SLE characteristics in males vs. females utilizing a population-based registry.

Methods: As part of the ongoing MILES active surveillance program, detailed record reviews are performed for all SLE cases residing in the catchment area (source population ~2.5 million) and meeting eligibility criteria. Two-sided t-tests and chi-squared statistics were performed to compare summary statistics.

Results: Of the n=1928 currently confirmed SLE patients fulfilling >=4 ACR criteria, 183 (9.5%) were male. The total number of ACR criteria was similar between sexes (mean±SD: F 5.6±1.4, M 5.4±1.5; p=NS), as was age at diagnosis (F 33.5±13.1 yrs, M 35.0±16.1; p=NS). However, males on average had a significantly shorter disease duration (defined as time from diagnosis until most recent follow-up: F 12.3 ± 9.0 vs M 9.9 ± 8.2 yrs, p=0.002).

ACR criteria among SLE patients, according to sex

	Female n=1745 no. (%)	Male n=183 no. (%)	P-value
Malar	889 (51.0) *	72 (39.3)	0.003
Discoid	399 (22.9)	51 (27.9)	NS
Photosensitivity	882 (50.6) *	59 (32.4)	<0.001
Mucosal ulcers	795 (45.8) *	46 (25.1)	<0.001
Arthritis	1,329 (76.2) *	122 (67.0)	0.006
Serositis	751 (43.0)	75 (41.0)	NS
Renal	535 (30.7)	78 (42.6) *	0.001
Neurologic	307 (17.6)	47 (25.7) *	0.007
Hematologic	1,041 (59.7)	124 (67.8) *	0.033
ANA	1,639 (94.7)	170 (94.4)	NS
Immunologic	1,125 (64.5)	141 (77.1) *	0.001

* designates sex with significantly greater proportion positive for criterion

Conclusion: Though females had a significantly higher proportion of skin and joint manifestations, males had significantly higher end-organ threatening involvement (renal, neurologic) and both immunologic and hematologic manifestations, which accumulated during a shorter average disease duration. These data support anecdotal evidence that males have more aggressive disease.

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Study of Clinical Expression and Morbidity of Systemic Lupus Erythematosus During a 5 Year Follow up After the Diagnosis in Male Patients (THESSALONIKI LUPUS STUDY GROUP). Styliani Stefanidou, Alexios Benos and Alexandros Garyfallos, Thessaloniki, Greece

Purpose: Systemic lupus erythematosus (SLE) is the most clinically and serologically diverse of the autoimmune connective tissue diseases as it may affect any organ of the body. However, some studies suggest that this condition can be divided into more homogenous subsets of pathogenetic, therapeutic, and prognostic significance. For instance, the sex of the patient, among other factors, may influence disease expression. Several studies have been conducted in search of prognostic factors of morbidity and mortality in male patients.

Method: In the present retrospective study we have analyzed the prevalence and the characteristics of the most relevant clinical features at the diagnosis of the disease in 59 male patients out of 594 data of patients with SLE that we collected.

Results: Several differences in the expression of the disease were found in relation to the gender of the patient. Male patients had higher prevalence of thrombosis (O.R.: 5,832 και C.I.: 2,698-12,608), nephropathy (O.R.: 2,806 και C.I.: 1,462-5,384), symptoms from the gastrointestinal system (O.R.:2,237, C.I.:1,043-4,796), strokes (O.R.: 12,289 και C.I.: 3,176-47,545), positive titers of antidsDNA (O.R.:2,226, C.I.:1,009-4,908) and increased values of SGPT (O.R.:3,034, C.I.:1,052-8,752) but tended to appear less often arthralgia (O.R.: 0,425 και C.I.: 0,237-0,719), hair loss (O.R.:0,187 και C.I.:0,044-0,782), Raynaud phenomenon (O.R.:0,386, C.I.: 0,161-0,927) and photosensitivity (O.R.:0,301, C.I.:0,132-0,685) as initial clinical manifestations in comparison to female.

During the five year follow up the predominant symptoms in male were nephropathy, neurologic involvement and arthritis. Positive associations have been found between male sex and the incidence of tendonitis (O.R.:5,594, C.I.:1,593-19,645), myositis (O.R.:5,262, C.I.:1,253-22,106). nephropathy (O.R.:2,959 και C.I.:1,315-6,660) and infections, particularly of the respiratory tract (O.R.:3,925 και C.I.:1,440-10,699), during the 5 year follow up.

Conclusion: This study has shown that SLE has a wide spectrum of manifestations, but still it is possible to recognize relatively homogeneous SLE subsets of clinical significance. Furthermore, our study has provided updated information of SLE morbidity characteristics in male patients. Assessing the incidence rates and delineating the prognostic factors associated with morbidity will be helpful for future management of patients with SLE using evidence-based medicine models.

Disclosure: S. Stefanidou, None; **A. Benos**, None; **A. Garyfallos**, None.

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The Effect of Age-of-Onset On Disease Manifestations in a Large Multi-Ethnic Cohort of SLE Patients. Ryan Webb[1], Emily C. Somers[2], Jennifer A. Kelly[3], Gail R. Bruner[4], Gary S. Gilkeson[5], Diane L. Kamen[6], John B. Harley[7] and Amr H. Sawalha[8], [1]Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]University of Michigan, Ann Arbor, MI, [3]Oklahoma Medical Res Fnd, Oklahoma City, OK, [4]OMRF, Oklahoma City, [5]MUSC, Charleston, SC, [6]Medical Univ South Carolina, Charleston, SC, [7]OMRF, OU, VA, Oklahoma City, OK, [8]University of Oklahoma, Oklahoma Medical Research Foundation, Department of Veterans Affairs Medical Center, Oklahoma City, OK

Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse manifestations. Herein, we explored the relationship between the age of disease onset and the clinical and serological manifestations of SLE.

Methods: Our study population included 1317 patients with SLE enrolled in the Lupus Family Registry and Repository at OMRF. We performed univariate analyses on the age of disease onset and the various clinical and serological disease manifestations, and then proceeded to logistic regression modeling with manifestations that had a p-value of <0.20. Next, we fit two logistic regression models for each manifestation: one for childhood-onset (<18 yrs) versus adult-onset disease (≥18 yrs), and one for early adult-onset (18-49 yrs) versus late adult-onset disease (≥50 yrs). Each logistic regression model used the disease manifestation as the dependent variable, and age of onset as the independent variable of interest, while controlling for gender, race and disease duration.

Results: The odds of having proteinuria, malar rash, anti-dsDNA antibody, hemolytic anemia, arthritis, cellular casts and leucopenia were lower in adult-onset compared to childhood-onset SLE (odds ratios = 0.33, 0.47, 0.48, 0.40, 0.53, 0.58, 0.65, respectively, and p-values <0.0001, 0.0004, 0.0005, 0.0024, 0.011, 0.031, 0.045, respectively). Proteinuria, malar rash, anti-dsDNA antibody, and hemolytic anemia all

remained significant after Bonferroni correction for multiple testing. The odds of having proteinuria, cellular casts, anti-nRNP antibody, anti-Sm antibody, anti-dsDNA antibody, and seizures were lower in late adult-onset compared to early adult-onset disease (odds ratios= 0.34, 0.25, 0.55, 0.36, 0.62, 0.35, respectively, and p-values <0.0001, 0.0013, 0.011, 0.013, 0.021, 0.026, respectively). Late adult-onset SLE patients have 1.58 times the odds of developing photosensitivity compared with early adult-onset SLE patients (p=0.0097). Proteinuria and cellular casts remain significant after Bonferroni correction for multiple testing.

Conclusion: Childhood-onset SLE is associated with a more severe disease with higher odds of proteinuria, malar rash, anti-dsDNA antibody, and hemolytic anemia compared to adult-onset disease. In adult-onset SLE, patients with a disease onset at <50 yrs of age are about 3-4 times more likely to develop renal involvement compared to patients with a disease onset ≥ 50 yrs of age.

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Variable Health-Related Quality of Life Among African American Cohorts of Patients with Systemic Lupus Erythematosus. Anisha Dua[1], Diane L. Kamen[2], April L. Barnado[3], Gary S. Gilkeson[4], Rachel Mikolaitis[5], Anna Meyer[6], Winston Sequeira[5], Joel A. Block[5] and Meenakshi Jolly[5], [1]Rush University Hospital, Chicago, IL, [2]Medical Univ South Carolina, Charleston, SC, [3]Duke Univ SOM, Durham, NC, [4]MUSC, Charleston, SC, [5]Rush University Medical Center, Chicago, IL, [6]Charleston, SC

Purpose: Systemic Lupus Erythematosus (SLE) predominantly affects young women, affects multiple organ systems, is influenced by genetics, and impacts physical and emotional quality of life. In our previous work, a trend towards greater prevalence of SLE specific serologies were present among urban African Americans (UAA) with more genetic admixture than rural Gullah African Americans (GAA) SLE patients with lower genetic admixture. We now aim to determine if health related quality of life (HRQOL) is significantly different among SLE between different African American cohorts.

Method: Urban African American SLE patients receiving care at a University and County Hospital in Chicago were compared with rural African American subjects from South Carolina. Previously collected demographic, clinical and quality of life data from 137 urban SLE subjects with high genetic admixture (20-30%) and 35 SLE subjects from GAA (with low genetic admixture, 8-12%) were analyzed. The variables analyzed were demographics and health related quality of life (SF-36), domains: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (V), Social Functioning (SF), Mental Health (MH) and Role Emotional (RE). It also provides two summary scores: Physical Component Score (PCS) and Mental Component Score (MCS). Data were compared using non-parametric t-tests chi square tests. A p-value of ≤0.05 was considered statistically significant on one tailed tests.

Results: The study population was predominantly female with a median age (IQR) of 43 (21) vs 37(14) yrs in UAA vs. GAA subjects, respectively. Age at diagnosis was significantly older in CAA when compared with SC subjects (Median (IQR) 29.5 (19) vs 28.0 (13), p=0.03) respectively. HRQOL (Median (IQR) was significantly worse in UAA when compared with GAA subjects: RP (24(75) vs 50 (56.3), p=0.01), V (50 (26.25) vs 65.0 (16.3), p=0.00), RE (50(100) vs 75 (66.7), p=0.07), and PCS 35.5 (18.3) vs 40.5 (20.7), p=0.05). Trend towards better SF (62.5 (37.5) vs 50 (21.9), p= 0.06) was observed among UAA vs GAA.

Conclusion: Health related quality of life is significantly worse in UAA as compared to age and gender matched GAA SLE patients. Larger scale studies need to be undertaken to determine the role of genetic vs. social support vs. disease severity on the health-related quality of life in patients with SLE.

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Ancestral Differences in Associations Between Disease Manifestations and Serum IFN-a. Corinna E. Weckerle[1], Beverly S. Franek[1], Jennifer A. Kelly[2], Gail R. Bruner[2], Judith A. James[2], John B. Harley[2] and Timothy B. Niewold[1], [1]U of Chicago, Chicago, IL, [2]Oklahoma Medical Rsrch, Oklahoma City, OK

Purpose: Interferon alpha (IFN-α) is a primary pathogenic factor in systemic lupus erythematosus (SLE), and high IFN-α levels may be associated with particular clinical manifestations. SLE disease manifestations are highly variable between patients, and the prevalence of individual clinical features differs significantly by ancestry. Additionally, different clinical features in SLE may demonstrate significant associations with each other that may also differ by ancestry. We used logistic regression modeling to establish the network of associations between different clinical manifestations in large SLE cohorts of several different ancestries, and examined the correlation between ACR criteria and serum IFN-α to detect cytokine-phenotype associations in each background.

Methods: We analyzed data reporting presence or absence of ACR criteria as well as IFN-α levels from 724 SLE patients from the LFRR registry at OMRF. IFN-α levels were binned as a high vs. low categorical variable using a cut-off value of 2 standard deviations above the mean of healthy controls. The cohort was first stratified by self-reported ancestral background into 224 African-Americans, 105 Hispanic-Americans and 395 European-Americans. Iterative logistic regression was performed in each background using each of the ACR criteria and the IFN-α variable as an outcome variable serially, with the other variables used as predictor variables. Variables from this initial analysis with a p-value below 0.20 were then used in a repeat logistic regression, and results with $p<0.05$ in this analysis were considered significant. Positive and inverse correlations between different clinical variables were represented visually in a network diagram.

Results: Of over 100 million possible associations between ACR criteria in our background stratified populations, we found 39 unique associations, forming network maps of relatively sparse density in each background. Of those, only 11 associations were shared by more than one different ancestral background. Using Fisher's Exact test, we found that this differed significantly from a model in which associations between clinical manifestations were shared by at least 2 of the 3 ancestral backgrounds ($p<10^{-7}$). The network maps of interactions between clinical features were strikingly different in different ancestral backgrounds. IFN-α showed no common associations with clinical features in different ancestral backgrounds. In European-Americans, high IFN-α was linked to malar rash and hematologic manifestations of SLE. In African-Americans, it was linked to immunological manifestations. In Hispanic-Americans it was linked to oral ulcers, photosensitivity, and the absence of arthritis.

Conclusion: We found strikingly different associations between ACR criteria in different ancestral backgrounds, and IFN-α was associated with different clinical manifestations in each background. These data suggest that both the patterns of clinical manifestations and the underlying molecular pathogenesis of SLE differ significantly by ancestry.

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Is Familial SLE Different From Non-Familial SLE?-Data From a Multiethnic US Cohort. Paula I. Burgos[1], Gerald McGwin Jr.[1], John D. Reveille[2], Luis M. Vila[3], Elizabeth Brown[1] and Graciela S. Alarcon[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ Texas Health Sci Ctr, Houston, TX, [3]Univ of PuertoRico Schl of Med, San Juan, PR

Purpose: To characterize the clinical features of familial SLE, and its influence on damage accrual and survival using a longitudinal cohort of SLE patients.

Method: SLE patients studied met ACR criteria, were age ≥16 years with disease duration ≤5years (T0) and were African-American, Hispanic (Texan or Puerto Rican) or Caucasian ethnicity. Familial SLE was defined as those with any first degree relative with SLE. Relative risk was estimated using odds ratios (OR) and corresponding 95% confidence intervals (CI) with logistic regression; relative hazards were calculated using Cox proportional hazards for time-dependent data adjusted for potential confounders.

Results: Of the 644 patients evaluated, 32 had familial SLE (mean age 36.7 [±12.5]) and 612 had non-familial SLE (mean age 36.4 [±12.6]). The majority of familial SLE patients were female (90.6% vs. 89.7%; p= 0.8673); first degree relatives were in decreasing order of frequency siblings, parents and children. In multivariable analyses, familial SLE patients were more likely to have a history of oral ulcers (OR = 1.92, 95% CI 0.65-5.70), mitral valve prolapse (OR = 1.74, 95% CI 0.50-6.10), cerebrovascular disease (OR = 4.18, 95% CI 0.98-17.76), oral contraceptive use (ever/never; OR = 2.51, 95% CI 0.88-7.19) and less likely to have had a history of low platelets ($<150{,}000/mm^3$; OR = 0.31, 95% CI 0.08-1.17) and pulmonary disease activity (OR = 0.39, 95% CI 0.14-1.20), albeit not significantly. Familial lupus was associated with a non-significant shorter time to damage accrual and survival (HR 0.77, 95% CI 0.37-1.59, p = 0.4746 and HR 0.20, 95% CI 0.03-1.47, p = 0.202 , respectively).

Conclusion: Although some differences were observed between familial and non-familial patients, no clear clinical pattern emerged suggesting that familial SLE is associated with a significantly greater disease burden than non-familial SLE.

Table 1. Risk factors associated with Familial lupus

Variable	OR	95% CI	P Value
Age	1.01	0.97 – 1.05	0.5751
Male Gender	0.49	0.12 – 2.01	0.3247
Ethnicity			
Hispanic	0.40	0.08 – 2.16	0.2866
Caucasian	0.64	0.19 – 2.18	0.4703
Puerto Rican	0.56	0.13 – 2.47	0.4454
African American	Reference group		
Disease duration	1.08	0.97 – 1.22	0.1753
Social support score	1.24	0.92 – 1.67	0.1603
SLAM-R* score average	1.07	0.92 – 1.25	0.3871
Oral ulcers	1.92	0.65 – 5.70	0.2403
Mitral valve prolapse	1.74	0.50 – 6.10	0.3849
Cerebrovascular disease	4.18	0.98 – 17.76	0.0526
Oral contraceptive use (ever/never)	2.51	0.88 – 7.19	0.0856
Low platelets (<150,000)	0.31	0.08 – 1.17	0.0833
ESR >25†	0.88	0.29 – 2.70	0.8251
SLAM* pulmonary domain	0.39	0.14 – 1.20	0.0746
HLA-DRB1*1503	1.51	0.44 – 5.19	0.5133

* Systemic Lupus Activity Measure-Revised; † Erythrocyte Sedimentation Rate

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ACR Poster Session A

Quality Measures and Innovations in Practice Management and Delivery of Care

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Predictors of Rheumatology Clinic Visit Times. Molly M. Larson, Lisa A. Davis and Liron Caplan, Univ of CO Denver School of Med, Aurora, CO

Purpose: Studies have examined the amount of time spent in various parts of non-rheumatology patient visits (Med Group Manage J 1995; 42:18) while others have established that waiting time is a major contributor to patient dissatisfaction with their clinic experiences (Ann Rheum Dis 1992; 51:195 and J Ambulatory Care Manage 2003; 26:138). The purpose of our study was to describe the components of patient visits according to the time they require and their contribution to the overall clinic visit time.

Methods: All data were collected as a part of a Performance Improvement Project (PIP) initiated by the Rheumatology Division. Outpatient visits occurred from January until March of 2008. Check-in and check-out times were stamped on preprinted cards by a tamper-resistant machine clock. Interim visit times were recorded in ink by the staff responsible for each component and confirmed by the staff responsible for the subsequent component. We calculated: patient arrival time relative to scheduled appointment time (amount of time patient checks in late), wait times between check-in and rooming/vitals, wait time between checking of vitals and physician arrival, actual physician visit duration, and time interval from completion of provider's duration and completion of phlebotomy. We also recorded whether the patient was seen in a teaching clinic (resident or fellow) or whether the visit was scheduled for an afternoon appointment (binary variables). We used linear regression to determine whether the amount of time for each component and the characteristics of clinics predicted the visit duration, defined as time elapsed between appointment time and recorded check-out time.

Results: Based on a sample of 130 patients, the amount of time the patient was late to his or her appointment, the waiting room time after check-in, and the amount of time spent taking vitals each prolonged the overall visit duration by equivalent amount (e.g. each minute the patient arrived late prolonged the overall time in clinic by one minute). Being seen by a resident or fellow significantly extended the overall duration of the visit (by 20 and 25 minutes, respectively) while afternoon clinic visits lasted over eight minutes longer than morning clinics. The amount of time during phlebotomy did not predict the overall visit duration.

Conclusion: Teaching and afternoon clinics greatly increased total patient visit duration. The clinic staff is not able to "compensate" for patients arriving late (i.e. every minute that patient arrives lengthens the overall visit duration by an equal amount). These factors should be considered when scheduling patient appointments in order to improve timeliness and patient satisfaction in clinic.

Variable	**P value**	**Coefficient** (effect of variable on total patient visit duration, minutes)	**95% Conf. Interval**	
Days since initiation of the PIP	0.667	-.05	-.34	.22
Patient time in waiting room	**<0.001**	1.13	.78	1.47
Duration of vitals	**0.006**	1.13	.71	1.47
Resident (Y/N)	**0.002**	20.67	7.66	33.69
Fellow (Y/N)	**<0.001**	25.00	11.94	38.0
Phlebotomy duration	0.065	.55	-.03	1.14
Afternoon appointment (Y/N)	**0.038**	8.68	.48	16.88
Amount of time patient checks in late to appointment	**<0.001**	.96	.66	1.27

Disclosure: M. M. Larson, None; **L. A. Davis**, None; **L. Caplan**, None.

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Improving Osteoporosis Screening through Patient Activation and Self-Scheduling. Ryan C. Outman, Amy H. Warriner, Kenneth G. Saag and Jeffrey R. Curtis, UAB, Birmingham, AL

Purpose: Current U.S. guidelines recommend bone density screening with central dual energy x-ray absorptiometry (DXA) in all women 65 years or older; testing can be repeated as often as every 2 years. However, based on national data, less than one-third of eligible U.S. women have undergone DXA testing. The main barrier in achieving greater rates of osteoporosis screening has been devising a more effective and generalizable way for healthcare providers and patients to most efficiently schedule and receive DXAs.

Method: We conducted a group randomized, controlled trial involving 39 primary care physicians at the University of Alabama at Birmingham (UAB). Women 65 years or older, cared for by these physicians, with no identifiable DXA scan in the past 4 years were identified (n=2999). Approximately 30 patients per physician were randomized to either an intervention group (sent materials in the mail) or the control group (received no mailing). The intervention prompted physicians to review their patients to determine whether a DXA was medically appropriate; if so, an osteoporosis and fracture-risk brochure and a letter providing patients the opportunity to self-schedule a DXA scan were mailed to the patient.

Results: Of 2999 identified women meeting inclusion criteria, 520 women were randomized into the intervention group and 2479 to the control group. Of the 520 women in the intervention group, 135 (26%) women were determined to be medically inappropriate for DXA by their physicians and did not receive the intervention. Of the remaining 385 women, 114 (29.6%) women in the intervention group scheduled a DXA scan. Of these scheduled DXA scans, 64 (56%) were self-scheduled by the patient and 50 (44%) were scheduled by their physician after being prompted by the intervention. In comparison, 150 (6.4%) women in the control group completed a DXA scan (all physician-scheduled). Compared to control, the intervention increased DXA testing by 23.6% (95% CI 19.1 – 28.4%). Under the assumption that a similar proportion of the control group would be medically inappropriate for DXA testing as the intervention group, the intervention increased the proportion of women receiving a DXA by 21.4%, 95% CI (16.9% to 26.3%).

Conclusion: Scheduling and receipt of DXA testing was improved significantly through the use of a simple mailed osteoporosis brochure and the solicited opportunity for patients to self-schedule their own scans. Mailed materials sent directly to patients, in conjunction with minimizing barriers to self-scheduling of DXAs, may be an effective component of a multi-faceted quality improvement program to increase rates of osteoporosis screening.

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High Risk Osteoporosis Clinic (HiROC) - Closing the Loop in Clinical Osteoporosis Care. Thomas Olenginski[1], Gwynne Maloney-Saxon[1], Judy Reardon[2], Brian Oppermann[3], Stephanie Morris[1], Lindsay J. Ledwich[4] and Eric Newman[1], [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, PA, [3]Geisinger Health System, Danville, PA, [4]Geisinger Medical Center, Danville

Purpose: Ineffective care pathways and process flows continue to hinder osteoporosis care. In an effort to enhance the care of high risk osteoporosis patients across our health system, our rheumatology department created a unique clinical care model – HiROC (High Risk Osteoporosis Clinic).

Method: HiROC utilizes rheumatology physician experts, nurse specialists, electronic tools, and redesigned care processes in an efficient manner to “close the loop” on osteoporotic care. HiROC has both outpatient and inpatient components. Outpatient HiROC is available to primary care physicians and has been operationalized in 9 locations across our health system. Inpatient HiROC involves an auto-consult to the Inpatient HiROC Team on all patients admitted with a low-impact fracture. Patients are logged into a task management database and vitamin D supplementation is initiated. At 4-6 weeks post-fracture, all Inpatient HiROC patients are contacted to re-assess their status. They are then either seen in Outpatient HiROC, or their treating physician is contacted and given a consultative osteoporosis management plan. We report on the first 200 Outpatient HiROC and 100 Inpatient HiROC patients, including baseline demographics, treatment decisions, adherence and financial performance to understand program sustainability.

Results: ***Outpatient HiROC:*** 44.0 % had a previous fragility fracture and 86.5 % were classified as high risk for fracture (Table 1). Vitamin D levels were low in 38 % of patients. 145 patients (80.4% of the high risk group) received treatment. Treatment decisions included IV bisphosphonates (40%), oral bisphosphonates (26%), teraparatide (5%), other agents (1.5%) - 15.5 % of patients refused treatment/remained undecided and 12% did not need treatment. Treatment adherence at 3 months was 98% (94% oral/subcutaneous meds, 100% IV, p=0.051). ***Inpatient HiROC:*** 37 % had previous fragility fractures, yet only 8 % were taking prescription treatment prior to admission. Vitamin D levels were low in 78 %. Admission fracture type included hip (54%), vertebral (14%), pelvic (4%), other (30%). 66 patients reached their 6 week assessment point. The care loop was closed in 92.4% of these patients: 51.5 % transitioning to Outpatient HiROC, 30.3 % returning to their PCP with a consultative osteoporosis care plan, and 10.6 % dying within the 6 weeks of their fracture. ***Financial Performance:*** Inpatient and Outpatient HiROC generated over $110,000 of net revenue for fiscal year 09.

Conclusion: By combining inpatient and outpatient components, well-defined pathways of care, task management, osteoporosis expertise, and electronic tools, our Rheumatology department developed a seamless comprehensive osteoporosis program for our health care system. Provisions were made for inpatients incapable of returning back to the outpatient setting by proactive contact and consultative assistance for their treating provider. HiROC is self-sustainable, and scalable, and may serve as a model for other groups to improve osteoporosis care for the patients they serve.

Table 1. Outpatient and Inpatient HiROC

Outpatient HiROC (n=200) Demographics	
Women	86.6%
Age (mean - years)	67.6 ± 13.4
Risks	
Previous Fracture	44.0%
Chronic Steroids	9.5%
High Risk for Fracture	86.5%
Vitamin D level low	38.0%
Outcomes	
Treatment Started (High Risk Patients)	80.4%
Adherence (at 3 months)	98.0%

Inpatient HiROC (n=100) Demographics	
Women	68.0%
Age (mean - years)	74.1 ± 14.2
Risks	
Previous Fracture	37.0%
Chronic Steroids	9.0%
High Risk for Fracture	78.0%
Vitamin D level low	78.0%
Death	10.6%
Outpatient HiROC Care	51.5%
PCP Care	30.3%

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DXA Testing in Women >65 - Closing the Osteoporosis Quality Care Gap at the Point of Service Using An Electronic Health Record Best Practice Alert. Eric D. Newman[1], Tammy Anderer[2], Fred Bloom[3] and Lester Kirchner[4], [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Geisinger Health System, Danville, PA, [4]Geisinger Center for Health Research, Danville

Purpose: Bone density testing (DXA) in women > 65 is uniformly recommended. Nationally <30% of such women have had a DXA in the preceding several years. Electronic Health Record (EHR) systems can be programmed to notify about the need for DXA testing using 2 types of alerts – Health Maintenance reminders (HM) and Best Practice Alerts (BPA). HM are passive – the clinician is given a visual clue that there is a HM present, but needs to proactively seek and address it during the clinic visit. BPAs are active – upon opening the encounter, the clinician is presented with a pop-up box defining the BPA and a simple order set to fulfill the BPA. We studied the secular trends of DXA ordering in our health care system, followed by the sequential effect of turning on a DXA HM then a DXA BPA to ascertain the differential effect of each type of alert.

Method: Our Rheumatology Department and Primary Care Best Practice Team designed and programmed a DXA HM and a DXA BPA for women > 65 using our EHR (Epic). The DXA HM was turned on March 2007 and the DXA BPA was turned on October 2008. Education to all Primary Care Sites included a "fast facts" summary and live web-based training. The percent of women >65 with a previous DXA was calculated for the year prior to the DXA HM reminder to establish a stable baseline, and compared with the same metric for 18 months after the DXA HM reminder was activated and the 6 months after the DXA BPA was activated (for a total of 3 years observation). A Poisson regression model was used to estimate and compare the quality indicators over time (i.e., HM, BPA). To estimate the effect of the interventions the average post-intervention average was compared to the pre-intervention average. Comparisons between BPA versus HM, and between HM versus pre-HM were performed.

Results: Over the course of three years of observation, the number of eligible women >65 increased from 22,309 to 26,735. The percent of women >65 with a DXA showed a clinically insignificant rise (3%) in the year prior to the DXA HM Reminder, indicating very little background secular trend. After the DXA HM Reminder was turned on, the percent of women over 65 with a DXA rose significantly (Table 1). DXA testing rose 31% (from an average of 40.0% pre-intervention to 52.3% post-intervention) for all women >65, as indicated by the intervention effect of 1.31. Each age subgroup also rose significantly – Women 65-74 by 24%, women 75-84 by 29%, and women >84 by 43%. After the DXA BPA reminder, additional significant improvements were noted – 12% for women 65-74, 15% for women 75-84, and 25% for women > 85 – 14% improvement for all women > 65. These improvements were all significant comparing the DXA BPA to the DXA HM Reminder (P<0.0001).

Conclusion: DXA testing in women over 65 is a nationally accepted osteoporosis quality indicator, and usual point-of-care methods are ineffective in improving this measure. However, EHR-based DXA Reminders were highly effective in improving the percent of over 26,000 women > 65 in receiving a DXA. Finally, a BPA (active alert) is additive in effect to a HM (passive alert).

Table 1: Average Pre-HM, HM and BPA DXA Quality Indicator

	Pre-HM	HM	BPA	HM vs. Pre-HM	BPA vs. HM	P-value
Female 65-74	44.70%	67.40%	64.00%	1.28 (1.26, 1.31)	1.12 (1.10, 1.14)	<0.0001
Female 75-84	39.10%	62.80%	60.60%	1.36 (1.32, 1.38)	1.16 (1.12, 1.17)	<0.0001
Female > 85	21.60%	32.60%	40.60%	1.61 (1.44, 1.69)	1.26 (1.19, 1.30)	<0.0001
All	40.00%	62.30%	69.60%	1.31 (1.29, 1.32)	1.14 (1.12, 1.16)	<0.0001

Disclosure: E. D. Newman, None; **T. Anderer**, None; **F. Bloom**, None; **L. Kirchner**, None.

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Assessing Care Using New Quality Indicators for Osteoporosis and Cardiovascular Disease Management in SLE. Kristina Demas[1], Brendan T. Keenan[2], Daniel H. Solomon[3], J. Yazdany[4] and K. H. Costenbader[3], [1]George Washington University School of Medicine, Washington, DC, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham & Women's Hospital, Boston, MA, [4]UCSF, SF, CA

Purpose: Quality indicators (QIs) for assessment of health care quality in SLE have been proposed (**Table 1**). We aimed to assess quality of care for osteoporosis (OP) and cardiovascular disease (CVD) among SLE patients at our institution.

Method: We randomly identified 200 patients meeting ACR Criteria for SLE Classification, with ≥ 2 visits to our academic rheumatology practice in 2007-8. We performed a structured electronic medical record review of rheumatologists' notes, medical history, medications, laboratories and bone mineral density (BMD) results. We assessed adherence with proposed SLE QIs for OP and CVD.

Results: 94% of patients were female; 64% were white, mean age was 46.3 years (SD 14.1), mean SLE duration was 15.3 years (SD 11.1). 29% received ≥ 7.5 mg prednisone/day for ≥ 3 months during the year. 57% had received indicated BMD, 62% indicated calcium + vitamin D, and 86% indicated anti-resorptive/anabolic agents. 26% had ≥ 4 and 60% had ≥ 3 CVD risk factors documented in the year. Only 3%, all current smokers, had smoking status documented. Having a primary care physician within our healthcare network was a significant predictor of documented QI adherence (p=0.03 for indicated BMD and p <0.01 for CVD risk factor documentation).

Conclusion: Documented compliance with newly proposed QIs for OP and CVD in SLE was sub-optimal in our center. We found opportunities for improvement in academic rheumatologists' care, and for revisions of proposed QIs to capture the most meaningful clinical data.

Table 1. SLE Quality Indicators (Yazdany et al, A&R 2009; 61:370)
I. Osteoporosis
A. IF SLE patient has received prednisone ≥7.5 mg/d for ≥3 mo, THEN patient should have BMD testing recorded in medical record*, unless patient is c receiving anti-resorptive** or anabolic therapy†.
B. IF SLE patient with SLE has received prednisone ≥7.5 mg/d for ≥3 mo, THEN should receive calcium + vitamin D.
C. IF SLE patient has received prednisone ≥7.5 mg/d for ≥1 mo, and has t-score ≤-2.5 or fragility fracture, THEN should receive anti-resorptive/anabolic agent.
II. CVD
For all SLE patients, CVD risk factors (smoking, blood pressure, BMI, diabetes,slipids) should be documented annually.

Disclosure: K. Demas, None; **B. T. Keenan**, None; **D. H. Solomon**, Amgen and Abbott, 2 ; **J. Yazdany**, None; **K. H. Costenbader**, None.

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Adherence with Screening Guidelines for Hepatitis B and C Testing Among U.S. Veterans with Rheumatoid Arthritis (RA). Scott A. Stoerner[1], Ted R. Mikuls[2], Andreas M. Reimold[3] and Grant W. Cannon[4], [1]VAMC and University of utah, Salt Lake City, UT, [2]VAMC and University of Nebraska, Omaha, NE, [3]VAMC and University of Texas Southwestern, Dallas, TX, [4]VAMC and University of Utah, Salt Lake City, UT

Purpose: The Centers for Disease Control and Prevention (CDC) recommend screening for all hepatitis B markers prior to immunosuppressive therapy for rheumatologic disorders. Hepatitis B and C screening is recommended by the American College of Rheumatology (ACR) prior to starting methotrexate or leflunomide in patients with defined risk factors for hepatitis. There have been reports of reactivated hepatitis B with immunosuppression. The purpose of this study was to determine adherence with these screening guidelines in U.S. Veterans with RA and determine the indication for hepatitis testing when undertaken.

Methods: Study subjects included participants in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry from the Dallas, Salt Lake City, and Omaha active collection sites(n=305). The Computerized Patient Record System (CPRS) was used to obtain hepatitis risk factors, ALT/AST values, rheumatologic medications, and hepatitis serologies. When hepatitis serologies were obtained, clinic notes from multiple physicians were reviewed to determine the clinical indication behind this testing. These indications were then classified into the following categories: screening in adherence with the ACR and CDC guidelines, elevated ALT/AST of unknown etiology, and unknown. Hepatitis C had an additional category for those serologies obtained to help diagnose hepatitis C associated arthritis.

Results: Sixty-five (21.3%) patients were tested for a hepatitis B serology. The indications for hepatitis B testing were 35 (53.8%) for screening, 16 (24.6%) for elevated ALT/AST of unknown etiology, and 14 (21.5%) unknown. Hepatitis C testing was done in 136 (44.6%) of patients. The indications for hepatitis C testing included 53 (39.0%) for screening, 19 (14.0%) for elevated ALT/AST of unknown etiology, 53 (39.0%) for diagnosis of hepatitis C arthritis, and 11 (8.1%) for other. The presence and/or absence of risk factors for hepatitis B and/or C infection could not be consistently identified in the current chart review. One hundred and ten (36.1%) patients received biologic therapy, while 267 (87.5%) patients received either methotrexate or leflunomide. One (0.3%) patient tested positive for hepatitis B and 11 (3.6%) patients tested positive for hepatitis C.

Conclusion: Adherence with CDC screening guidelines for hepatitis B in this population was low. Our review could not ascertain the presence of hepatitis B and/or C risk factors to sufficiently determine if ACR guidelines were being followed. The higher rate of testing for hepatitis C in comparison to hepatitis B appeared to the result of increased diagnostic testing for hepatitis C associated arthritis. Hepatitis B was noted to be rare among this population. These results support the need for greater evaluation of these guidelines in clinical practice to determine their best application and impact.

Disclosure: S. A. Stoerner, None; **T. R. Mikuls**, None; **A. M. Reimold**, None; **G. W. Cannon**, None.

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Does My Rheumatologist Know My Pregnancy Risk? Rochelle R. Clementine[1], Bobby J. Dupre[2], Justin S. Lyman[1], William E. Davis[3], Eve Scopelitis[4], Leonard Serebro[4], Tamika Webb-Detiege[1], Jerald M. Zakem[3] and Robert J. Quinet[5], [1]New Orleans, LA, [2]Ochsner Health System, Baton Rouge, LA, [3]Ochsner Clinic, New Orleans, LA, [4]Ochsner Clinic Foundation, New Orleans, LA, [5]Ochsner Med Ctr-New Orleans, New Orleans, LA

Purpose: Many rheumatic diseases occur in women of childbearing age. Most of these diseases require therapy with potentially teratogenic drugs. The objective of the study is to assess the frequency of contraceptive counseling rates among six rheumatology staff physicians during routine clinic visits at Ochsner Department of Rheumatology, a large group practice in New Orleans, LA.

Methods: Retrospective review of ninety charts in women aged 16-40. Diagnoses included systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, scleroderma, antiphospholipid antibody syndrome, fibromyalgia and steroid induced osteoporosis. Routine clinic visits were reviewed during October 2006 through January 2009. The rates of contraceptive counseling, the medications prescribed with respective FDA pregnancy categories and the number of patients prescribed each medication were reviewed and recorded.

Results: Approximately forty different medications were prescribed to the ninety patients reviewed. Four of these medications are classified as FDA pregnancy category X, which has been shown to *cause* fetal abnormalities in either animal or human studies. Six of these medications are classified as FDA pregnancy category D, in which there is positive evidence of human fetal risk. The contraceptive counseling rates in our department ranged from 17-78% among staff physicians. Of the ninety charts reviewed, six of these patients conceived while taking potentially teratogenic medications during this the frame. Of these six patients, two were not counseled on contraception prior to conceiving.

Conclusion: Previous studies have reported that women of childbearing age are frequently not counseled on potentially teratogenic medications. In our department, prescriptions for potentially teratogenic medications were frequently given to women of childbearing age without documentation of contraceptive counseling. It is important to discuss the teratogenic risks of these medications with patients. Each of the six staff physicians reviewed their respective contraceptive counseling rate. Ochsner Department of Rheumatology, in conjuction with Ochsner Quality Assurance department, is in the process of implementing an alert mechanism into the electronic medical record of women of child bearing age in an attempt to prompt physicians to address contraceptive counseling. Further review of contraceptive counseling rates will be obtained pending implementation of the alert system into the electronic medical record.

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From Recommendations to Clinical Practice: Experience Applying the 2008 ACR RA Recommendations for the Use of Biologic DMARDs to An Urban, County Hospital Cohort. J. Barton[1], Vladimir Chernitskiy[2], Jonathan Graf[1], John Imboden[1], E.H. Yelin[3] and J. Yazdany[3], [1]UCSF, San Francisco, CA, [2]University of California, San Francisco, CA, [3]UCSF, SF, CA

Purpose: In 2008, the ACR developed a clinical algorithm for the use of biological DMARDs in RA. The recommendations provide a framework for clinicians to make treatment decisions. This study examined the feasibility of applying the algorithms to a multiethnic cohort of adults with RA at an urban, county hospital clinic.

Method: We performed a retrospective medical record review from October 2006 to March 2009. Subjects are enrolled in the UCSF RA cohort, a population of adults ≥ 18 years, with confirmed RA who were seen at least twice over a one-year period and were not on a biologic at the time of data extraction. We extracted patient characteristics (age, gender, ethnicity, country of origin) and variables required to follow the algorithms, including: disease duration, prognostic factors (rheumatoid factor or CCP, erosions), assessment of disease activity, and contraindications to treatment.

Results: Among 125 subjects, mean age was 53 ± 13 years, 88% were female, 83% were RF positive, 78% were CCP positive, and 62% had radiographic erosions. Fifty-three subjects were Latino (42%), 51 Asian (41%), 12 African American (10%), 8 White or Other (7%), and 98 (78%) were non-U.S. born. At the time of assessment, 116 (94%) were on a non-biologic DMARD. Of the 125 subjects, 43 (34%) did not meet eligibility criteria for a biologic DMARD due to low disease activity; 41 (33%) met criteria, but were not eligible due to the following: 1) infectious diseases (latent TB, n=33; acute bacterial infection or infection currently on antibiotics, n=4); 2) pregnancy or breastfeeding (n=2); and 3) other (compliance/patient safety, n=2). The remaining 41 (33%) met criteria without contraindication; 21 were prescribed a biologic. Of the eligible subjects, only 11 of 41 were on a biologic at the next visit.

Conclusion: Although applying the 2008 ACR recommendations was technically feasible in our cohort, 33% of subjects were ineligible for the clinical algorithms. In most cases, infectious disease (most commonly latent tuberculosis) rendered a subject ineligible. Clinical practice followed the ACR recommendations in half of the cases; however, only 11 of 41 eligible subjects were on a biologic at follow-up. Understanding such gaps between recommendations and practice will inform the design of future clinical trials that address barriers to care in vulnerable populations.

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Monitoring Adherence to Hydroxychloroquine (HCQ) in Childhood-Onset Systemic Lupus Erythematosus (cSLE) and Possible Impact of Successful Self-Management in Improving Medication Adherence. Deepa P. Kudalkar[1], Tracy V. Ting[2], Shannen Nelson[2], Jennifer L. Huggins[2], Avis E. Ware[1], Jamie Eaton[2], Jennifer Rammel[2], Shweta Srivastava[2], Dennis Drotar[2] and Hermine Brunner[2], [1]University of Cincinnati, Cincinnati, OH, [2]Cincinnati Children's Hosp, Cincinnati, OH

Purpose: Prior research suggests that almost half of the cSLE patients do not take their medications as prescribed. Diagnosis and management of sub-optimal adherence is an unsolved problem.HCQ remains the cornerstone drug for cSLE. A commercial bioassay is available to measure blood levels. Successful self-management, as measured by Patient Activation Measure (PAM), relies upon patient ability to play an active role in self-care, which has a positive impact on health outcomes in chronic disease models. Objectives: 1)To assess the value of blood HCQ levels as an objective measure of medication (HCQ) adherence in cSLE; and 2) To determine the relationship between medication(HCQ) adherence and successful self-management as measured by the PAM.

Methods: Adolescents & young adults with cSLE (15-25 yrs) taking HCQ for ≥ 6 months were identified. Medication adherence (0 – 100%) was measured using self-report (Medication Adherence Self-Reported Inventory [MASRI]), pharmacy refill data, and whole blood HCQ levels assayed by HPLC method (lowest detectable level 100mcg/L). HCQ levels < 130mcg/L were considered to reflect non-adherence when taking HCQ at 400mg/day. Non-adherence was defined by MASRI <90% or pharmacy refill <80%, as previously suggested. The PAM questionnaire was also completed.

Results: Among the 39 subjects (93% Female, 67% African American), the HCQ dose ranged from 100-400mg/day. Using the MASRI, 50% of the subjects were non-adherent, while pharmacy refill data suggested non-adherence among 61%. There were 12/39 (30%) subjects with undetectable HCQ levels. HCQ levels reached the suggested target of 1,000 mcg/L in only 8/39 (20%) of the subjects. HCQ levels correlated moderately with adherence by self-report (r=0.45, p=0.006) and pharmacy data (r=0.39, p=0.02). Based on HCQ levels, patients taking 400 mg/day dose were more likely to be non-adherent to HCQ compared to those taking 200 mg/day, which was not affected by frequency of dosing. There was a statistically significant correlation between PAM and both self-reported adherence (r = 0.38; p=0.02) and pharmacy refill adherence (r=0.43; p=0.01).

Conclusion: Whole blood HCQ levels may be used in conjunction with other measures of medication adherence. Ongoing research to assess individual trends in HCQ levels over time may help to more accurately identify patients with poor or non-adherence. Also, patients who are better in self-managing their SLE appear to have higher adherence. Improvement of self- management skills may help improve medication adherence.

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Pneumovax Vaccination Among Rheumatology Outpatients On Immunosuppressive Medications: The Development of a Quality Indicator. Sonali P. Desai[1], Alexander Turchin[1], Lara E. Szent-Gyorgyi[1], Michael E. Weinblatt[2], Jonathan S. Coblyn[2], Daniel H. Solomon[1] and Allen Kachalia[1], [1]Brigham & Women's Hospital, Boston, MA, [2]Brigham & Women's Hosp, Boston, MA

Purpose: Providing Pneumovax to immunocompromised patients is recommended by the Centers for Disease Control (CDC), but prior data suggest that rates of vaccination are not optimal. For rheumatology outpatients on immunosuppressive medications (IM), we sought to: 1) develop a quality indicator (QI), 2) measure the proportion of patients up-to-date with Pneumovax prior to starting IM in the past 12 months and the proportion for patients on IM and 3) examine whether years in practice of the rheumatologist influenced performance for this QI.

Methods: Data were aggregated from administrative (billing code data) and clinical (electronic health record [EHR]) sources. We assessed the proportion of patients on IM in our rheumatology practice over a 24-month period (1/1/07 to 1/1/09). We included only patients who had at least 2 visits to the rheumatology clinic within the 24-months and were prescribed an IM by a rheumatologist. Up-to-date with Pneumovax was defined according to CDC guidelines. Two QIs were calculated: 1) up-to-date with Pneumovax prior to starting an IM and 2) up-to-date with Pneumovax while on an IM. Random manual review of patient records confirmed that our methodology accurately captured rheumatology patients on IM who had received Pneumovax and excluded patients not on IM.

Results: We identified 2,471 patients on IM with 634 newly started in the past 12 months. The mean age was 57 and 76% female. The most frequent disease was RA (54%). Corticosteroids (41%) and MTX (32%) were the most common IMs prescribed. 45% on IM were up-to-date with Pneumovax. Among new initiators of IM, 27% (176/634) were up-to-date prior to starting the IM. Provider-level data demonstrated variability between individual rheumatologists and based on years in practice (**Table 1**). Patients treated by rheumatologists in practice for ≤ 10 years were more likely to have received Pneumovax.

Conclusion: Less than half of all patients on IMs were up-to-date with Pneumovax, similar to prior reports. Differences in rates based on years in practice were observed.Future studies will focus on interventions to improve Pneumovax administration prior to initiating IMs.

Table 1. Pnemovax Quality Indicator performance based on years in practice of rheumatologist

	Practicing ≤ 10 years (N)	**Practicing > 10 years** (N)	**p value**
Ongoing immunosuppressive medication	60 ± 9 % (76/127)	44 ± 2 % (1026/2313)	p = 0.0006
Newly initiated immunosuppressive medication	40 ± 14 % (19/48)	27 ± 4 % (157/586)	p = 0.057

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Erythrocyte Sedimentation Rate (ESR) Is the Least Likely of Core Data Set Measures to Identify An "Abnormal State" in New Patients with RA to Monitor Therapeutic Responses, According to 3 Definitions of "Abnormal State". Theodore Pincus[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: A single "gold standard" measure, such as blood pressure or cholesterol, is not available in rheumatoid arthritis (RA) to assess and monitor each individual patient. Therefore, a Core Data Set of 7 RA measures was developed: 3 from a health professional, swollen joint count (SJC), tender joint count (TJC) and physician/assessor global estimate of status (MDGL); 3 from a patient, physical function (FN), pain (PN) and patient global estimate (PTGL), on a health assessment questionnaire (HAQ) or derivative such as a multidimensional HAQ (MDHAQ); and 1 laboratory test, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Indices of 3-4 of these measures are widely used in clinical research, but not in usual care, in which a laboratory test such as ESR often is the only quantitative measure. We analyzed the capacity of 6 of the Core Data measures to depict an "abnormal state" to monitor 487 new patients with RA seen at a weekly academic rheumatology clinic from 1980-2005.

Method: All patients seen from 1980-2005 completed a patient questionnaire that evolved from a HAQ to a multidimensional HAQ (MDHAQ). The MDHAQ included FN and PN since 1980, and PTGL since 1996. SJC and TJC were assessed in on consecutive patients in certain periods, without selection for severity, but MDGL not until 2005. The proportion of patients in an "abnormal state" was analyzed for 6 of the 7 Core Data Set measures by 3 definitions, "least stringent," "moderately stringent" and "most stringent." Cutpoints for the 3 definitions were >0, >1 and >2 for SJC28 (0-28), TJC28 (0-28), PN (0-10) and PTGL (0-10); for MDHAQ-FN (0-3), >0, >0.25 and >0.5; for ESR, >10 for males/>20 for females, >20 for males/>30 for females, and >28 (commonly used for inclusion in clinical trials). DAS28, RAPID3 (routine assessment of patient index data, composed of only FN, PN and PTGL) and RAPID3-EST (does not include PTGL in patients seen prior to 1996; correlated with RAPID3 at levels rho□0.9), were also analyzed in 3 categories: for DAS28 (0-28), >2.6, □3.2 and >3.2; for RAPID3 and RAPID3-EST (0-30), >0, >3 and >6. The proportion of patients in an "abnormal state" by 3 definitions was analyzed using descriptive statistics.

Results: All measures other than ESR (abnormal in 71%) indicated an abnormal state in >88% of patients, according to the least stringent definition. For the moderately stringent definition, all measures other than ESR (abnormal in 54%) were abnormal in >82% of patients. For the most stringent definition, all measures were abnormal in >79%, other than ESR in 53% and MDHAQ-FN in 67%.

Table. Normal / Abnormal Measurements at First Visit of 487 Rheumatoid Arthritis Patients

Measure	Range	Definition #1	% Abnormal	Definition #2	% Abnormal	Definition #3	% Abnormal
SJC28	0-28	>0	92.3%	>1	86.5%	>2	83.6%
TJC28	0-28	>0	87.6%	>1	84.8%	>2	79.0%
ESR	0-150	Male >10 Female >20	71.3%	Male >20 Female >30	54.4%	>28	52.6%
MDHAQ-FN	0-3	>0	92.8%	>0.25	83.3%	>0.50	66.9%
Pain	0-10	>0	98.4%	>1	92.1%	>2	84.9%
PTGL	0-10	>0	98.6%	>1	91.8%	>2	85.0%
DAS28	0-10	>2.6	92.3%	≥3.2	82.0%	>3.2	82.0%
RAPID3-EST	0-30	>0	99.5%	>3	93.4%	>6	84.5%

Conclusion: Any of 3 definitions identified most new RA patients as in an abnormal state. ESR stood out as considerably less likely to be abnormal than any other Core Data Set measure. Although monitoring of ESR is effective in some RA patients, quantitative measures other than ESR should be collected in clinical care of most patients, to monitor and document responses to therapy of patients with RA.

Disclosure: T. Pincus, None; **C. J. Swearingen**, None.

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Disease Activity Differences in Patients On DMARD Therapy: Use of the Rheumatology Health Tracker (RHT) An Electronic Data Capture System to Measure Patient Outcomes. Sita A. Narayanan[1], Todd Hofeling[2], Jeffrey R. Lisse[3], Berchman A. Vaz[1], Oscar Furet[3], Alexis A. Alvarez[3], Kari Koerner[3] and Catherine Lo[3], [1]Univ of Arizona, Tucson, AZ, [2]Tucson, AZ, [3]University of Arizona, Tucson, AZ

Purpose: Measurement of disease activity and its response to disease modifying antirheumatic drug (DMARD) therapy is an important component of the decision making process in patients with rheumatoid arthritis. There is however, controversy concerning what measures to use, how to measure them, and the amount of time and effort this entails. Comparisons of the DAS and HAQ scores between drugs may reflect channeling bias due to practitioner preferences, but can be important in detecting outcomes.

Methods: Patients with rheumatoid arthritis were invited to participate in an observational study using a web based electronic capture system. After informed consent, at each visit they were asked to record the following outcome parameters: Involved Joint Count (IJC), Short Form 12 (SF-12), Health Assessment Questionnaire (HAQ), and Visual Analog Scale of their overall disease activity (VAS), demographic information, and information on health care utilization. Practitioners then filled out a Tender Joint Count (TJC), Swollen Joint Count (SJC), and a visual analog scale. Information was also recorded concerning adverse events and medications.

Results: There were 100 patients enrolled in the study who were on biologic DMARDs. Overall HAQ was 0.839, DAS was 4.485, SJC was 5.062, TJC was 6.662, SF-12 was 35.302, and VAS was 24.175. Initial visit HAQ scores for the different biologics was 0.548 for etanercept (n=28), 0.805 for infliximab (n=28), 0.658 for adalimumab (n=29), 0.99 for rituximab (n=9), and 1.1 for abatacept (n=6). The change in HAQ score between the baseline and the first follow up visit was +0.007 for etanercept (over avg 57 days), +0.113 for infliximab (over avg 65 days), -0.017 for adalimumab (over avg 18 days), and +0.08 for abatacept (over avg 18 days). The change in DAS between the initial visit and the first follow up visit was 0.007 for etanercept (over avg 57 days) and 0.035 for infliximab (over avg 65 days).

Conclusion: The Rheumatology Health Tracker (RHT) tracks the outcome in patients with rheumatoid arthritis on different DMARDs. Differences in outcome parameters over time may reflect the use of different biologics in our practice. To date, patients receiving each biologic displayed mostly similar efficacy without a significant change in the DAS or HAQ scores. Use of the RHT is easy, web-based, and takes little practitioner time. In the new era of electronic medical records, it can be an accessible, reproducible source for multiple practitioners to assess their patients over time.

Disclosure: S. A. Narayanan, Centocor, Inc., 2 ; **T. Hofeling**, Centocor, Inc., 2 ; **J. R. Lisse**, Pfizer Inc, 9, Genentech and Biogen IDEC Inc., 9, Bristol-Myers Squibb, 9 ; **B. A. Vaz**, Centocor, Inc., 9, Biogen Idec, 9 ; **O. Furet**, None; **A. A. Alvarez**, None; **K. Koerner**, None; **C. Lo**, None.

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Perceived Barriers to Determine Disease Activity in RA Patients in Daily Clinical Practice: a Qualitative Study. Laura T.C. van Hulst, Jaap Fransen, Nicolien L. Beld, Piet L.C.M. van Riel, Richard Grol and Marlies E.J.L. Hulscher, UMC St Radboud, Nijmegen, Netherlands

Purpose: Several tight control studies and guidelines for the management for RA, recommend that RA patients' disease activity should be assessed with a valid composite score, such as the DAS28. However from surveys and medical record examinations, it is known that a disease activity assessment is infrequently performed in daily clinical practice. The objective of this study was to determine which barriers are perceived for disease activity assessment in daily clinical practice.

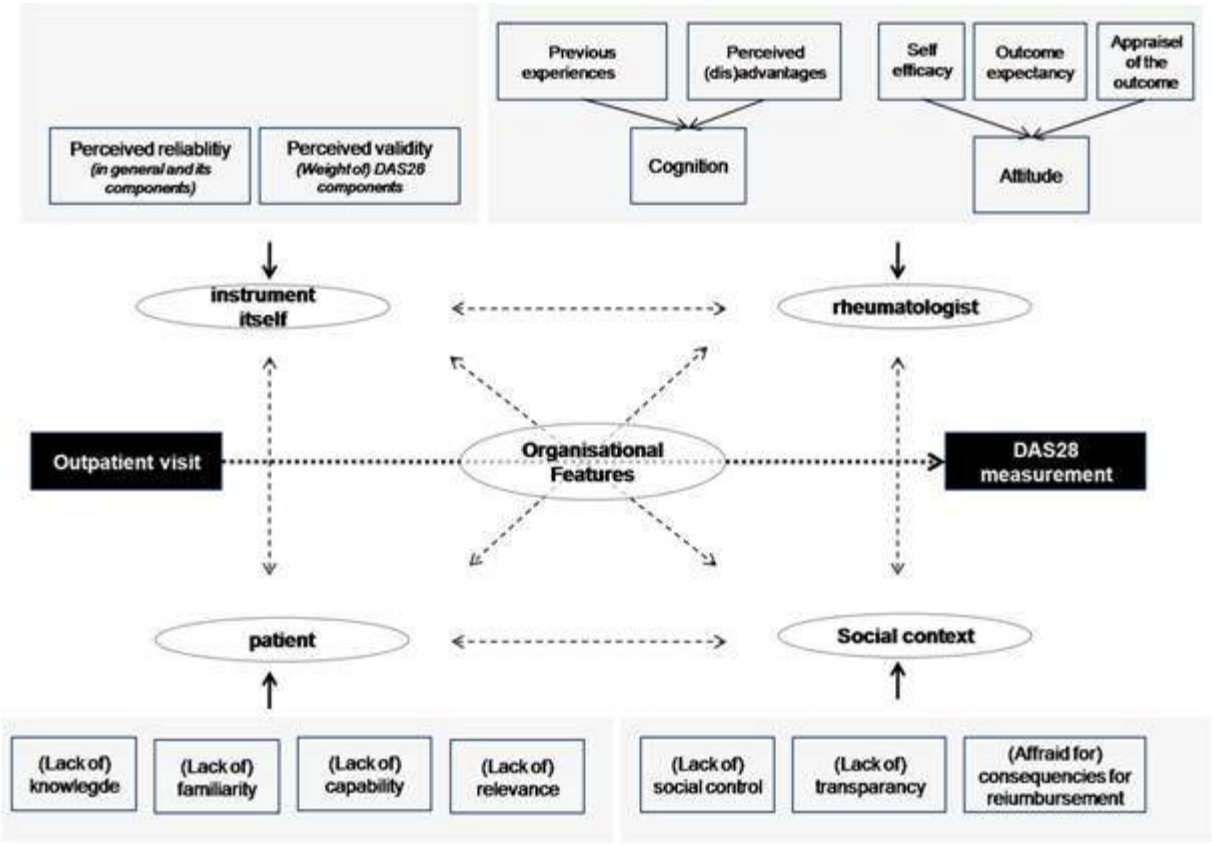
Method: A qualitative study was performed with 15 Dutch rheumatologists who were users or non-users of the DAS28, invited based on survey data. Semi-structured interviews were performed, recorded, transcribed verbatim and analyzed with Atlas.ti 6.0.11. according to Grounded Theory. Citations were coded independently by two researchers (LvH and NB) and the final codes were formulated on the basis of consensus. Ultimately, codes were categorized in domains and levels if they discussed similar concepts.

Results: A wide number of perceived barriers to assess the DAS28 in daily clinical practice were identified, covering five domains: the instrument itself, rheumatologist related, patient related, organization features and the social context (see Figure 1.) For example, rheumatologists doubted the reliability and validity of the DAS28 (instrument itself), did not think that DAS28 assessments would lead to another outcome compared with their current given care (rheumatologist related), mentioned that blood markers were not available on time (organization), they were afraid for reimbursement consequences (social context) and felt that patients were not sufficiently familiar with disease activity measures such as the DAS28 (patient related). The complete list of barriers discussed in the interviews is illustrated in Figure 1.

Conclusion: Rheumatologists perceived many barriers, covering 5 domains, for disease activity assessment in daily clinical practice. The organizational barriers usually receive most attention, but several other barriers are experienced as well. Future efforts to improve the use of

disease activity assessment in daily practice should also take into account barriers on the other domains: the rheumatologist, the patient, the social context and the perceived validity and reliability of the assessment itself.

Figure 1. Overview of perceived barriers with respect to DAS28 assessment in daily clinical practice.



Disclosure: L. T. C. van Hulst, None; **J. Fransen**, None; **N. L. Beld**, None; **P. L. C. M. van Riel**, None; **R. Grol**, None; **M. E. J. L. Hulscher**, None.

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Construct Validity, Feasibility and Acceptability of EQ-5D to Assess Physical and Mental Quality of Life in Systemic Sclerosis Patients. Roberta Gualtierotti[1], Luciana Scalone[2], Francesca Ingegnoli[1], Silvana Zeni[1], Paolo Cortesi[2] and Flavio Fantini[1], [1]Istituto Gaetano Pini, University of Milano, Italy, Milano, Italy, [2]Center for Health Technology Assessment and Outcomes Research, University of Milan, Milano, Italy

Purpose: Systemic sclerosis (SSc) is a systemic chronic inflammatory disease and a progressive disabling condition. It compromises ability to perform basic activities. Patients' emotional sphere is also compromised, with anxiety reported as one major aspect negatively affected. EQ-5D, a simple and quickly self-completable tool for quality of life (QoL) assessment, whose reliability and validity have never been tested in SSc, may be useful in evaluating physical and mental state of these patients.

Method: Thirty-five patients aged 27-88 years (median=61), 85.7% female, monthly administered with prostacyclin treatment, were given EQ-5D and Health Assessment Questionnaire (HAQ) for self-completion before the treatment. Acceptability and feasibility were estimated

on the basis of patients' comments/complains on the tool and missing data respectively. The construct validity was tested by computing the Spearman's coerrelation coefficient between response of EQ-5D and HAQ.

Results: Acceptability of EQ-5D was good. With the HAQ, 31.4% of the patients reported difficulties to walk, 42.9% difficulties to arise, 48.6% difficulties to dress, 41.2% difficulties to wash, 57.1% difficulties to eat, 64.7% had difficulties to reach objects, 41.2% difficulties to grip things, 58.8% difficulties to do other common activities. With the EQ-5D, 45.7% had some difficulties to walk, 28.6% some and 5.7% severe difficulties with self-care, 45.7% had some and 8.6% severe difficulties to perform usual activities, 74.3% perceived some and 11.4% severe pain/discomfort, 54.3% were moderately and 2.9% extremely anxious or depressed. Mean VAS was 66.7 (30-90). Correlation coefficients between domains considered conceptually similar were: EQ-5D-mobility with HAQ-walking r=0.614; EQ-5D-self-care with HAQ-dressing r=0.715 and with HAQ-eating r=0.662, with hygiene r=0.443; EQ-5D-usual activities with HAQ-eating r=0.584, with HAQ-reach r=0.544, with HAQ-grip r=0.510 with other common activities r=0.495. The highest correlation of pain/discomfort and anxiety/depression was found with hygiene (0.552 and 0.436, respectively). Correlation coefficient between EQ-5D-VAS and HAQ total disability score was -0.597 ($p<0.001$).

Conclusion: EQ-5D was suitable for self-completion and well accepted in SSc patients; its construct validity was acceptable to good regarding mobility, self-care, usual activities. EQ-5D, differently from HAQ, also includes a mental/psychic domain. Furthermore, compared with other QoL tools such as SF-36, it can be fulfilled quickly and its score can be simply interpreted. Our results suggest that EQ-5D could be included in clinical practice to routinely assess SSc patients' QoL.

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Workforce Planning in Paediatric Rheumatology in the United Kingdom (UK). C.E Pain[1], M.J Harrison[2], H.E Foster[3], D.P.M Symmons[2] and E.M Baildam[1], [1]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [2]arc Epidemiology Unit, University of Manchester, United Kingdom, [3]University of Newcastle, United Kingdom

Purpose: The British Society for Paediatric and Adolescent Rheumatology (BSPAR) recommends that all children with rheumatic disease are managed by specialist multidisciplinary teams with appropriate training in paediatric rheumatology (PRh). In the UK and many other parts of the world, adult rheumatologists have historically provided clinical care for children with rheumatic disease and increasingly there has changes been development of multidisciplinary PRh services working in clinical networks with adult rheumatologists or paediatricians. Recent in clinical training in the UK have resulted in PRh becoming a paediatric sub-speciality. Adult rheumatology trainees are no longer being trained in PRh and will be ill-equipped to manage children when incumbent adult rheumatology specialists retire.

Methods: In 2007 a questionnaire was sent to all UK adult rheumatology specialists. One aim was to identify the number of adult rheumatologists seeing children under 16 years, describe the clinical setting for consultations and to estimate numbers due to retire based on a retirement age of 65 years. This information will be used to determine future numbers of PRh consultants.

Results: The questionnaire was sent to 584 adult rheumatology specialists with 403 (69%) responding to questions about PRh service provision. 75/403 (19%) reported seeing patients aged under 16. The median (IQR) number of patients seen per month was 10 (6, 15), accounting for 931 paediatric patients seen in a year. Many rheumatologists will retire in the next 5 and 10 years (13/73 (18%) and 35/73 (48%) respectively). The majority (58/75, 78%) of respondents hold separate clinics for all paediatric patients, often alongside another health care professional (38/58 (57%) consultant paediatrician, 5/58 (9%) PRh specialist, 5/58 (9%) with both present and 7/58 (12%) with another healthcare professional). 3/58 (5%) of adult rheumatologists ran paediatric clinics without another healthcare professional present and 4/75 (5%) of all specialists seeing children did so on their own without paediatric input.

Conclusion: Throughout the UK many adult rheumatologists are involved in managing children with rheumatic disease, and this is similar to that reported in other health care systems. Compared to the US, most adult rheumatologists in the UK see children within a shared care model with paediatric rheumatologists or paediatricians [1]. Over the next 10 years a large number of adult rheumatologists who manage children with rheumatic disease will retire. Their departure will result in a large shortfall in service provision. Unless addressed urgently in workforce planning and training within PRh, along with appropriate expansion of clinical services, these changes will results in marked inequity of access to specialist care for children with rheumatic disease.

[1] Mayer ML et al. Role of Pediatric and Internist Rheumatologists in Treating Children With Rheumatic Diseases. Peds. 2004 March 1, 2004; 113(3):e173-81.

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The Canadian Arthritis Referral Study (CARS): An Initial Evaluation of the Canadian Arthritis Referral Tool (CART). Andrew Thompson[1], Sara Graydon[2] and Elaine Zibrowski[2], [1]St Joseph's Hlth Ctr, London, ON, [2]St Joseph Hosp/Monsignor Roney, London, ON

Purpose: The importance of triage strategies for rheumatologic referrals is highlighted by the now well-accepted concept that rheumatoid arthritis (RA), in its early stages, is a relative emergency and early intervention may significantly improve outcomes. Given the burden of musculoskeletal disease, as well as the increasing wait times for rheumatologist consultation, various practice management and referral triage strategies have been developed. Success of all triage strategies requires accurate transfer of clinical information between the primary care giver and rheumatologist. We describe the initial evaluation of a prototype single page rheumatology referral form, the Canadian Arthritis Referral Tool (CART), and those factors that improve the ability to accurately triage rheumatology referrals as urgent vs non-urgent.

Method: From September 1, 2007 to August 31, 2008 six rheumatologists at a single academic centre prospectively collected referrals on the CART. All data from the CART was coded and entered into a database. Referrals were prospectively graded on a 4-point scale4 by a single rheumatologist as emergency (1), urgent (2), semi-urgent (3), or elective (4). After the initial rheumatologic consultation a post-hoc grade was assigned to each case based on the clinical information gathered. A binary logistic regression model exploring 17 co-variates was developed using the dependent dichotomous outcome of urgent vs non-urgent at the time of consultation. Agreement between referral and consultation grades was also assessed.

Results: From September 1, 2007 to August 31, 2008, 952 referrals were received on the CART tool. From September 1, 2008 until present 529 of those referrals have been evaluated in consultation and 469 cases were appropriate for this analysis. Using a binary logistic regression model, those factors that were predictive or protective for an urgent vs non-urgent consultation are outlined in Table 1. The probability of assigning an urgent grade at referral for those patients who were deemed to be truly urgent at consultation was 76.9% (sensitivity). The probability of assigning a non-urgent grade at referral among those patients who were deemed to be truly non-urgent at consult was 75.4% (specificity). Factor Odds Ratio, p-value Gender (Male vs Female) 0.62, p=0.05 Patient Reported Joint Swelling (No vs Yes) 2.2, p=0.03 Physician Reported Joint Swelling (No vs Yes) 2.2, p=0.01 History or family history of psoriasis (no vs yes) 1.6, p=0.09 Prior visit to a rheumatologist (no vs yes) 2.3, p=0.002 Rheumatoid factor (negative vs positive) 2.8, p<0.001 Age (<60 vs >60) 0.61, p=0.05 ESR (normal vs elevated) 1.9, p=0.03 CRP (normal vs elevated) 1.8, p=0.05 Duration (<12 months vs >12 months) 1.6, p=0.07

Conclusion: The use of a standardized rheumatology referral tool has significantly increased the ability to detect urgent referrals with our previously measured sensitivity4 increasing from 59% to 76.9%. Using the results of the binary logistic regression model and the analysis of the urgent referrals not identified in the screening process the tool has been further refined. A multi-centre project of the refined referral tool is currently underway.

Disclosure: A. Thompson, Schering Canada, 5, Abbott Immunology Pharmaceuticals, 5, Amgen, 5, Bristol Myers Squibb, 5, UCB, 5 ; **S. Graydon**, None; **E. Zibrowski**, None.

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A Decision Aid for Rheumatoid Arthritis Patients Considering Methotrexate Therapy. Richard W. Martin[1], Patience J. Gallagher[2], Aaron T. Eggebeen[1] and Andrew J. Head[1], [1]Michigan State University, Grand Rapids, MI, [2]Calvin College, Grand Rapids, MI

Purpose: Patient decision aids (PtDA) are tools that medical providers use as a supplement to clinical discussion. PtDAs contain information with choices and outcome probabilities, help patients clarify their values, and provide structured guidance about deliberation. This study sought to develop and pilot test an inexpensive PtDA that could be used during and following a clinical encounter by rheumatoid arthritis (RA) patients considering methotrexate (MTX) therapy.

Method: The PtDA was developed following International Patient Decision Aid Standards Consortium (IPDAS) criteria[1]. Outcome probabilities were identified from the published literature. A preliminary PtDA was pre-tested in 5 RA patients and 10 rheumatology

professionals. After revision, formal pilot testing was conducted in RA patients who had made the decision to start MTX in the past 2 years. Evaluation included visual screening, health literacy screening, time to complete the PtDA, formative and summative questionnaires, and extended structured interviews to illicit feedback to improve the usability of the materials.

Results: The decision aid was developed using plain language (SMOG score of 9.9) and expressing outcome probabilities simultaneously in narrative, natural frequencies, and pictographs. Outcome values clarification and preferred decision making role were elicited with social matching exercises. Deliberation was guided with a modified balance and leaning scale. Of the 17 participants, 76.5% were female, 94.1% were white, 17.6% attained less than high school graduation and 23.5% displayed low or marginal health literacy. Mean completion time was 12.7 minutes (SD 4.0). Persons with lower levels of confidence in ($p<.01$) and satisfaction with ($p<.02$) their previous decision to take MTX took significantly more time to work through the PtDA. Responses about the acceptability, clarity and usefulness of the PtDA were significantly more positive when compared to the neutral value of 3 ($p<.02$) using a one sample t-test for each of the 15 formative evaluation questions. Pre-post PtDA testing of MTX-related knowledge disclosed a significantly increased score from 71.5 to 82.9% correct ($p<.01$), which translates into an effect size of 0.35 for the intervention. Qualitative responses from structured interviews revealed patients felt the PtDA was enjoyable to read, the contents were logical and understandable, and the length was about right. Appraisal with the IPDAS instrument[2] disclosed a quality score of 74 (0-100) which is in the range of existing benchmark decision aids.

Conclusion: Pilot testing suggests that the PtDA is acceptable to patients and effectively informs them of the risks and benefits of MTX. This PtDA could be used as an adjunct to a rheumatology office encounter to encourage shared decision making and increase patients' choice of preference-based care.

Reference: [1]British Medical Journal. 2006;333:417. [2] PLoS ONE 4(3):e4705.doi:10.1371/journal.pone.0004705.

Disclosure: R. W. Martin, None; **P. J. Gallagher**, None; **A. T. Eggebeen**, None; **A. J. Head**, None.

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Quality Assurance Project: Implementing a Cost-Effective Solution for a Rheumatology Electronic Prescription. Steven J. Katz and Elaine Yacyshyn, University of Alberta, Edmonton, AB

Purpose: Hand written physician prescriptions are fraught with potential medical errors; illegibility, mistakes in dosing, and record keeping are all issues of concern. A prescription error by a pharmacy led to this quality assurance project. With improving patient safety in mind, electronic health records (EHR) and electronic (e) prescription programs are becoming more common, but they remain cost-prohibitive and can be technically difficult to implement. Our aim was to design and implement a cost-effective e-prescription program specifically for the rheumatologist.

Methods: The University of Alberta clinical area is equipped with desktop computers in each room and one central printer. There is no centralized EHR. Microsoft Office 2003 was installed on each computer. Using Microsoft Excel 2003, a prescribing template was created by the rheumatology resident with the 30 most commonly used medications for a rheumatology practice. The password protected program was listed on a website for download, with a link provided to the website on each clinic computer for easy access. A printed copy of the prescription was provided to the patient.

Results: The Edmonton Rheumatology Prescription Software (E-RPS) program was developed in the fall of 2008, with initial programming time under one day. E-RPS was successfully trialed between December 2008 and February 2009 by the division's rheumatology residents, with changes made based on their suggestions, including an automatic second printed copy for the chart and improved esthetics. The program was then expanded to include all rheumatologists on site. Since implementation, no rheumatologist has received a phone call from a pharmacy to clarify an e-prescription and no medication errors have been identified. Ongoing disadvantages of the software include no inclusion of an electronic record of medications prescribed and difficulties prescribing titrating doses.

Conclusion: A rheumatology centered e-prescription program was successfully implemented and is now in use by rheumatologists at our site. We believe this is a cost effective and practical alternative to more expensive EHRs or e-prescribing software to provide quality assurance in improving patient safety. Improvement of the program will be ongoing based on user suggestions and expanded upon request.

Disclosure: S. J. Katz, None; **E. Yacyshyn**, None.

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The Impact of a Centralized Referral System in Rheumatology. Glen S. Hazlewood, Liam Martin and Susan G. Barr, University of Calgary, Calgary, AB

Purpose: With resources in rheumatology becoming increasingly strained, efficient referral systems are needed. The purpose of this project was to evaluate the success of a centralized rheumatology referral system in our city.

Method: A centralized referral system for rheumatology was implemented in 2006. All rheumatologists in academic and community practice in our city were invited to participate. All referrals are sent to a common referral center, triaged, and distributed amongst the participating rheumatologists. Referring physicians could refer to a specific rheumatologist if they desired. Data on the triage category, wait times and feedback from the rheumatologists on referral quality were collected prospectively in a database. Where appropriate, we compared our results to a pre-implementation practice audit.

Results: Overall, 13/14 rheumatologists (93%) participated in the centralized referral process. During the 2-year study period (Jan 1, 2007-Dec 31, 2008) 9182 referrals were received (383 per month). 80% were booked with the next available rheumatologist, 9% were booked directly with a rheumatologist, 2% were redirected and the remaining 9% were not booked or were waitlisted. Consults were triaged as routine (74%), moderate (19%), or urgent (7%). Feedback was received from the rheumatologist for 3779 referrals (41%). Rheumatologists rated referral quality as moderate or high in 91% of referrals, and the completeness of information as moderate or high in 87% of referrals. The triage category was felt to be appropriate for 90% of referrals. Of the consults triaged inappropriately, 104 (2.8% of all referrals) were "under-triaged" as routine or moderate when they should have been urgent. Of these, referral completeness was deemed "Low" in 31%. There were 14 routine or moderate cases that were "over-triaged" as urgent. There were 254 no-shows (6.7%) which was similar to a prior practice audit. Duplicate referrals were eliminated, which was identified as a significant problem at baseline with a rate of >= 6%. Mean wait times, when compared to baseline, were similar for routine referrals (pre 155±88 days, post 148.9±65, p=0.11), and improved for moderate (pre 110±57, post 77.7±56, p<0.001), and urgent referrals (pre 29±46, post 18.3±22.8 p=0.01). Wait time variability improved significantly, with mean wait times for individual rheumatologists ranging from 44-271 days pre- to 109-178 post-implementation (p<0.01).

Conclusion: A centralized referral system to rheumatology eliminates duplicate consults and improves wait times and wait time variability between rheumatologists. The urgency of referral can be categorized correctly in a high percentage of cases.

Disclosure: G. S. Hazlewood, None; **L. Martin**, None; **S. G. Barr**, None.

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Rheumatologists' Practice for Prescribing Pneumocystis Prophylaxis. Deanna Cettomai, Allan C. Gelber and Lisa Christopher-Stine, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Consensus guidelines for *Pneumocystis* pneumonia (PCP) prophylaxis in HIV-negative patients with rheumatologic disorders are lacking. We assessed rheumatologists' practice patterns for prescribing PCP prophylaxis.

Method: Invitations to participate in an online international survey were emailed to 3150 American College of Rheumatology members.

Results: Surveys were retuned by 727 (23.14%) individuals, of whom 505 (69.5%) reported prescribing prophylaxis. In univariate analyses, factors associated with significantly higher odds of prescribing PCP prophylaxis included female gender, US-based and academic practice of <10 years duration, having previously treated a patient with PCP pneumonia, and a practice with a higher proportion of patients on chronic glucocorticoids or other immunosuppressant medications. In multivariate analysis, rheumatologists early in their careers and those with a US-based practice, or a higher proportion of patients treated with chronic glucocorticoid therapy were most likely to prescribe PCP prophylaxis. Among the prescribers, the most important determinant factors for prescribing prophylaxis were treatment regimen (68.6%), rheumatologic diagnosis (9.3%), and medication dosage (8.3%).

	Prescribe PCP Prophylaxis	Univariate Logistic Regression		Multivariate Logistic Regression	
Demographic Characteristic	n (%)[†]	OR (95% CI)	p	OR (95% CI)	p

Female gender	191 (74.9)	1.47 (1.04, 2.08)	0.03	1.01 (0.68, 1.50)	0.97
Male gender	308 (67.0)				
US-based practice	420 (72.0)	1.77 (1.20, 2.61)	0.004	1.974 (1.27, 3.05)	0.003
Internationally-based practice	80 (59.2)				
Academic practice	248 (81.0)	2.75 (1.94, 3.89)	< 0.001	1.81 (1.23, 2.66)	0.003
Non-academic practice	252 (60.9)				
≤ 10 years in practice	206 (86.6)	4.08 (2.69, 6.18)	< 0.001	4.13 (2.62, 6.51)	< 0.001
> 10 years in practice	292 (61.2)				
≥ 10% patients on chronic glucocorticoids	414 (72.8)	2.04 (1.40, 2.96)	< 0.001	2.11 (1.38, 3.23)	0.001
< 10% patients on chronic glucocorticoids	84 (56.8)				
≥ 10% patients on other immunosuppressants	488 (70.5)	3.19 (1.48, 6.86)	0.003	2.26 (0.98, 5.26)	0.06
< 10% patients on other immunosuppressants	12 (42.8)				
Caring for a patient who developed PCP	159 (82.8)	2.62 (1.73, 3.98)	< 0.001	3.04 (1.92, 4.82)	< 0.001
Never caring for a patient who developed PCP	345 (64.7)				
≤ 10 patients with rheumatologic diagnosis under clinical care each week	43 (76.8)	1.48 (0.78, 2.82)	0.23	---*	---*
> 10 patients with rheumatologic diagnosis under care each week	455 (69.0)				

[†]Proportion of respondents with characteristic prescribing PCP prophylaxis.

*Not included in multivariate analysis because variable did not reach statistical significance in the univariate analysis.

Conclusion: Nearly one-third (30%) of rheumatologists surveyed reported that they never prescribed PCP prophylaxis. While the patients for whom physicians would prescribe prophylaxis varied widely, physician demographic characteristics were strongly predictive of prophylaxis use. Consensus guidelines would be helpful to guide clinical decision-making regarding PCP prophylaxis in HIV-negative patients with rheumatologic diagnoses.

Disclosure: D. Cettomai, None; **A. C. Gelber**, None; **L. Christopher-Stine**, None.

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Validity of Performance–Based Measures of Physical Functioning in Patients with Ankylosing Spondylitis. Salima F.E. van Weely[1], J. Christiaan van Denderen[1], Martijn P.M. Steultjens[2], Michael T. Nurmohamed[1], Joost Dekker[2], Ben A.C. Dijkmans[3] and Irene E. van der Horst-Bruinsma[2], [1]Jan van Breemen Institute, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands

Purpose: Patients with Ankylosing Spondylitis (AS), gradually experience a reduction in physical functioning and quality of life over time. Physical function is an important domain in core sets of outcome measures in AS research. A widely used outcome measure for this domain is the self-administered Bath AS Functional Index (BASFI) questionnaire, which reflects the patient's point of view. However, it is unclear whether this self-assessment reflects the actual physical performance of patients with AS. Therefore, eight performance-based tests of activities were developed based on BASFI-items.

The objective of this study was to assess the validity of these performance-based tests.

Method: 105 patients with AS completed a BASFI questionnaire and 8 performance tests. The performance tests were extracted from the BASFI. (1.Putting on socks. 2. Bending forward. 3. Reaching up. 4. Getting out of a chair. 5. Getting up off the floor. 6. Climbing 12-15 steps. 7. Looking over the shoulder. 8. Doing physically demanding activities). For tests 1-6 and 8 the time to actually perform the test was measured. For test 7 the ability to look over one shoulder was measured by the range of vision while looking over the shoulder.

Spearman correlation coefficients were calculated and factor analyses were performed to asses the association between the BASFI and the performance tests.

Results: Only modest correlations were found between performance tests and BASFI ranging from 0.25 to 0.57 ($p < 0.05$) Factor analyses including performance tests and corresponding BASFI items produced two independent domains; one for self-reported and one for performed physical functioning. Repeating this analysis and replacing the performance test scores with a compound score comprising time, pain and fatigue resulted in one factor incorporating both self-report and performance.

Conclusion: Self-reported and performance measures of physical functioning in AS produce different outcomes. Consequently, performance tests and self-reported questionnaires on physical functioning measure different constructs of the domain physical functioning. Integrating experienced pain and fatigue in the performance score bridges the gap with self-report and gives relevant additional information on physical function.

Disclosure: S. F. E. van Weely, None; **J. C. van Denderen**, None; **M. P. M. Steultjens**, None; **M. T. Nurmohamed**, None; **J. Dekker**, None; **B. A. C. Dijkmans**, None; **I. E. van der Horst-Bruinsma**, None.

ACR Poster Session A

Rheumatoid Arthritis - Human Etiology And Pathogenesis I

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Smoking Intensifies Rheumatoid Arthritis Susceptibility in Individuals Carrying the HLA-DRB1 Shared Epitope Regardless of Serologic Markers. So-Young Bang[1], Kyoung-Ho Lee[2], Soo-Kyung Cho[1], Hye-Soon Lee[1], Kyung Wha Lee[3] and S.-C. Bae[1], [1]Hanyang Univ Medical Center, Seoul, South Korea, [2]Seoul National University, Seoul, South Korea, [3]Hallym University Sacred Heart Hospital, Anyang, South Korea

Purpose: Smoking is associated with rheumatoid arthritis (RA) in individuals with the HLA-DRB1 shared epitope (SE). SE alleles have been found to be predominantly associated with anti-cyclic citrullinated peptide antibodies (ACPA)-positive RA. These risk factors have not been identified for ACPA-negative RA. We investigated whether SE-containing HLA-DRB1 alleles, smoking, or the combination contribute to the development of RA depending on the presence or absence of serologic markers in a Korean population.

Method: All RA patients (n =1482) and controls (n = 1119) were Korean.Four-digit HLA-DRB1 typing was performed by a conventional PCR-SBT method. Information about smoking history was obtained through a questionnaire. RA patients were tested for ACPA and rheumatoid factor (RF).

Results: The SE alleles had significant effects on ACPA and RF formation. The DRB1*0901 allele was independently associated with the presence of ACPA (OR 2.49) and RF (OR 2.09). SE alleles and smoking were associated with both ACPA-positive and ACPA-negative RA. The combination of smoking and double SE copies increased the risk for ACPA-positive RA 36.11-fold and ACPA-negative RA 12.29-fold, compared with the risk among nonsmokers not carrying the SE alleles. Gene-environment interactions between SE alleles and smoking were observed for both ACPA-positive and RF-positive RA.

Conclusion: We demonstrated that SE alleles and smoking are associated with RA susceptibility, regardless of ACPA or RF status. The SE-smoking interactions were present in both ACPA-positive and RF-positive RA.

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Relationship Between Synovial Blood Flow Signals and Angiogenesis Factors in Patients with Rheumatoid Arthritis by Power Doppler Ultrasonography. Kenichiro Hirai, Daitaro Kurosaka, Makiko Nishioka, Yukio Miyamoto, Ken Yoshida, Isamu Kingetsu, Kunihiko Fukuda and Akio Yamada, The Jikei University School of Medicine, Tokyo, Japan

Purpose: To study the relationship between increases in the blood flow of the synovial blood vessels and vascularization observed in the synovial membrane of patients with rheumatoid arthritis by power Doppler ultrasonography (PDUS).

Methods: The subjects were 70 patients with RA who fulfilled the diagnostic criteria of the American College of Rheumatology. Ten joints: the bilateral wrists, elbows, shoulders, knees, and ankles, were examined by PDUS. The blood flow signals at synovial sites of each joint were scored 0-2, and the total blood flow scores of the 10 joints was calculated as the total signal score (TSS). The vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and interleukin-6 (IL-6) levels were determined by ELISA.

Results: Significant correlations were observed between the TSS and serum VEGF, Ang-2, and IL-6 levels but not between the TSS and serum Ang-1 level.

Conclusion: The increases in the synovial blood flow signals in joints of RA patients observed by PDUS are likely to be caused by vascularization in synovial proliferation areas. They are particularly likely to represent the pathology in the period of marked vascularization, in which Ang-2 plays a dominant role.

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GSTM1, HLA-DBR1, and Smoking Interactions Suggest a Role for Oxidative Stress in the Pathogenesis of APCA-Positive Rheumatoid Arthrtits. T. R. Mikuls[1], Karen A. Gould[2], Kimberly K. Bynote[2], Fang Yu[2], Tricia D. LeVan[2], Geoffrey M. Thiele[3], Kaleb D. Michaud[4], James R. O'Dell[1], A.M. Reimold[5], R.S. Hooker[6], Liron Caplan[7], Dannette S. Johnson[8], G.S. Kerr[9], J.S. Richards[10], Lindsey A. Criswell[11], Peter K. Gregersen[12] and Gw Cannon[13], [1]U Nebraska, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Univ of NE Medical Ctr, Omaha, NE, [4]University of Nebraska and NDB, Omaha, NE, [5]VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [6]Department of Veterans Affairs, Dallas, TX, [7]Univ of CO Denver School of Med, Aurora, CO, [8]University of MS Med Ctr, Jackson, MS, [9]VAMC, Georgetown University, Washington, DC, [10]Veterans Affairs Medical Ctr, Washington, DC, [11]University of California, San Francisco, [12]Feinstein Institute for Medical Research, Manhasset, NY, [13]VA and University of Utah, Salt Lake City, UT

Purpose: Approximately half of Caucasians are homozygous for a deletion allele in *glutathione S-transferase Mu-1 (GSTM1-null*), a genotype previously associated with rheumatoid arthritis (RA). The purpose of this study was to examine the associations of *GSTM1* status with anti-cyclic citrullinated peptide antibody (ACPA) positivity and to assess interactions of this genotype with other known RA risk factors.

Methods: Associations of *GSTM1-null, HLA-DRB1 shared epitope (SE),* and smoking with autoantibody positivity were examined in U.S. veterans with RA (n = 595). Additive *gene-gene* and *gene*-smoking interactions were examined by calculating an attributable proportion (AP) due to interaction.

Results: Patients were predominantly men (93%) with a history of ever smoking (79%). Most were positive for ACPA (77%), rheumatoid factor (RF) (81%), and *SE* (75%) while 53% were *GSTM1-null*. *GSTM1-null* (vs. *GSTM1-present*) was associated with a significantly higher odds of ACPA positivity (OR = 1.58; 95% CI 1.07 to 2.32) but not with RF positivity. There were significant additive interactions between *SE*-smoking (AP = 0.56; 95% CI 0.27 to 0.86) and *SE-GSTM1* (AP = 0.49; 95% CI 0.21 to 0.77) in ACPA positivity, the latter most striking in ever smokers (Figure, right panel, O.R. 58.2 [95% CI 7.4 to 456.6] in SE+ 2 copy/GSTM1-null) vs. never smokers (left panel). Study results were not changed after the exclusion of women.

Conclusion: The *GSTM1-null* genotype adds substantially to the risk of ACPA positivity already imposed by *HLA-DRB1 SE* in RA, a risk that is most pronounced in smokers. With an antioxidant function of *GSTM1*, these data suggest that oxidative stress may play an important pathogenic role in ACPA-positive RA.

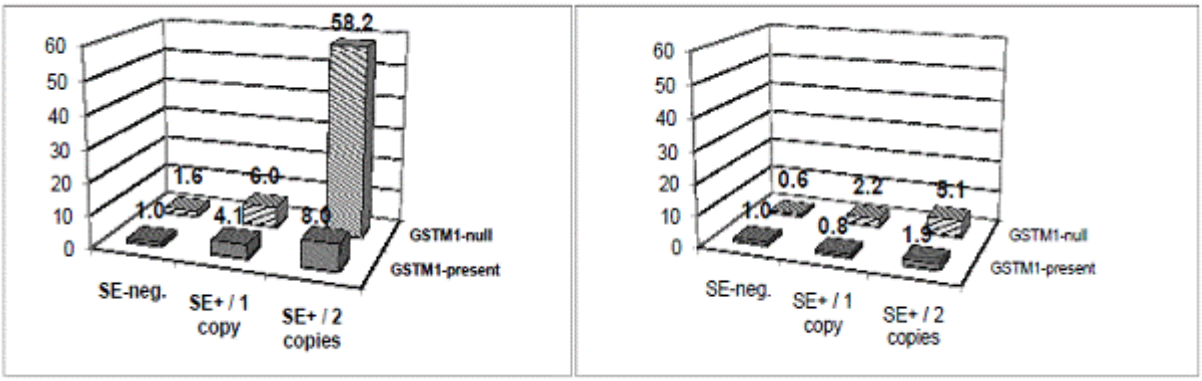

Figure: Odds ratios (ORs) of ACPA positivity based on SE copy number and GSTM1-null status among ever smokers (left panel) and never smokers (right panel)

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Citrullinated Proteins Activate IgE-ACPA+ Cells in Rheumatoid Arthritis. Annemie JM Schuerwegh, Andreea Ioan-Facsinay, Annemarie L. Dorjée, Ellen IH van der Voort, Tom WJ Huizinga and René EM Toes, Leiden University Medical Center, Leiden, Netherlands

Purpose: Untill now, the mechanisms on the basis of the chronic inflammation and cartilage destruction in Rheumatoid Arthritis (RA) are unknown. The discovery of antibodies against cyclic citrullinated proteins (ACPA) was a breakthrough. In humans, a direct functional/pathogenic role for ACPA is never shown. The few MCs in the normal synovium of healthy subjects expand to constitute 5% of all synovial cells in RA patients. In this study, it is hypothesized that citrullinated proteins activate immune cells by cross-linking specific IgE-ACPA molecules, bound on FcεRI receptors. The objective of this study is to investigate the presence and the functional role of IgE-ACPA in RA patients.

Method: A sandwich ELISA was performed for anti-citrullinated protein (fibrinogen) IgE antibody detection. The ability of these sera to activate basophils via the human FcepsilonRI was investigated by performing a passive sensitization of human FcεRI transfected Rat Basophil cells (RBL). A basophil activation test was performed with peripheral blood of ACPA-, ACPA+ RA patients and healthy controls to evaluate the potency of citrullinated proteins to directly activate basophils. FACS analysis visualized citrullinated protein (FITC coupled) binding to basophils. IgE and Fc\epsiRI expression were studied by FACS on synovial MC obtained by joint replacement surgery or arthroscopic biopsy in RA and osteoarthritis (OA) patients. Histamin (competitive ELISA) and IgE levels (UniCap) were measured in synovial fluid (SF) of ACPA-, ACPA+ RA and OA patients.

Results: IgE antibodies against citrullinated antigens could be detected in sera of ACPA+ RA patients. No IgE antibodies were found against their uncitrullinated counterparts. Sensitizing human Fc\epsi RI expressing RBL cells with serum from ACPA+ RA patients (but not from ACPA- RA patients) lead to a rapid activation of these cells to ACPA- RA patients and healthy controls, when RBL cells were stimulated by citrullinated antigens but not by uncitrullinated antigens. Non-transfected RBL cells were not activated, showing the specificity of citrullinated antigens to crosslink IgE-ACPA via FcεRI. Direct ex vivo activation (i.e. within 20 minutes) of basophils from ACPA+ RA patients but not from ACPA- RA patients after exposure to citrullinated antigens (but not uncitrullinated control antigens) was observed. This activation was correlated to the binding of citrullinated proteins in basophils and to the presence of immunoglobulins on the surface of these cells. FcεRI and IgE expression was increased in synovial mast cells of ACPA+ patients compared to ACPA- patients and OA patients. Histamine levels correlated with IgE levels in ACPA+ RA SF, but not in ACPA- RA, suggesting degranulation of MC by crosslinking IgE-ACPA.

Conclusion: For the first time, a direct biological response to citrullinated antigens of immune cells is shown in ACPA+ RA patients only. In addition, these results indicate that IgE-ACPA and FcεRI-positive cells (such as mast cells) could be involved in the pathogenesis of RA.

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Investigating the Complex Associations of MHC with RA Susceptibility. G. Orozco, W. Thomson, A. Barton, S. Eyre, J. Worthington and Xiayi Ke, arc Epidemiology Unit, Manchester, United Kingdom

Purpose: The major rheumatoid arthritis (RA) susceptibility locus, *HLA-DRB1*, lies within the major histocompatibility complex (MHC) at 6p21. There is evidence of additional RA loci in the MHC, although interpretation of these associations is made difficult by the presence of strong linkage disequilibrium across this region. Our aim was to investigate the complex association pattern of the MHC region with RA susceptibility to identify effects independent of *HLA-DRB1*.

Methods: A total of 1,804 RA cases and 1,474 1958 Birth Cohort controls were included in the study.

High resolution *HLA-DRB1* typing was performed using Dynal RELI^{TM} SSO kits. Subjects were genotyped for 1,546 single nucleotide polymorphisms (SNPs) within the extended MHC region using Affymetrix GeneChip 500K, as part of the Wellcome Trust Case Control Consortium (WTCCC) study. Statistical analysis was carried out using PLINK and Stata.

Results: Shared epitope (SE) alleles were strongly associated with RA (OR 4.25 95% CI 3.52-5.12 and OR 17.44 95% CI 13.18-23.07) for the carriage of one and two copies of the SE, respectively). In particular, the *0101, *0404 and *0408 alleles showed the strongest association with increased RA risk. Therefore, our RA cohort showed a similar pattern of HLA associations to that previously shown for other European populations.

We found 745 SNPs significantly associated with RA (P trend<0.05). Of these, 398 SNPs showed association at a significance level of P trend<0.001. Many of the strongest associations were observed in the vicinity of the *HLA–DRB1* locus.

To avoid confounding by RA-associated DRB1 alleles, we analyzed MHC SNPs using a data set with pairwise matching of cases and controls on HLA-DRB1 genotypes. Analsysis of the 594 case–control pairs with identical HLA-DRB1 genotypes revealed 104 SNPs significantly associated with RA (P<0.05), suggesting that additional effects can be found in the HLA region. Of these, 3 loci showed the strongest associations with RA (P<0.003):

Locus 1: close to *ZNF391* in extended class I

Locus 2: close to *OR2H1* in extended class I

Locus 3: close to *HLA-DPB1/DPB2* class II

Conclusion: This analysis has revealed that multiple independent effects contribute to RA susceptibility in the MHC region. Validation is now being carried out using independent external datasets.

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HLA-DRB1*15 Non-Shared Epitope Allele Regulates Production of Very High Levels of ACPA in RA. Judit Laki[1], Emeli Lundström[1], Bo Ding[2], Lars Alfredsson[2], Lars Klareskog[1] and Leonid Padyukov[1], [1]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Purpose: Production of anti-cyclic citrullinated peptide antibodies (ACPA) is an important biomarker for the major subgroup of rheumatoid arthritis (RA). It has been demonstrated that capability to develop these antibodies is associated with HLA-DRB1 shared epitope (SE) alleles. Interestingly, the level of ACPA does not correlate with disease activity. Nevertheless, there is a distinct group of ACPA positive RA patients characterized by very high ACPA levels exceeding the upper limit of the ELISA test. So far there are no data available whether there is a distinct genetic predisposition for this very high ACPA level. Our goal was to determine, whether HLA-DRB1 alleles are involved in regulation of production of very high ACPA in comparison with regular/moderate level in ACPA positive RA.

Methods: In the cohort of 1073 ACPA positive RA patients from the Swedish EIRA study HLA-DRB1 alleles were detected by SSP-PCR genotyping. Baseline DAS28 data from the time of diagnosis were available in 515 patients. Using provisional cut-off with 1,500 units, we found that 283 patients (26.4%) had very high ACPA levels, the rest of patients were considered as with regular ACPA levels.

Results: Though we did not observe any significant differences in baseline DAS28 data between patients with very high and regular ACPA levels, there were marked differences in the genetic background of the two groups. DRB1*15 in combination with smoking was associated with very high ACPA levels (p=0.0002, OR=2.322). Presence of DRB1*03 in combination with shared epitope (SE) alleles was asssociated with moderate or low ACPA levels (p=0.0009, OR=0.3029), however this effect was not independent from DRB1*15. Neither HLA-DRB1 SE alleles nor smoking had any independent effect on production of very high ACPA.

Conclusion: Our data indicate that presence of DRB1*15 may promote very high ACPA levels, in particular in smokers. Our data illustrate the complex nature of the genetic regulation of ACPA levels, and demonstrate the need for additional mechanistic studies on the regulation of ACPA and ACPA-positive RA.

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A Functional RANKL Promoter SNP Associated with Younger Age at Onset of Rheumatoid Arthritis. W. Tan[1], H. Wu[1], L. A. Derber[2], D. M. Lee[3], N. A. Shadick[3], E. A. Smith[4], V. H. Gersuk[5], G. T. Nepom[5], L. W. Moreland[6], D. E. Furst[1], S. D. Thompson[7], B. L. Jonas[8], V. M. Holers[9], P. P. Chen[1], D. N. Glass[7], S. L. Bridges[10], M. E. Weinblatt[3], H. E. Paulus[11] and B. P. Tsao[1], [1]UCLA, LA, CA, [2]U Colorado Denver, Aurora, CO, [3]Brigham and Women's Hosp, Boston, MA, [4]MUSC, Charleston, SC, [5]Benaroya Rsch Ini., Seattle, WA, [6]U Pittsburgh, Pittsburgh, PA, [7]Children's Hosp, Cincinnati, OH, [8]UNC-Chapel Hill, Chapel Hill, NC, [9]U Colo Denver, Aurora, CO, [10]UAB, Birmingham, AL, [11]David Geffen School of Medicine at UCLA, LA, CA

Purpose: We previously reported the association of co-occurrence of HLA-DRB1 shared epitope (SE) and R*ANKL* SNPs with younger at onset of RA in 182 RF+ European American (EA) early RA patients, which prompted us to fine map *RANKL* causal SNPs and study additional cohorts: 298 African-Americans (AA) RA (RF+ = 211, CCP+ = 172), 501 EA RA (RF+ = 317, CCP+ = 344) and 80 RF+ EA JIA.

Methods: SNPs were genotyped using TaqMan or pyrosequencing. *RANKL* expression levels in plasma, PBMC and isolated T cells were quantified using ELISA and RT-PCR. In vitro site-directed mutagenesis of rs7984870 within the 2kb *RANKL* promoter was performed to drive the luciferase reporter gene in transfected cells.

Results: Fine-mapping a 64-kb *RANKL* region using 19 SNPs in an extended 210 EA RF+ early RA patients showed association of minor allele homozygotes of 4 *RANKL* SNPs (rs5803141, rs7984870 and rs9525641 in the promoter region, and rs1054016 in the 3'UTR) with 5 yrs earlier mean age at RA onset ($p < 0.05$). The minor allele homozygote frequency for those 4 SNPs had increasing proportions in EA normals (10-11%), RF+ RA (18-20%), and RF+ EA polyarticular JIA (23-26%) patients ($p = 0.02$-0.009). Among those, rs7984870 CC genotype exhibited the strongest statistical significance ($p = 0.009$). This association was confirmed in 172 anti-CCP+ AA patients (7 and 5 yrs earlier for rs5803141 and rs7984870, respectively, $p < 0.05$), and replicated in an independent 344 anti-CCP+ EA early RA patients (4

yrs earlier for rs7984870, $p < 0.05$). Co-occurrence of rs7984870 CC genotype and HLA-DRB1*04 showed a strong younger age (mean 9.2 yrs earlier) at onset in RF+ and anti-CCP+ subgroups of both EA and AA patients ($p = 0.01$-0.00003). Plasma levels of RANKL were 2-fold higher in RF+ RA patients carrying rs7984870 CC vs. GG (10 vs. 13, $p < 0.001$) but not in normals (5 vs. 19). Levels of *RANKL* mRNA in normal PBMCs (17 vs. 21) or T cells (4 vs. 4) were not different in those carrying either homozygous rs7984870 genotypes. However, after 48h incubation with IL-2, significantly elevated *RANKL* mRNAs were observed in normal control T cells carrying the rs798470 CC genotype compared to those carrying the GG genotype (4 vs. 4, $p < 0.05$). Transfection of the rs7984870 CC *RANKL* promoter displayed higher transcription activity than the GG genotype in both stromal and osteoblast cell lines only after stimulation with b-FGF or TNFa ($p < 0.05$).

Conclusion: Association of CC genotype of rs7984870 with younger RA onset has been replicated in several independent cohorts, and confers an elevated promoter activity after stimulation. Elevated inducible *RANKL* mRNA and protein levels may predispose to earlier development of seropositive (RF+ or anti-CCP+) RA in EA and AA patients.

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Prevalence of Anti-Cyclic Citrullinated Peptide Antibody and Its Association with Smoking in General Population: A Cross Sectional Study. Shunichi Kumagai, Nobuhide Hayashi, Seiji Kawano, Daisuke Sugiyama, Kunihiro Nishimura, Shimpei Kasagi, Jun Saegusa and Akio Morinobu, Kobe University Graduate School of Medicine, Kobe, Japan

Purpose: We have shown impact of smoking for developing rheumatoid arthritis (RA) by a meta-analysis.Some studies reported anti-cyclic citrullinated peptide antibody (anti-CCP) was related to smoking especially in RA patients with HLA-DR shared epitopes. Aim of this study is to determine the prevalence of anti-CCP and its relationship to RA in a general population and to clarify potential correlations between anti-CCP positivity and smoking.

Methods: Anti-CCP, rheumatoid factor (RF), and CRP were examined in 1,213 residents in a Japanese town. Serum MMP-3 levels were also measured in subjects positive for anti-CCP or RF. Multiple regression analysis was applied to clarify relationships with blood and urine tests results and life habit at physical examinations

Results: Of 1,213 subjects, 29 were positive for anti-CCP (2.4%). Five of seven RA patients were positive for both anti-CCP and RF, one was positive only for anti-CCP, and one was negative for both. Sensitivity and specificity were 85.7% and 98.1% for anti-CCP. Positive predictive value (PPV) of anti-CCP for RA was 20.7% and that of RF was 6.3%. Age and sex adjusted odds ratio (OR) of anti-CCP in current smoking was 4.40 [95% confidence interval (CI); 1.38-14.03] for whole population ($P = 0.012$). Age adjusted OR of anti-CCP was 5.27 [95%CI; 1.06-26.29] for man ($P=0.043$), 3.16 [95%CI; 0.38-26.43] for women ($P=0.28$), although the smoking rate was 43.8% and 2.9% for men (188/428) and women (23/784), respectively. No relation to smoking in past and current/past smoking was found for anti-CCP. In current smoking, age adjusted OR of RF was 1.87 [95%CI; 0.89-3.94] for men ($P=0.098$), 0.81 [95%CI; 0.11-6.25] for women ($P=0.28$).

Conclusion: Prevalence of anti-CCP in a Japanese general population was 2.4%. Anti-CCP was significantly associated with current smoking in the general population, but RF positivity was not.

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Different Cartilage Oligomeric Matrix Protein (COMP) Patterns in Untreated Anti-CCP Positive and Negative Rheumatoid Arthritis (RA). AF. Christensen[1], P. Junker[1], H. Lindegaard[1], T. Lottenburger[2], B. Ejbjerg[3], M. L. Hetland[3], K. Stengaard-Pedersen[4], Soren Jacobsen[3], T. Ellingsen[4], Lis S. Andersen[5], I. Hansen[4], H. Skjødt[3], Jk Pedersen[2], UB Lauridsen[3], A. Svendsen[1], U. Tarp[4], J. Pødenphant[3], AG Jurik[4], M. Østergaard[3] and K. Hørslev-Petersen[2], [1]Odense University Hospital, Odense, Denmark, [2]Graasten Rheumatism Hospital, Graasten, Denmark, [3]Copenhagen University Hospital, Copenhagen, Denmark, [4]Aarhus University Hospital, Aarhus, Denmark, [5]Graasten

Purpose: COMP is an extracellular matrix protein, which is primarily localized in cartilage. The protein is believed to regulate collagen fibril formation and matrix assembly. In RA and osteoarthritis there is an altered distribution of COMP in cartilage and COMP release to synovial fluid is increased. The aims were to measure COMP in serum and paired synovial fluid samples in early, untreated RA and to study the predictive value of baseline COMP on structural joint damage at 5 years.

Method: One-hundred-and-sixty patients with DMARD naïve and newly-diagnosed RA were included in the CIMESTRA trial [1]. 90 blood donors served as controls. Disease activity measures (e.g. CRP), x-ray (n=160) and magnetic resonance imaging (MRI) of non-dominant wrist (n=135) were obtained at baseline. In addition, x-ray status was obtained at 5 years. Radiographic progression was defined as the minimal detectable difference from baseline using Sharp/van der Heijde Score. MRI synovitis, oedema and erosion score were assessed according to OMERACT criteria. Anti-CCP was assayed at baseline. COMP was measured in serum and synovial fluids at baseline by ELISA (AnaMar, Sweden). Synovial fluids were collected from 22 patients at baseline.

Results: COMP was increased in RA serum as compared with controls ($p<0.001$). However, anti-CCP positive patients had significantly lower COMP than anti-CCP negative subjects ($p=0.048$), although still elevated compared with controls ($p=0.042$). In both subsets COMP correlated with DAS28 and joint counts. In anti-CCP positive patients COMP was positively correlated to MRI erosion and oedema score ($rho=0.37$, $p<0.001$ and $rho=0.26$, $p=0.02$). In anti-CCP negatives there was a positive correlation between COMP and MRI synovitis score ($rho=0.32$, $p=0.02$). Baseline COMP did not predict x-ray progression at 5 years. Synovial fluid COMP was 3.8 times higher than COMP in serum, but did not correlate to serum values ($p=0.95$).

Conclusion: COMP is increased in early DMARD naïve RA. Anti-CCP negative patients had higher COMP in serum than anti-CCP positives. These findings indicate that anti-CCP antibodies are disease modifiers in RA as also reflected by the differential association of COMP with erosion and synovitis score at baseline in these two subsets.

[1] Hetland ML et al. Arthritis Rheum 2006:54:1401-9

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Uncoupling of Collagen II Metabolism in Newly-Diagnosed Rheumatoid Arthritis (RA) Is Linked to Inflammation and Antibodies against Cyclic Citrullinated Peptides. AF. Christensen[1], P. Junker[1], H. Lindegaard[1], S. Christgau[2], T. Lottenburger[3], M.L. Hetland[4], K. Stengaard-Pedersen[5], Soren Jacobsen[4], T. Ellingsen[5], Lis S. Andersen[6], I. Hansen[5], H. Skjødt[4], Jk Pedersen[3], UB Lauridsen[4], A. Svendsen[1], U. Tarp[5], J. Pødenphant[4], AG Jurik[5], M. Østergaard[4] and K. Hørslev-Petersen[3], [1]Odense University Hospital, Odense, Denmark, [2]Novo Seeds, Novo A/S, Bagsvaerd, Denmark, [3]Graasten Rheumatism Hospital, Graasten, Denmark, [4]Copenhagen University Hospital, Copenhagen, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark, [6]Graasten

Purpose: Type IIA procollagen is an alternatively spliced collagen II variant, which is present in fetal and diseased cartilage [1]. The N-propeptide of procollagen IIA (PIIANP) is suggested to be a marker of collagen IIA synthesis. The cross-linked C-telopeptide of collagen II (CTX-II) reflects collagen degradation.

The aim was to investigate the relationship between molecular markers of cartilage collagen synthesis and degradation with disease activity measures, auto-antibodies and radiographic outcome in a prospective 5-year protocol on newly diagnosed, DMARD naïve RA.

Method: One-hundred-and-sixty patients with newly-diagnosed, untreated RA entered the CIMESTRA trial [2]. Disease activity, anti-CCP and x-ray status were measured at baseline with additional recordings of synovitis score and radiographic changes after 5 years. CTX-II and PIIANP were measured at baseline by ELISA. PIIANP was also recorded at 2 and 4 years. An uncoupling index for cartilage collagen

metabolism was calculated from *z-scores* for PIIANP and CTX-II defined as numbers of standard deviations from control mean. 120 blood donors served as controls. P-values≤0.05 were regarded as significant.

Results: PIIANP was decreased at diagnosis and 4 years on ($p<0.001$), irrespective of treatment and disease activity. PIIANP was lowest in anti-CCP positive patients ($p=0.006$), and there was a negative correlation between PIIANP and anti-CCP titer (rho=-0.25, $p=0.002$). CTX-II was increased in RA patients ($p<0.001$) and correlated positively with conventional disease activity measures, but not with anti-CCP ($p=0.93$). CTX-II and the uncoupling index were associated with estimated x-ray progression, and joint space narrowing progressors had significantly higher CTX-II and uncoupling index than non-progressors.

Conclusion: Cartilage collagen formation and degradation are un-balanced when RA is diagnosed. The uncoupling of collagen II metabolism is most pronounced in anti-CCP positive patients. Collagen II degradation (CTX-II) is increased and positively correlated to synovitis, while collagen II anabolism (PIIANP) is decreased and negatively correlated with anti-CCP titer.

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Association of rs8192284 IL-6 Receptor α Polymorphism and Soluble IL-6 Receptor Plasma Concentration with Disease Activity in Rheumatoid Arthritis. L. Rodriguez-Rodriguez[1], José Ramón Lamas[1], A. González-Vigo[2], P. Lopez-Romero[3], P. Tornero-Esteban[1], L. Abasolo[1], J. Varade[2], N. Perdigones[4], E. Urcelay[4] and Benjamin Fernandez-Gutierrez[5], [1]Hospital Clínico San Carlos, Madrid, Spain, [2]Immunology Service, Hospital Clinico San Carlos, Madrid, Spain, [3]CNIC, Madrid, Spain, [4]Immunology Service, Hospital Clínico San Carlos, Madrid, Spain, [5]Hospital Clinico San Carlos, Madrid, Spain

Purpose: Interleukin 6 soluble receptor α subunit (sIL-6R) is mainly generated by shedding of the membrane-bound form. This process is influenced by the single nucleotide polymorphism rs8192284 (A>C) resulting in an Aspartic acid to Alanine substitution (D358A) located at the proteolitic cleavage site. The aim of this paper is to characterize whether plasma levels of sIL6R may be influenced by rs8192284 in Rheumatoid Arthritis patients and to address the association of sIL-6R plasma levels and SNP with disease activity.

Method: 39 patients were randomly selected from a cohort of RA patients of Spaniard descent. Plasma sIL-6R concentration was measured using an ELISA sandwich. Genotyping of rs8192284 (A>C) polymorphism was done using a Fast Real-Time PCR System. DAS 28 score was used to assess disease activity. Data are indicated as mean (standard deviation).

Results: sIL-6R plasma levels are positively associated to the number of C alleles (AA: 35.27 (3.50) ng/ml, AC: 45.50 (4.58) ng/ml, CC: 52.55 (3.18) ng/ml, $p<0.0001$). DAS28 and sIL-6R plasma levels showed a positive association in the anti-CCP positive subgroup ($r^2=0.4257$, $p=0.0482$) and a negative association in the anti-CCP negative subgroup ($r^2= -0.5466$, $p=0.0284$). Also an association between DAS28 and SNP was showed: C allele carrier was positively related to DAS28 in the anti-CCP positive subgroup (4.68 (1.11) vs. 3.57 (1.12), $p=0.0310$) and it was negatively associated in the anti-CCP negative subgroup (3.36 (1.03) vs. 6.37 (1.10), $p=0.0002$).

Conclusion: Our findings showed that rs8192284 polymorphism is operative in RA patients. The presence of anti-CCP antibodies determines the relationship between sIL-6R concentration, genotype and disease activity. RA anti-CCP positive patients carrying the C allele of rs8192284 SNP would be the ideal target for IL-6R blocking agents.

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Altered ADAR2 Gene Expression and Altered Editing of PDE8A1 Gene Transcripts in Rheumatoid Arthritis (RA) T Cells. Dama Laxminarayana[1], Kenneth O'Rourke[2] and Irene Olorenshaw[2], [1]Wake Forest Univ Sch of Med, Winston-Salem, NC, [2]Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: Rheumatoid Arthritis (RA) is an autoimmune disorder of indeterminate etiology characterized by B and T lymphocyte immune effector dysfunctions. The etiopathogenesis of the abnormal immune response in RA is associated with altered gene expressions. Adenosine to Inosine (A to I) editing is the post-transcriptional site-specific modification of precursor mRNAs catalyzed by the members of ADAR family genes. Such RNA editing plays an important role in the regulation of gene expression and produces phenotypic variability. Therefore, we hypothesize that the altered expression and function of ADARs is a mechanism for the immunopathogenesis of RA.

Methods: In the present study, we analyzed expression of ADAR1 and ADAR2 gene transcripts in RA and control T cells by competitive polymerase chain reaction (CPCR). 10 RA subjects and 10 healthy controls were studied. The Cyclic Nucleotide Phosphodiesterase 8A1 (PDE8A1) gene transcripts are edited by ADAR enzymes. Therefore, we assessed the role of altered ADAR2 enzyme expression in editing of PDE8A1 gene transcripts of RA T cells. The base position numbers of PDE8A1 gene transcripts reported here are used from the accession number AK001647. The PDE8A1 gene transcripts from normal and RA T cell samples were amplified and cloned into pCR2.1-TOPO vectors. A total of 100 clones from RA and 100 clones from controls were sequenced using T7 and M13 primers and an automated ABI-377 sequencer.

Results: The results revealed that the mean content of ADAR1 mRNA was 1.84 ±0.41 attomoles/µg total RNA in RA vs 1.79 ± 0.32 attomoles/µg total RNA in controls. The mean content of ADAR2 mRNA was 1.10 ±0.35 attomoles/µg total RNA in RA vs 1.70 ± 0.28 attomoles/µg total RNA in controls (p£0.05). Sequence analyses demonstrated altered A to I editing in the PDE8A1 gene transcripts of RA T cells. There are two hot spots for A to I editing in the PDE8A1 gene transcripts. The first hot spot consists of previously known edited nucleotides 42423 and 42424 and are called site 1. The A to I editing frequency at this site in RA and control samples is 18% and 29% respectively (p£0.001). The second hot spot is found between base positions 42454 and 42457 and called site 2. The A to I editing frequency at the second site was 2% for RA, and 8% for control subjects (p£0.001). In general, A to I editing is impaired in RA T cells compared to normal controls.

Conclusion: It is proposed that, the altered expression of ADAR enzymes tilt the balance of editing machinery and alter editing in RA transcriptome. Such altered editing may contribute to the modulation of gene regulation and ultimately, immune functions in RA patients and play an important role in the initiation and propagation of RA pathogenesis.

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Alcohol Consumption Is Inversely Associated with Risk and Severity of Rheumatoid Arthritis. James R. Maxwell[1], Isobel R. Gowers[1], David J. Moore[2] and Anthony G. Wilson[1], [1]University of Sheffield, Sheffield, United Kingdom, [2]Royal Hallamshire Hospital, Sheffield, Sheffield, United Kingdom

Purpose: Studies have suggested that consumption of alcohol associates with a lower risk for rheumatoid arthritis (RA), but the effect of alcohol on disease severity has not yet been investigated. Our objectives were to study the association between alcohol consumption, and susceptibility and severity of RA.

Method: Frequency of alcohol consumption was recorded by patients and controls in a self completed questionnaire. Odds ratios for RA risk were calculated according to alcohol consumption, adjusted for age, gender and smoking status. Median values of all RA severity measures were then calculated according to frequency of alcohol consumption, and the non-parametric trend test was used to assess association. A quantile regression model was used to adjust for potential confounding.

Results: 873 patients with erosive RA, and 1004 healthy controls were included in the study. Risk of RA decreased according to frequency of alcohol consumption, such that non drinkers had an odds ratio for RA of 4.17 (3.01 – 5.77) compared to subjects consuming alcohol on >10 days per month (p for trend <0.0001). All measures of RA severity including C-reactive protein, 28 joint disease activity score, pain visual analogue scale , modified Health Assessment Questionnaire, and modified Larsen score were inversely associated with increasing

frequency of alcohol consumption (p for trend, each <0.0001). After adjustment for potential confounders in a multivariate regression model, frequency of alcohol consumption remained significantly and inversely associated with X ray damage (p=0.002).

Conclusion: This study suggests that alcohol consumption has an inverse and dose related association with both risk and severity of RA, but we would recommend a prospective study to confirm our findings.

Table 1. RA Severity by frequency of alcohol consumption

Severity Marker		Frequency of Alcohol (days / month)				P for trend
		0	**1-5**	**6-10**	**>10**	
LS	All	38 (54)	33 (47)	29 (45)	27 (47)	<0.0001
	Men	41 (44)	30 (46)	21 (45)	19.5 (34)	0.004
	Women	37 (57)	33 (47.5)	32 (52)	30 (54)	0.03
	ACPA+	40 (56)	36.5 (50)	32 (56)	33 (53)	0.02
	ACPA-	27 (52)	22.5 (39.5)	17.5 (23)	16 (35)	0.02
DAS28CRP		4.29 (1.66)	4.01 (1.50)	3.82 (1.63)	3.72 (1.41)	<0.0001
CRP (mg/l)		13 (18.6)	10 (14.7)	8.7 (9.5)	8.0 (8.8)	<0.0001
Modified HAQ		1.0 (0.94)	0.75 (0.75)	0.5 (0.88)	0.63 (0.75)	<0.0001
Pain VAS (cm)		4.1 (4.5)	3.0 (4)	3.1 (3.5)	2.75 (3.5)	<0.0001

The values stated are the median for each severity marker, interquartile

range in brackets. LS = Larsen Score. P values are for the non parametric trend test

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Smoking Rates in Patients with Rheumatoid Arthritis Are Similar to the General Population but Smoking Cessation Rates Are Higher in RA Patients: Data From the QUEST-RA Multinational Database. H. Makinen[1], Tuulikki Sokka[2], Theodore Pincus[3], B. Abelson[3], A. Naranjo[4] and QUEST-RA Investigators, [1]Tampere University Hospital, Tampere, Finland, [2]Central Hospital, Jyvaskyla, Finland, [3]NYU Hospital for Joint Diseases, New York, NY, [4]Hospital Doctor Negrin, Las Palmas GC, Spain

Purpose: Smoking has been implicated in the pathogenesis of rheumatoid arthritis (RA), particularly in association with antibodies to cyclic citrullinated peptides (anti-CCP) and the shared epitope. However, relatively little information is available concerning the proportion of people with RA who smoke and/or discontinued smoking compared to the general population. The QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis) multinational cross-sectional database of 8,040 patients from 86 sites in 33 countries provided an opportunity to analyze rates of smoking and smoking cessation in 6,870 RA patients.

Method: QUEST-RA was established in 2005 to promote quantitative assessment in usual rheumatology care and develop a baseline cross-sectional database of consecutive RA patients seen in usual care in many countries. Three or more rheumatologists were asked to enroll 100 consecutive unselected patients in each country, using a standard protocol to evaluate RA (SPERA), with a clinical assessment and 4-page patient self-report questionnaire. Smoking status was assessed by self-report as “never smoked,” “smoked in the past but stopped” and “currently smoking.” Data for the proportions of the general population who smoked and did not smoke were available from all 33 countries. General population data for people who ceased smoking were found for 7 countries: Argentina, Canada, Finland, Germany, Italy, Sweden, and USA. Statistical significance of possible differences was calculated by chi-square analyses.

Results: Overall, 12.8% of 5,436 female QUEST-RA patients and 25.9% of 1,374 males were current smokers, compared to 22.7% of females and 36.8% of males in the general population. Among female QUEST-RA patients, 16.3% had stopped smoking and 70.8% never smoked; in males the proportions were 36.8% and 37.3%, respectively. In the 7 countries for which data concerning ex-smokers were found, 52.9% of patients vs. 52.4% in the general population had never smoked, 18.0% vs 26.6% were current smokers, and 29.1% vs 21.0% were ex-smokers.

	QUEST-RA					General Population			
Country	n	Never smoked	Ever smoked	Ex-smoker	Current smoker	Never smoked	Ever smoked	Ex-smoker	Current smoker
Argentina	243	52.9%	47.1%	25.7%	21.4%	45.5%	54.5%	22.6%	31.9%
Canada	99	31.3%	68.7%	38.4%	30.3%	53.0%	47.0%	26.0%	21.0%
Finland	301	60.2%	39.8%	25.2%	14.6%	49.1%	50.9%	20.8%	30.1%
Germany	222	54.3%	45.7%	32.7%	13.1%	54.0%	46.0%	19.0%	27.0%
Italy	333	58.9%	41.1%	25.2%	15.9%	57.6%	42.4%	18.1%	24.3%
Sweden	257	40.7%	59.3%	40.6%	18.7%	48.0%	52.0%	23.2%	28.8%
USA	296	55.7%	44.3%	24.4%	19.9%	58.2%	41.8%	21.0%	20.8%
TOTAL	1751	52.9%	47.1%	29.1%	18.0%	52.4%	47.6%	21.0%	26.6%

Conclusion: A lower proportion of patients with RA were current smokers than in the general population. The proportions of QUEST-RA patients who ever or never smoked were similar to the general population. Therefore, the likelihood of patients with RA having discontinued smoking was greater than in the general population.

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PADI4 Haplotypes Do Not Interact with Smoking, but Interact with Shared Epitope Regardless of Antibodies to Cyclic Citrullinated Pepeptide. So-Young Bang[1], Yoon-Kyoung Sung[1], Kyounghee Jung[1], Tae-Un Han[2], Changwon Kang[2] and S.-C. Bae[1], [1]Hanyang Univ Medical Center, Seoul, South Korea, [2]Korea Advanced Institute of Science and Technology(KAIST), Daejeon, South Korea

Purpose: The association of the peptidyl arginine deiminase 4 (PADI4) gene with rheumatoid arthritis (RA) has been replicated in several Asian populations. Anti–cyclic citrullinated peptide antibodies (ACPA) are most specific serologic markers of RA. We investigated whether PADI4 polymorphisms contribute differently to two subsets of RA depending on the presence or absence of ACPA and whether PADI4 polymorphisms interact with the HLA-DRB1 shared epitope (SE) alleles or with smoking in a Korean population.

Method: All RA patients (n =1313) and controls (n = 1009) were Korean. Four exonic SNPs of the *PADI4* gene (padi4_89, padi4_90, padi4_92, and padi4_104) were genotyped using the MassArray SNP genotyping system. Odds ratios (OR) with 95% confidence intervals (CI) were examined using logistic regression analyses.

Results: The four SNPs and functional haplotype of *PADI4* gene were significantly associated with developing ACPA-positive RA and ACPA-negative RA. No interaction was seen between smoking and *PADI4* polymorphisms. Gene-gene interactions between homozygous GTT haplotypes and SE alleles were observed in the development of ACPA-positive and ACPA-negative RA (attributable proportion 0.44 [95% CI 0.18-0.69], 0.57 [95% CI 0.22-0.91], respectively).

Conclusion: Our findings indicate that PADI4 polymorphisms play a role in the development RA regardless of ACPA status. We could not find a gene-environment interaction between PADI4 polymorphisms and smoking. Gene-gene interaction between homozygous *PADI4* haplotypes and SE alleles occurs in conferring an increased risk of ACPA-positive as well as ACPA-negative RA.

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Smoking and Aryl Hydrocarbon Receptor Function in Rheumatoid Arthritis. Marina Kazantseva[1], John Highton[1], Lisa K. Stamp[2] and Paul A. Hessian[1], [1]University of Otago, Dunedin, New Zealand, [2]University of Otago, Christchurch, New Zealand

Purpose: A number of environmental factors are believed to contribute to or protect against the development of rheumatoid arthritis (RA). Tobacco smoking is recognised as the main environmental risk factor for the development RA and is associated with increased incidence of extra-articular manifestations, including the development of subcutaneous rheumatoid nodules. How exposure to cigarette smoke contributes to the pathogenesis of RA remains to be established. The aim of this study was to identify the pathogenic mechanism(s) within inflamed RA tissues, which are triggered by smoking and engagement of the aryl hydrocarbon receptor (AhR).

Method: Total RNA was isolated from 19 synovial membrane samples, obtained at surgery from patients fulfilling ACR criteria for RA. A further 20 subcutaneous nodule samples were also obtained from a separate group of patients with RA. Two nodules were paired with synovial samples from the same patients. All synovial and nodule samples were assessed for AhR, CYP1A1, interleukin (IL)-17A, IL-17F, IL-22 and interferon (IFN)-γ gene expression by quantitative real-time PCR (Applied Biosystems).

Results: AhR was expressed significantly more in joint synovium when compared to rheumatoid nodules (7.10 ± 1.18 vs 2.77 ± 0.34 ng RNA respectively; mean ± SE; $P < 0.001$). To investigate AhR activation, CYP1A1 gene expression was assessed. CYP1A1 transcript was detected in 7/19 synovial membranes (37% CYP1A1+); 6/7 CYP1A1+ synovia were from patients who smoked at the time the sample was obtained, whereas 11/12 CYP1A1- synovia were from patients who never smoked or did not smoke for ≥ 5 years prior (Fisher's exact test; $P = 0.008$). 7/20 nodules (35%) were CYP1A1+ (4/7 smokers) and 13/20 were CYP1A1- (11/13 non-smokers). CYP1A1 expression was significantly higher in synovial tissue from smokers vs non-smokers but there was no such difference in nodule tissue. We investigated whether AhR activation influenced Th1 or Th17 pathways in RA. Contrary to expectation, we found significantly greater expression of IL-17A in CYP1A1- synovia vs CYP1A1+ synovia (0.11 ± 0.03 vs 0.02 ± 0.01 ng RNA; $P < 0.05$). In addition, there was a positive and significant association between IL-17A and AHR gene expression in CYP1A1- synovial tissue ($r = 0.58$; $P < 0.05$). IL-17F expression was restricted to 6/19 CYP1A1- synovia. IL-22 was not detected in synovia and IFN-γ expression was not different between CYP1A1+ and CYP1A1- synovia.

Conclusion: Our results show that in RA, smoking has a demonstrable impact on joint synovial tissue, activating AhR and inducing CYP1A1 expression. The same effect was not seen in rheumatoid nodules. We found that in CYP1A1- synovia from non-smokers, IL-17A gene expression is higher, IL-17F expression is exclusive and that there is a significant positive correlation between AhR and IL-17A expression. The results suggest that smoking induces expression of CYP1A1 (and probably other genes) in an AhR ligand-dependent manner in RA synovial tissue. However smoking appears to have a negative impact on expression of IL-17 related cytokines.

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In Early RA, Increased IL-6 Levels Drive B-Cell Activation and Are Associated with Disease Activity and 1-Year Radiographic Progression, Independently From CRP and Other Proinflammatory Cytokines: Results From the ESPOIR Cohort. Jacques-Eric Gottenberg[1], Pascale Roux-Lombard[2], Beatrice Ducot[3], Jean-Michel Dayer[4], Xavier Mariette[5] and Cedric Lukas[6], [1]University Hospital of Strasbourg, Strasbourg, France, [2]Hôpitaux Universitaires de Geneve, Genève, Switzerland, [3]Biostatistics, Bicetre Hospital, France, [4]CMU. Office 9000, Geneva 4, [5]Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France, [6]Lapeyronie hospital, Montpellier, France

Purpose: Serum markers of B-cell activation are increased in early RA compared with undifferentiated arthritis (UA), independently from BAFF secretion. We investigated whether a specific pattern of serum cytokines could explain B-cell activation and correlate with diagnosis, activity and severity of RA.

Method: In the ESPOIR early arthritis cohort, 710 patients were assessed at 1 year and either met the 1987 ACR criteria for RA (n= 578) or had UA (n= 132). Baseline serum samples of patients naïve to corticosteroid and DMARD treatment and 50 healthy controls were assessed

for IL-1beta, IL1-RA, IL-2, IL-4, IL-6, IL-10 IL-17, MCP-1, TNF-alpha, IFN-gamma using Luminex. Radiographic progression was defined as an increase of total Sharp/van der Heijde score (SHS) greater or equal to 1 between inclusion and 1 year.

Results:

- Diagnosis of RA

Levels of all cytokines were significantly higher in patients with RA or UA compared with healthy controls. IL-6 was the only cytokine to discriminate RA from UA, with a significantly higher proportion of detection in RA than UA (70.2 vs 44.3%, $P<0.0001$). Moreover, IL-6 was associated with diagnosis of RA at 1 year on multivariate analysis (OR 1.9, 95%CI [1.2-2.9], $P= 0.004$), along with anti-CCP-positivity (OR 5.1 [2.9-8.7], $P<0.001$) whereas ESR and CRP were not (OR 0.99, [0.9-1.0], $P= 0.6$ and OR 1.0 [0.9-1.1], $P= 0.5$, respectively).

- Disease activity

Baseline detectable IL-6, IL-10 or IFN-gamma were associated with increased disease activity in patients with early RA.

- Serum markers of B-cell activation and autoantibody secretion

Patients with baseline detectable IL-6 had significantly higher levels of beta2-microglobulin, IgG kappa and lamba FLCs and were more frequently RF- or anti-CCP-positive. Patients with detectable IL-10 had higher levels of beta2-microglobulin, IgG, kappa and lambda FLCs and were more frequently anti-CCP-positive.

- Radiographic progression

The proportion of RA patients with baseline erosions and with radiographic progression was higher in patients with detectable IL-6. On multivariate analysis, detectable IL-6 at enrollment (OR 2.5 [1.4-4.3], $P= 0.001$) was associated with 1-year radiographic progression, along with anti-CCP positivity (2.0 [1.1-3.7], $P= 0.02$) and presence of erosions at inclusion (3.3 [2.1-5.3], $P< 0.001$) whereas ESR and CRP were not.

Conclusion: Serum levels of IL-6 are elevated in patients with early RA, compared with UA, independently of inflammation and of TH1/Th17 cytokines secretion. In early RA, increased IL-6 levels are associated with higher disease activity, activation of B-cells and increased 1-year radiographic progression on multivariate analysis. This study suggests that targeting IL-6 might be a useful therapeutic strategy in early RA.

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Relationship Between Foxp3+ Tregs in Synovium of Rheumatoid Arthritis and Clinical Activity. Zeng Yan[1], Zheng Dong-hui[1], Dai Lie[1], Zhang Bai-yu[1], MO Ying-qian[1] and LI Zhi-xun[2], [1]2nd Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, [2]Department of Pathology, Sun Yai-sen University, Guangzhou, China

Purpose: $CD4^+CD25^+$Tregs play an important role to keep balance of immune system in patients with rheumatoid arthritis (RA). Foxp3 (forkhead box P3/winged-helix transcription factor), the prototypic transcription factor of Tregs, is not only specific but also critical to Tregs function. In this study, Foxp3 was used to identify Tregs and the relationship between synovial $Foxp3^+$Tregs and clinical activity of RA was analyzed.

Method: Synovium from active RA patients was taken by closed needle biopsy. Synovium from patients with OA and non-inflammatory orthopedic arthropathies was chosen as controls. Synovial serial sections were measured by HE staining and immunohistochemistry staining for Foxp3, CD3, CD20, CD34, CD38 and CD68. The cell count of the $Foxp3^+$Tregs and the percentage of $Foxp3^+$Tregs/$CD3^+$Tcells were analyzed. The relationship between $Foxp3^+$Tregs expression in RA synovium and the histological synovitis scores, clinical activity was analyzed. RA patients were divided into two groups according to the DAS28: intermediate active group (DAS28 3.2~5.1, n=12) and severe active group (DAS28 >5.1, n=13).

Results: (1) Foxp3 was expressed in RA synovium , mainly in nuclei of $CD3^+$T cells, and Foxp3 expression was negative in controls. (2)The cell count of $Foxp3^+$Tregs and the percentage of $Foxp3^+$Tregs /$CD3^+$Tcells were less in severe RA group than those in the intermediate group(P=0.005, 0.001).(3)There was an inverse relationship between the cell count of $Foxp3^+$Tregs and the synovitis scores, synovial

hyperplasia, the percentage of CD68 positive cells in intimal lining layer (r=-0.622,-0.916,-0.935, P=0.001,0.000,0.000). (4)There was an inverse relationship between the cell count of Foxp3^{+}Tregs in RA synovium and 28 tenderness joints' indexes or DAS28(r=-0.568,-0.656, P=0.003,0.000).

Conclusion: Foxp3^{+}Tregs invasion in synovium may correlate with rheumatoid synovitis and clinical activity. Synovial Foxp3 expression may be a new diagnostic biomarker for clinical activity of RA patients.

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Relation of the Pesticide Exposure and the Occurrence of Rheumatoid Arthritis – A Cross Sectional Study of the NHANES 2005 – 2006 Data. Venkata Subhash Gorrepati[1], Ashok Valluri[1] and Pramil Cheriyath[2], [1]Harrisburg Hospital: Pinnacle Health, Harrisburg, PA, [2]Harrisburg Hospital: Pinnacle Health, Harrisburg

Purpose: There is an estimate of 1.2 billion pounds of pesticide use in the United States (US) and about 5 billion pounds worldwide. Deleterious effects of pesticide on the health of the exposed are well known. Rheumatoid Arthritis (RA) is a chronic, autoimmune disorder disabling a considerable amount of US population leading to major burden on the healthcare expenditure. Some studies have shown the incidence of RA to be greater in certain occupations which involves chemical exposure. Here we hypothesize that there is an increased risk of RA in the people who were exposed to pesticide.

Method: The National Health and Nutrition Examination Survey (NHANES) consists of demographic, physical characteristics and laboratory values of a randomly selected non institutionalized civilian US population. Presence of RA was assessed by the questions "Do you have any Arthritis?" and "if so, which type of Arthritis?" Pesticide exposure was evaluated using the questions "Products used in home to control insects?" and "Products used to kill weeds?" The analysis was done using statistical software SAS version 9.1 PROC SURVEY methods.

Results: Out of the 10,348 participants who took part in the survey, our study consisted of 4,680 people after excluding those with age less than 20 and with a missing Body Mass Index (BMI) values. The use of pesticide was positively correlated with RA (odds ratio of 1.43, 95% CI of 1.05 to 1.96). After adjusting the model for age, gender, race, education, smoking and BM, odds ratio was still remained significant (OR of 1.39, 95% CI of 1.03 to 1.88).

Conclusion: Our study showed a positive association between RA and pesticide use. Based on the magnitude of use and variety of products they could be present in, pesticides should be taught to be used in caution. More research is needed to confirm this relationship and to classify the pesticides into groups depending on the strength of the association with RA.

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T Cell Immunoglobulin and Mucin Domain 3 (TIM3) Genetic Polymorphisms Are Associated with Rheumatoid Arthritis, Independently of Shared Epitope Status. Churl Hyun Im[1], Eun Ha Kang[2], Joonwan Kim[1], Ran Song[1], Jin Hyun Kim[1], Yun Jong Lee[2], Kyung Sook Park[3], Eun Young Lee[1], Eun Bong Lee[1] and Yeong Wook Song[1], [1]Seoul National University Hospital, Seoul, South Korea, [2]Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Sungshin Women's University, Seoul, South Korea

Purpose: T cell immunoglobulin and mucin domain 3 (TIM3) proteins are T cell surface glycoproteins, and regulate auto- or alloimmune responses. Rheumatoid arthritis (RA) is an immune mediated inflammatory polyarthritis, and defects of TIM3 may have a pathogenic role in immune response during development of RA. TIM3 genetic polymorphism was reported to be associated with RA. We investigated genetic polymorphisms of TIM3 and RA susceptibility according to shared epitope (SE) status.

Method: 368 RA patients and 389 healthy controls were enrolled. 6 single nucleotide polymorphisms (SNPs - rs11742259 (C/T), rs10515746 (C/A), rs35960726 (A/G), rs1036199 (A/C), rs4704846 (A/G), rs11134551 (A/G)) in TIM3 gene were investigated using the

real-time polymerase chain reaction method. SE status of 165 RA patients were investigated. Genetic polymorphisms and their associations were analyzed by SPSS program (ver 12.0). Haplotype associations were analyzed by Unphased program (ver 3.1.2)

Results: TIM3 polymorphisms of rs10515746 (A allele 3.1 % vs 1.4 %, OR 2.249, 95 % CI 1.089 - 4.647, p value = 0.036) and rs35690726 (G allele 4.3 % vs 0.9 %, OR 5.006, 95 % CI 2.196 - 11.415, p value < 0.001) were significantly associated with RA patients compared with healthy controls. These associations were significant in RA patients with (p value = 0.007, < 0.001) or without SE (p value = 0.015, 0.001). Polymorphisms of rs11742259 (p value < 0.001) and rs1036199 (p value = 0.001) were associated in RA patients with SE but not in RA patients without SE. There were no significant associations of polymorphisms in rs4704846 (p value = 0.851), rs11134551 (p value = 0.521). In haplotype analysis, CAAAAA, CCAAAA, CCACAA, CCGAAA, CCGCAA, CCGCAG, TCAAAA haplotypes were significantly associated with RA patients compared with healthy controls.

Conclusion: TIM3 genetic polymorphisms may have a role in development of RA independent of SE status.

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Genome Wide Association Analysis of Rheumatoid Arthritis Patients Treated with Anti-TNF Medication. Marieke JH Coenen[1], Erik JM Toonen[1], Annette T. Lee[2], Franak Batliwalla[2], Wietske Kievit[1], Hans Scheffer[1], Timothy RDJ Radstake[1], Pilar Barrera[1], Piet LCM van Riel[1], Dutch Rheumatoid Arthritis Monitoring registry, Peter K. Gregersen[2] and Barbara Franke[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Feinstein Institute for Medical Research, Manhasset, NY

Purpose: Treatment strategies blocking tumour necrosis factor (TNF) have proven very successful in patients with rheumatoid arthritis (RA) showing beneficial effects in at least 60% of the patients. However, a significant subset of patients does not respond for reasons that are unknown, and there is currently no means of identifying these patients.

Method: In this study we performed a genome-wide association (GWA) analysis on 213 patients with RA treated with antibodies directed to TNF (anti-TNF) from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. For patient selection, we used an extreme groups approach, limiting inclusion to only very good responders (n=96) and total non-responders (n=117) to anti-TNF, based on the EULAR response criteria. Single nucleotide polymorphisms (SNPs) markers were genotyped using the Illumina HumanHap550-Duo BeadChip. Association analysis was performed using the whole genome association analysis toolset PLINK.

Results: 496.659 SNPs and 207 patients passed quality control. Thirty-three SNPs showed association (uncorrected p-value < 0.0001) with anti-TNF treatment response. The top 10 associated markers were located in regions including the nardilysin (*NRD1*) gene on chromosome 1; the solute carrier family 35, member F3 (*SLC35F3*) gene on chromosome 1; the latrophilin 3 (*LPHN3*) gene on chromosome 4; the translocation associated membrane protein 1-like 1 (*TRAM1L1*) gene on chromosome 4; the ADAM metallopeptidase with thrombospondin type 1 motif, 16 (*ADAMTS16*) gene on chromosome 5; the glutamate receptor, metabotropic 4 (*GRM4*) gene on chromosome 16; and a region on chromosome 14 that includes the beta-spectrin (*SPTB*) gene.

solute carrier family 35, member F3 latrophilin 3 translocation associated membrane protein 1-like 1 (ADAM metallopeptidase with thrombospondin type 1 motif, 16 (glutamate receptor, metabotropic 4 beta-spectrin

Conclusion: The most interesting candidate is *NRD1* for which it is documented that it is involved in TNF alpha shedding. To validate the present results we will extend the GWA analysis with an additional 362 patients from the DREAM registry. Significant findings will be replicated in other patient cohorts. The identified genes may serve as new biomarkers predicting anti-TNF response.

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The ACPA Isotype Repertoire Reflects Long-Term Radiographic Progression in Rheumatoid Arthritis. Diane van der Woude[1], Silje W. Syversen[2], Ellen IH van der Voort[1], Kirsten N. Verpoort[1], Guro L. Goll[2], Michael van der Linden[1], Annette H.M. van der Helm-van Mil[1], Désirée M.F.M. van der Heijde[1], Tom W.J. Huizinga[1], Tore K. Kvien[2] and René E.M. Toes[1], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway

Purpose: The presence of anti-citrullinated protein antibodies (ACPA) is a powerful predictive factor for the development and progression of rheumatoid arthritis (RA). The ACPA response has been shown to consist of various isotypes, but the consequences of differences in isotype-repertoire have not been extensively investigated. In this study, we investigated the relationship between ACPA isotypes and disease outcome.

Method: ACPA isotypes were determined in sera of CCP2-positive patients by enzyme-linked immunosorbent assay (ELISA). To investigate if the ACPA response continues to evolve during disease development, we studied the ACPA isotype repertoire during progression of undifferentiated arthritis (UA) to RA. The association of disease progression with ACPA isotype use was assessed using long-term radiographic follow-up data from RA patients in two independent cohorts.

Results: The ACPA isotype profile did not expand during disease progression from UA to RA, but was relatively stable over time. In both RA cohorts, the baseline ACPA isotype repertoire was a significant predictor of disease severity, with more isotypes indicating a higher risk of radiographic damage (odds ratio for every additional isotype: 1.4 (95% CI: 1.1-1.9) $p<0.001$). ACPA isotypes supplied additional prognostic information to ACPA-status alone, even after correction for other predictive factors.

Conclusion: The magnitude of the ACPA isotype repertoire at baseline reflects the risk of future radiographic damage. These results indicate that not only the presence, but also the constitution of the ACPA response, is relevant for the disease course of RA.

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Association of Functional RANKL Promoter Polymorphisms with Subsets of Rheumatoid Arthritis (RA) in Taiwanese. Ji Yih Chen[1], Chin-Man Wang[1] and J. Wu[2], [1]Chang Gung Memorial Hosp, Taoyuan, Taiwan, [2]PhD, Birmingham

Purpose: Rheumatoid arthritis (RA) is a common systemic autoimmune disease involving inflammation and destruction of joints. The aim of the current study was to investigate the functional implication of RANKL promoter polymorphisms and to examine whether RANKL promoter polymorphisms are associated with subtypes of RA in Taiwanese.

Method: RANKL polymorphisms (4-bp deletion/insertion polymorphism and three promoter SNPs) were genotyped in 672 RA patients and 681 age-matched healthy controls from the same geographic region in Taiwan. Genotyping was carried out using gene scan and MALDI-TOF (Mass Array matrix-assisted laser desorption ionisation-time-of-flight mass spectrometry). Genotype distributions, allele and haplotypes frequencies were compared between RA and healthy controls as aggregates or as stratified by X-ray findings, autoantibody profile within patient groups. In addition, EMSA (Electrophoretic Gel Mobility Shift Assay) and promoter reporter assays were carried out to examine whether RANKL SNP -290A>G affects transcription factor binding and promoter function.

Results: RANKL promoter SNP -290A>G significantly affected promoter activities. EMSA (Electrophoretic Gel Mobility Shift Assay) indicates that the SNP -290A>G is within a transcription element C/EBPβ and that -290A allele has higher binding affinity for transcription factor C/EBPβ. Notably, we observed a significant enrichment of -290GG genotype in C-spine involvement positive patients as compared with the C-spine negative RA patients (adjusted $p = 0.012$, OR 1.680 [95% CI 0.998 – 2.547]). Furthermore, the homozygotes -643 TT (adjusted $p = 0.032$ OR 1.967 [95% CI 1.148 – 3.037]) and -693 CC (adjusted $p = 0.05$, OR 1.680 [95% CI 0.998 – 2.547]) were significantly enriched in anti-CCP antibody positive patients compare to the anti-CCP negative RA patients. Haplotype 320/-290A was significantly reduced in RA ($p = 0.034$; odds ratio 0.689 [95% CI 0.488 – 0.973]) and destructive$^+$ RA ($p = 0.039$; odds ratio 0.655 [95% CI 0.437 – 0.981]) patients as compared with normal controls. Haplotype 316/-643C and 316/-693G were significantly reduced in destructive$^+$ RA patients as compared with destructive$^-$ RA patients ($p = 0.026$; odds ratio 0.558 [95% CI 0.331 – 0.939]. Among three RANKL SNPs haplotypes, haplotype -693G/-643C/-290A may have protective roles against CCP antibody production ($p = 0.007$; odds ratio 0.361 [95% CI 0.168 – 0.775]) and against destructive RA ($p = 0.006$; OR 0.354 [95% CI 0.163 – 0.769]).

Conclusion: RANKL promoter SNP affected promoter functions and RA phenotypes. Our data suggest that RANKL may contribute to the complex disease process of RA in Taiwanese.

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ACR Poster Session A

Rheumatoid Arthritis Clinical Aspects: Biomarkers

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Rheumatoid Factor and Anti-CCP Antibodies Are Independently Associated with Insulin Resistance in Early Inflammatory Polyarthritis-Results From the Norfolk Arthritis Register (NOAR). H. Mirjafari[1], T. Farragher[1], A. P. Yates[2], D. Bunn[3], T. Marshall[3], D. P. Symmons[1] and I. N. Bruce[1], [1]arc Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom, [3]Norfolk and Norwich University Hospital, Norwich, United Kingdom

Purpose: Cardiovascular disease (CVD) is the leading cause of death in patients with inflammatory polyarthritis (IP) and its subset rheumatoid arthritis (RA). Insulin resistance (IR) is predictive of the development of diabetes and CVD disease. IR is increased among patients with long-standing RA. We investigated the associated factors for IR in an early inception cohort of patients with IP.

Methods: Patients with IP (≥2 swollen joints for ≥4 weeks), between 18 and 65 years old, seen within 24 months of symptom onset, were recruited as a nested-cohort study within NOAR; a primary-care-based inception cohort of patients with early IP. At baseline patients provided information on therapy, underwent a joint examination and completed a health assessment questionnaire (HAQ). A fasting blood sample was taken for rheumatoid factor (RF), anti-CCP antibody (ACPA), C-reactive protein (CRP), lipid profile, glucose and insulin levels. IR was defined using the homeostatic model assessment of IR (HOMA-IR). The relationship between IR above the median and parameters known to increase the risk of CVD in the general population (smoking, hypertension, dyslipidaemia, diabetes) and IP related factors (RF, ACPA status, CRP, therapy, DAS28 and HAQ score) was assessed using age and gender adjusted logistic regression. We then used multivariable model analysis to explore the relationship of these associations.

Results: We studied 196 patients with median (IQR) symptom duration of 6.7 (4.6-10.7) months. 137 (70%) were female (Table). IR above the median was associated with higher triglycerides (OR (95% CI) 2.9 (1.7, 5.0). No association was found between IR and smoking, CRP, HAQ score, disease activity, symptom duration or therapy. On multivariable logistic regression modelling RF and ACPA status were each associated with IR, independent of all CVD and IP related factors (OR (95% CI) 3.2 (1.5, 7.0), 3.9 (1.7, 9.3) respectively). Exclusion of patients with diabetes did not alter this association. The relationship was strongest and only significant in those positive for both RF and ACPA, even on adjustment for all other factors (OR (95% CI) 4.7 (1.8, 11.9).

Table: Baseline characteristics.

Variable (n=196)	**Number (%)/mean (SD)/median (IQR)**
Age (years)	49 (40-57)
Female	137 (70%)
RF positive	90/193 (47%)
ACPA positive	61/182 (34%)
HOMA-IR score	2.7 (1.8-3.9)
Diabetic	21 (11%)
Fasting glucose (mmol/L)	4.8 (0.8)

HDL (mmol/L)	4.5 (0.4)
LDL (mmol/L)	3.2 (0.9)
Obese (BMI >30)	57 (30%)

Conclusion: In this inception cohort of patients with early IP, disease phenotype rather than symptom duration or therapy are associated with IR. IR may contribute to the excess CVD mortality found in seropositive IP. Modification of IR may attenuate this risk.

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The Predictive Value of the Anti-Cyclic Citrullinated Peptide (anti-CCP): A Study of Actual Test Requests. Christine Peoples[1], Ritu Valiyil[2], Roger Davis[1] and Robert H. Shmerling[1], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Past studies of anti-CCP antibody as a diagnostic test for rheumatoid arthritis (RA) have focused on its performance characteristics primarily among patients with RA and other selected rheumatic diseases. However, information is limited regarding this test's utility in actual practice, when those tested are less highly selected. The purpose of this study was to assess the diagnostic utility of testing for anti-CCP antibody among patients for whom the test was ordered by practicing clinicians.

Method: We reviewed the medical records of all patients for whom anti-CCP testing was requested during the first 6 months of 2005 and the first six months of 2007 in a single academic teaching hospital. Patients with RA were diagnosed by a rheumatologist and/or met ACR criteria. Sensitivity, specificity, and predictive value of anti-CCP results for RA were calculated combining data from both cohorts. In addition, a similar analysis was performed for rheumatoid factor (RF), comparing its performance characteristics with those of anti-CCP.

Results: Clinicians requested anti-CCP testing for 535 patients; 149 were ordered during the 2005 study period and 386 were ordered during the 2007 study period. In total, 90 (16.8%) of these tests were positive; 71 of these patients were diagnosed with RA (positive predictive value (PPV) = 78.9%). Of these 71 patients with RA, 37 had previously been diagnosed with and treated for RA. Among patients without a previous diagnosis of RA, sensitivity was 50.7% and specificity was 95.3%. PPV and negative predictive value (NPV) were 64.2% and 92.1%, respectively. Specificity and PPV were higher for anti-CCP than RF, although the two tests were concordant (both positive or both negative) in 83% of cases. For newly diagnosed RA, the cost per true-positive anti-CCP result was $1250.

Conclusion: The frequency of anti-CCP testing has increased dramatically in recent years, despite clinical utility that may be more limited than previously recognized. For patients without known RA, the PPV was only slightly better than the flip of a coin. In addition, the cost per true-positive anti-CCP result was high. Testing in settings of at least moderate pre-test probability of RA for patients without a prior diagnosis of the disease could improve its diagnostic utility.

Positive and Negative Predictive Value for anti-CCP and RF

	RA Prevalence	PPV		NPV	
		Anti-CCP	RF	Anti-CCP	RF
All patients	24.1%	78.9% (69.0-86.8)	59.5% (50.4-68.2)	87.0% (83.5-90.0)	86.3% (82.4-89.6)
New RA*	14.1%	64.2% (49.8-76.9)	40.0% (29.5-51.2)	92.1% (89.1-94.5)	91.1% (87.6-93.8)
Known RA**	13.2%	66.1% (52.2-78.2)	44.6% (34.2-55.3)	93.9% (91.2-96.0)	94.2% (91.2-96.4)

*New RA excludes patients with known RA **Known RA excludes patients with new RA

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Diagnostic Performance of Three Different Anti-Citrullinated Protein Antibodies-Evaluation in the Early Arthritis ESPOIR Cohort.

Pascale Nicaise-Roland[1], Leonor Nogueira[2], Christophe Demattei[3], Sabine Grootenboer-Mignot[1], Luc De Chaisemartin[1], N. Rincheval[4], Philippe Dieudé[1], Alain Cantagrel[5], Olivier Meyer[1], Guy Serre[2] and Sylvie Chollet-Martin[1], [1]Bichat Claude Bernard University Hospital, APHP, Paris, France, [2]Purpan University Hospital, Toulouse, France, [3]Caremeau University Hospital, Nimes, France, [4]Epidemiology unit, Montpellier, France, [5]JE 2510, Purpan University Hospital, Toulouse, France

Purpose: Anti-citrullinated protein antibodies (ACPA) are known to be sensitive and specific markers of rheumatoid arthritis (RA). However, their sensitivity in early RA needs to be better evaluated. We thus investigated the diagnostic sensitivity, individually or in association, of three assays for ACPA detection using different citrullinated antigens: cyclic peptide (CCP), mutated vimentin (MCV) or human fibrinogen (AhFibA) in a French cohort of recent (less than 6 month duration) undifferentiated arthritis (ESPOIR).

Method: 685 patients of the ESPOIR cohort were followed until 2 years after inclusion. Antibodies were determined by enzyme-linked immunosorbent assay at baseline. The cut-off of the different assays was calculated in order to obtain a 98% diagnostic specificity using a control population including healthy controls and other non-RA rheumatic diseases. In the ESPOIR cohort, the sensitivity of the three ACPA assays was determined in the patients classified as RA at 2 years according to the 1987 ACR criteria.

Results: 592 (86.4%) patients were classified as RA at 2 years. Sensitivity of the different assays is given in the table. ROC curve analysis could not detect any significant difference in diagnostic performance between the three ACPA assays. 317 (53.5%) RA patients were positive for at least one ACPA compared to a maximum of 48.5% for an individual ACPA. Interestingly, 8 patients were positive only for anti-CCP antibodies, 17 for anti-MCV antibodies and 16 for AhFibA. 95 of the patients classified as RA at 2 years were not classified as RA at baseline: 30 of them (31.5%) were positive for at least one ACPA assay at baseline. If the positivity of at least one ACPA is included in the criteria, 543 patients are classified as RA (79.3 %) at day 0, instead of 497 (72.5 %) without it.

Table.RA diagnosis sensitivities of the three ACPA assays

	Sensitivity
Anti-CCP	47%
Anti-MCV	47.3%
AhFibA	48.5%
Anti-CCP or anti-MCV	50.8%
Anti-CCP or AhFibA	50.7%
Anti-MCV or AhFibA	52.1%
At least one of the three ACPA	53.5%

Conclusion: Our results show that the performances of the three ACPA assays are very close to each other. However, in undifferentiated arthritis, the detection of the three ACPA subtypes increased the sensitivity of 6% as compared with the assays of only one marker with the risk of a slight decrease in specificity. Moreover, the positivity of one ACPA assay 2 years before the diagnosis, was predictive for RA in 30% of the 95 patients without a diagnosis at day 0. When ACPA were considered as a diagnosis criterion, 7 % more patients were classified as RA at day 0. This confirms that ACPA have to constitute an additional classification criterion for RA.

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Associations of Anti-CCP and Rheumatoid Factor Concentrations with Future Disease Activity in Rheumatoid Arthritis. Ben J. Miriovsky[1], Kaleb D. Michaud[2], Geoffrey M. Thiele[3], James R. O'Dell[4], Gw Cannon[5], G.S. Kerr[6], J.S. Richards[7], Dannette S. Johnson[8], Liron Caplan[9], A.M. Reimold[10], R.S. Hooker[11] and T. R. Mikuls[4], [1]University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska and NDB, Omaha, NE, [3]Univ of NE Medical Ctr, Omaha, NE, [4]U Nebraska, Omaha, NE, [5]VA and University of Utah, Salt Lake City, UT, [6]VAMC, Georgetown University, Washington, DC, [7]Veterans Affairs Medical Ctr, Washington, DC, [8]University of MS Med Ctr, Jackson, MS, [9]Univ of CO Denver School of Med, Aurora, CO, [10]VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [11]Department of Veterans Affairs, Dallas, TX

Purpose: To examine and compare associations of anti-CCP antibody (aCCP) and rheumatoid factor (RF) concentrations with future disease activity in patients with established rheumatoid arthritis (RA).

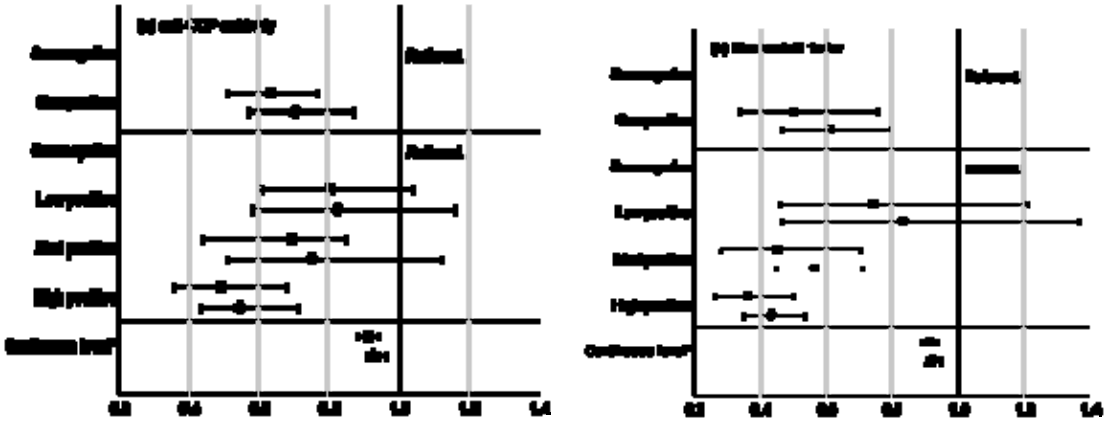
Methods: Study participants were U.S. veterans with RA (n = 855). Measures of disease activity included: 1) proportion of observation in remission, 2) remission for ≥ 3 consecutive months, and 3) area under the curve [AUC] for DAS28. Baseline aCCP and RF were examined dichotomously, as ordered categorical variables, and continuously. Associations of autoantibody status with disease activity outcomes were examined using multivariate regression.

Results: Patients were predominantly men (91%) with mean (SD) age of 66 (11) years and 2.3 (1.2) years of follow-up. Most were aCCP (75%) and RF (80%) positive. Associations of aCCP and RF status with sustained remission are shown in the figure below. After multivariate adjustment for age, sex, race/ethnicity, education, disease duration, follow-up time, smoking status, comorbidity, pharmacologic interventions, and disease status (DAS28 ≤ 2.6 vs. DAS28 > 2.6) at enrollment, aCCP and RF concentrations (per 100 unit increments) were associated with a lower proportion of observation in remission (b = -0.004, p = 0.054 and b = -0.002, p = 0.014, respectively), and greater AUC DAS28 (b = 0.02, p = 0.05 and b = 0.01, p = 0.002, respectively). In a sub-analysis of autoantibody discordant groups, higher aCCP concentrations in aCCP+ / RF- patients were associated with an increased likelihood of achieving remission (OR 1.10; 95% CI 1.00-1.20) (data not shown). In contrast, among aCCP- / RF+ patients, higher RF concentrations trended towards an inverse association with remission (OR 0.81; 95% CI 0.58-1.13) (data not shown).

Conclusion: Although higher aCCP concentrations are associated with greater future disease burden in patients with established RA, these associations appear to be related to concomitant elevations in serum RF.

Figure: Age- and sex-adjusted (■) and multivariate (○) ORs of aCCP and RF with the achievement of sustained remission (DAS28 ≤ 2.6). Shapes (■ and ○) correspond to ORs, horizontal bars represent 95%

CIs. ORs and CIs for ‘continuous level' correspond to 100 unit increments.



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Anti-CCP Antibodies, Rheumatoid Factor and Differences in Clinical Presentation of Early Arthritis: Results From the ESPOIR Cohort. Gaël Mouterde[1], Nathalie Rincheval[2], Cedric Lukas[1], RM Flipo[3], Philippe Goupille[4], Jean-Pierre Daures[2] and Bernard Combe[1], [1]Lapeyronie hospital, Montpellier, France, [2]Epidemiology unit, Montpellier, France, [3]Rheumatology,Lille University, Lille, [4]Université François Rabelais de Tours, CNRS, UMR 6239; CHRU de Tours, Tours, France

Purpose: To compare initial clinical, biological and radiological features of early arthritis patients depending on their positivity for rheumatoid factor (RF) and/or anti-CCP antibodies (anti-CCP). To valid a patient profile based on these serological data.

Method: Patients presenting with synovitis of at least 2 joints for 6 weeks to 6 months were included in the multicenter French ESPOIR cohort. They were tested for IgM RF (Elisa, Ménarini, France ; positive if > 9 UI/ml) and Anti-CCP2 antibodies (Elisa, DiaSorin, France ; positive if > 50 U/ ml) and divided into 4 groups : RF- and anti-CCP-, RF+ and anti-CCP-, RF- and anti-CCP+, RF+ and anti-CCP+. The following data were collected at baseline : clinical features, C-reactive protein, erythrocyte sedimentation rate (ESR), radiographs of hands, wrists, and feet (scored according to modified Sharp score). Quantitative variables were compared across the 4 groups by using Kruskal Wallis test, and the aggregate groups were compared using a Newman-Keuls like method. Khi2 test was performed for qualitative variables across the 4 groups, and recalculated with significant variables in order to constitute new poolings of interest.

Results: The 813 recruited patients had the following features : age 48±13 years, females: 77%, mean disease duration 103+/-52 days, DAS28 5.11±1.3, HAQ score 0.98±0.7, CRP 22.1±33.6 mg/l, HLA-DRB1*01 or 04 genes 57.6%. 406 (50%) were negative for both auto-antibodies (group 1), 91 (11.2%) were RF+ and anti-CCP- (group 2), 34 (4.1%) were RF- and anti-CCP+ (group 3), and 281 (34.6%) were positive for both auto-antibodies (group 4). Mean baseline ESR was higher in anti-CCP+ patients (group 3 and 4) ($p<0.0001$) and van der Heijde modified total Sharp score was higher in group 4 compared with the 3 other groups ($p=0.0018$). Clinical presentation did not show major informative correlation with serological profile. Group 2 and 4 (RF+ groups) had more frequent arthritis of second and third metacarpophalangeal and interphalangeal joints ($p<0.0001$). Group 4 (anti-CCP+ and RF+) had more frequent arthritis of 3 or more joints ($p=0.001$), fulfilled more frequently ACR criteria for RA ($p<0.0001$) compared with the 3 other groups. Group 1 (anti-CCP- and RF-) had less often positive squeeze test on metatarsophalangeal joints ($p<0.0001$), and arthritis of hand joints ($p<0.0001$). There were no differences in morning stiffness, DAS28 and HAQ score across the groups.

Conclusion: The phenotype of early arthritis patients with or without anti-CCP and/or RF was similar with respect to clinical presentation. However at baseline, mean ESR was higher in anti-CCP groups and radiographic damage was more severe in patients with both anti-CCP and RF, suggesting that these auto antibodies may be associated with the inflammatory process and progressive disease in patients with early arthritis.

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Levels of Anti-CCP and IgM RF Predict Persistent Arthritis in Patients with Very Early Undifferentiated Arthritis (UA). Maria D. Mjaavatten[1], Désirée M.F.M. van der Heijde[2], Till Uhlig[1], Anne J. Haugen[3], Halvor Nygaard[4], Göran Sidenvall[5], Knut Helgetveit[6] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Østfold Hospital, Moss, Norway, [4]Hospital for Rheumatic Diseases, Lillehammer, Norway, [5]Innlandet Hospital, Kongsvinger, Norway, [6]Martina Hansen's Hospital, Sandvika, Norway

Purpose: To assess the importance of increasing levels of anti-CCP and IgM RF in predicting development of persistent arthritis in UA patients.

Method: Patients with UA included in the Norwegian very early arthritis clinic(NOR-VEAC), which includes adult patients with at least one swollen joint of ≤16 weeks' duration. were assessed after 3, 6, and 12 months for development of persistent arthritic disease (persistent joint swelling or start of disease modifying anti-rheumatic drug). Sera frozen at inclusion were used to analyze anti-CCP2 (Inova Inc.) and IgM RF (in-house ELISA) levels in one batch. Cut-offs used to define a positive status were as recommended by the local laboratory: anti-CCP 25 units/ml, IgM RF 25 units/ml. Patients were divided into categories according to the levels of the respective antibodies (tertiles of patients

with a positive antibody status for anti-CCP and median for IgM RF), thus creating two categorized variables which were entered into univariate logistic regression analyses to determine the impact of increasing antibody levels on development of persistent arthritis.

Results: 376 UA patients were eligible for one year follow-up (58 % females, mean age 46 years, median duration of joint swelling 32 days). 59 (15.7 %) patients were positive for IgM RF, and 62 (16.5 %) for anti-CCP at baseline. 174 (46.3 %) had persistent arthritis after one year. There was a clear increase in the odds ratio and positive likelihood ratio with increasing levels of both anti-CCP and IgM RF.

Conclusion: The likelihood of developing persistent arthritis in UA patients increases with the level of anti-CCP and IgM RF. This finding suggests that patients should be stratified according to levels of these antibodies and not only according to positive or negative status when making risk assessments.

Table. Univariate logistic regression analyses with persistent arthritis as dependent variable.

Anti-CCP (units/ml)	OR (95 % C.I.)	p	LR+	LR-
≤25	1.0		ref	ref
>25-100	4.4 (1.6-12.54)	0.005	4.1 (1.5-11.0)	0.9 (0.9-1.0)
>100-250	9.4 (2.1-42.92)	0.004	8.7 (2.0-38.2)	0.9 (0.8-1.0)
>250	13.64 (4.04-46.04)	<0.001	11.4 (3.5-37.0)	0.8 (0.8-0.9)
IgM RF (units/ml)	OR (95 % C.I.)	p	LR+	LR-
≤25	1.0		ref	ref
>25-75	4.6 (2.0-10.6)	<0.001	4.0 (1.9-8.7)	0.9 (0.8-0.9)
>75	19.2 (4.5-82.5)	<0.001	16.2 (3.9-67.2)	0.8 (0.8-0.9)

OR, odds ratio; C.I., confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

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Do First-Year Levels of Autoantibodies Predict Two-Year Outcome Better Than Baseline Autoantibody Status in Early Arthritis Patients? Jennie Ursum[1], W.H. Bos[1], R.J. van de Stadt[2], Ben A.C. Dijkmans[3] and D. van Schaardenburg[2], [1]Jan van Breemen Institute, Amsterdam, Netherlands, [2]Jan van Breemen Intitute, Amsterdam, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands

Purpose: Several studies have demonstrated that the presence of anti-citrullinated protein antibodies (ACPA) or IgM rheumatoid factor (RF) are prognostic for disease activity, functional status and radiographic damage in patients with rheumatoid arthritis. However, data on the association between levels of ACPA or RF and outcome of RA are scarce.

Objectives: To investigate whether levels of autoantibodies provide additional prognostic information over baseline autoantibody status regarding disease activity, functional and radiographic outcome after two years in early arthritis patients.

Methods: In consecutive early arthritis patients with rheumatoid arthritis or undifferentiated oligo-/polyarthritis ACPA and RF levels, disease activity (DAS28), the Health Assessment Questionnaire (HAQ) and Sharp/Van der Heijde Score (SHS) were assessed annually. Baseline status and levels and first-year changes of the autoantibodies were associated with DAS28, HAQ and SHS at two years.

Results: Baseline characteristics of the 545 included patients were: mean age 53 years, 69% female, median disease duration 4 months, 56% ACPA positive, 47% IgM-RF positive. At two years the mean DAS28 was 2.88 and the median HAQ and SHS were 0.38 and 1, respectively. Of the ACPA positive patients at baseline 4% became ACPA negative after one year, whereas 2% of the ACPA negative

patients became positive. Of the RF positive patients at baseline 35% became RF negative after one year, while 3% of the RF negative patients became positive.

Positive baseline ACPA or RF status were both associated with 2-years SHS ($p<0.001$).

In baseline ACPA positive patients, baseline ACPA levels were modestly correlated to 2-year DAS28 and HAQ ($r=0.15$ and $r=0.13$, respectively, $p<0.05$), but not to SHS. No associations were found between baseline RF levels and outcome parameters.

ACPA and RF levels decreased in patients with a positive baseline autoantibody status in the first-year of follow-up with 31% and 56%, respectively. In patients with a positive status of either autoantibody, the first-year changes in ACPA and RF levels were not associated with the 2-year outcome parameters.

Conclusion: Baseline ACPA and RF status are associated with two-year SHS, whereas baseline ACPA levels are mildly associated only with two-year DAS28 and HAQ, and baseline RF levels are not associated with any of these outcome parameters. First-year changes in levels of either autoantibody are substantial, but are not associated with 2-year outcome. Since level changes are not associated with outcome and negative to positive seroconversion seldom occurs, it is not useful to repeat ACPA and RF measurements.

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Low Vitamin D Levels Are Associated with Insulin Resistance, Markers of Systemic Inflammation and Endothelial Activation in Rheumatoid Arthritis. Uzma Haque, Joan M. Bathon, Antony Rosen and Jon T. Giles, Johns Hopkins University, School of Medicine, Baltimore, MD

Purpose: Vitamin D deficiency has been identified as a possible risk factor for metabolic syndrome and adverse cardiovascular events in the general population. We investigated the association of vitamin D levels with traditional and non-traditional cardiovascular risk factors in a cohort of RA patients with no prior history of cardiovascular disease.

Method: Data are drawn from RA patients who met ACR criteria and were enrolled in an ongoing observational study of subclinical cardiovascular disease. Serum 25(OH)D levels were used to assess vitamin D status, with a level < 30ng/ml classified as deficient. Additional assessments included sociodemographics, traditional CV risk factors (diabetes, systolic and diastolic blood pressures, HDL, LDL, triglycerides, current and past smoking), body composition (body mass index, waist circumference), markers of systemic inflammation (CRP, fibrinogen), markers of endothelial activation (s-ICAM, E-selectin), and insulin resistance (using the Homeostatic Model Assessment (HOMA-IR). Spearman correlation coefficients were calculated to estimate the correlations between 25(OH)D levels (square root transformed to normality) and continuous CV risk factors (normally transformed where required). The associations of CV risk factors with vitamin D levels were calculated using multivariate linear regression, adjusting for pertinent confounders.

Results: Among the 179 RA patients studied (60% female, 88% White, mean age 61 ± 8 years), 73 (41%) had a 25(OH)D level < 30 ng/mL. Patients with low 25(OH)D levels were more likely to be non-White than those with higher levels (21% vs. 9%; $p=0.019$); however, other sociodemographics (age, gender, education), body composition characteristics, and non-lipid traditional CV risk factors did not differ by 25(OH)D status.

In contrast, significant positive correlations with HDL and inverse correlations with HOMA-IR, LDL, CRP,

s-ICAM, E-selectin, and fibrinogen with 25(OH)D level were observed in unadjusted analyses (Table). With the exception of LDL, these associations remained significant after adjustment for demographics, smoking, and season. 25(OH)D was not associated, in either crude or adjusted analyses, with triglycerides, homocysteine, or serum adipokines.

Conclusion: In this cross-sectional sample of RA patients, vitamin D levels were inversely associated with insulin resistance, markers of systemic inflammation and endothelial activation. These data suggest that vitamin D deficiency in RA may be an independent risk factor for metabolic syndrome and cardiovascular events, implicating a role of vitamin D supplementation in cardiovascular risk reduction.

Table. Crude and Adjusted Associations of Selected Laboratory Parameters with the Square Root of Serum 25-Hydroxy Vitamin D

Risk Factor	Unadjusted			Adjusted*	
	r**	β***	p	β***	p
log HOMA-IR, per log unit increase	-0.202	-0.265	0.007	-0.261	0.009
HDL-C, per mg/dL increase	0.157	0.008	0.018	0.011	0.009
LDL-C, per mg/dL increase	-0.167	-0.004	0.046	-0.003	0.18
log CRP, per log unit increase	-0.177	-0.121	0.018	-0.116	0.028
log s-ICAM, per log unit increase	-0.215	-0.625	0.004	-0.710	0.002
log E-selectin, per log unit increase	-0.264	-0.449	<0.001	-0.403	0.002
log Fibrinogen, per log unit increase	-0.231	-0.773	0.003	-0.743	0.006

* adjusted for age, gender, race/ethnicity, smoking, and season
** r = Spearman correlation coefficient
*** β = change in the square root of serum 25(OH)D per unit change in the covariate

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Relationship of Vitamin D and Parathyroid Hormone to Functional Disability and Disease Activity in RA. Colleen Doherty[1], Tamara Vokes[2], Linda M. Mileti[3], Maria Badaracco[1], Melinda Drum[2] and T.O. Utset[1], [1]University of Chicago, Chicago, IL, [2]University of Chicago, Chicago, [3]Northwestern University, Chicago, IL

Purpose: Vitamin D has immunomodulatory effects, and deficiency of this nutrient may impact inflammatory conditions such as rheumatoid arthritis. Conversely, the effect of chronic inflammation on calcium homeostasis is largely unstudied. We sought to determine if 25(OH) vitamin D level correlates with disease activity and functionality in RA, and whether parathyroid hormone (PTH) and calcium levels are impacted by chronic inflammation.

Method: In this cross-sectional study, the levels of 25(OH) vitamin D, calcium, and PTH were measured in postmenopausal women with RA. Disease activity was measured by erythrocyte sedimentation rate (ESR) and functional disability by the Health Assessment Questionnaire-II (HAQ-II). Statistical analysis of relevant clinical variables with ESR, HAQ-II score, and PTH were performed using t tests, and univariate and multivariate linear regression.

Results: Ninety-two subjects were analyzed. Average age was 66 years (SD 9.4), and mean disease duration was 12.1 yrs (SD 10.2); 61% of subjects were African-American, 32% Caucasian, and 8% Latino. Mean HAQ-II score was 0.91 (SD 0.68), and mean ESR was 41.2 (SD 28.4). Mean ESR was higher in African-American subjects (46.0 versus 33.8 mm/hour, p=0.046). Mean 25(OH) vitamin D level was 28.0 ng/mL (SD 11.3, range 2.5-54), and was lower in African-American subjects (25.5 versus 31.9 ng/mL, p=0.01). In univariate analysis, ESR trended closely toward association with 25(OH) vitamin D (p=0.06). After adjustment for age, creatinine, and ethnicity, the association of ESR with 25(OH) vitamin D was significant (p= 0.03). African-American ethnicity no longer significantly associated with ESR when adjusted for 25(OH) vitamin D (p=0.26). HAQ-II score correlated inversely with 25(OH) vitamin D level (p=0.03). Creatinine, African-American ethnicity, and calcium also correlated with HAQ-II score. In multivariate regression, HAQ-II score was positively associated with serum calcium (p=0.01) and serum creatinine (p=0.003), and trended closely toward an inverse association with 25(OH) vitamin D (p=0.06), but no longer varied by ethnicity. PTH level was positively correlated with ESR on both univariate regression (p=0.04) and multivariate regression adjusting for calcium, creatinine and 25(OH)vitamin D (p=0.01).

Conclusion: 25(OH) vitamin correlates inversely with ESR and trends toward correlation with HAQ-II score in RA, after adjustment for covariates. This supports a possible contribution of vitamin D insufficiency to disease activity and functional impairment in RA. The positive association of PTH with ESR suggests that parathyroid hormone production may be increased by a chronic inflammatory state.

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What Predicts Homocysteine in Rheumatoid Arthritis? Karen MJ Douglas[1], Vasileios F. Panoulas[1], Jacqueline Smith[1], Giorgos S. Metsios[1], A. Stavropoulos-Kalingolou[1], Tracey Toms[1], Gareth J. Treharne[2] and George D. Kitas[1], [1]Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [2]University of Otago, Dunedin, New Zealand

Purpose: Homocysteine (HOM) is a risk factor for Coronary Heart Disease (CHD). High levels of HOM in the general population relate to poor dietary folate intake and the MTHFR polymorphism. Methotrexate (MTX) is commonly used for the treatment of Rheumatoid Arthritis (RA) and, as a folate antagonist, has been implicated in raised HOM levels: this could potentially lead to increased CHD risk in RA, although current data suggests that MTX is protective. To address this apparent paradox, we aimed to determine whether HOM is higher in RA patients than controls, but also to identify predictors of its levels in RA.

Method: Fasting blood was collected for measurement of HOM, multiple other serological assessments and DNA extraction from 141 RA patients and 50 healthy local controls. MTHFR mutations were detected using commercial kits on the Roche Lightcyler™. Within the RA group, HOM levels were then considered in the context of multiple factors, including demographics (age and sex); anthropometrics (weight, BMI, body composition); RA characteristics (activity, seropositivity for rheumatoid factor and anti-CCP, severity (including extraarticular disease-EAD), duration, therapy), and comorbidities (including CHD, hypertension and insulin resistance). **Results:** were analyzed using t-tests, Mann-Whitney tests, Spearman's correlations and linear regression as appropriate. HOM levels were log-transformed for regression analysis; age and sex were controlled for throughout.

Results: HOM was higher in RA than controls (median 11.40mmol/l, IQR 9.08-14.2 vs. 9.0mmol/l, IQR 7.57-11.90, $Z=3.51$, $P<0.001$), and this remained significant after controlling for age and sex ($P<0.01$). Within the RA population, univariate analyses showed HOM to be higher in males and smokers ($P<0.01$), and to increase with age ($r=0.25$, $P<0.001$). HOM correlated significantly with disease activity [ESR ($r=0.19$, $P<0.05$), CRP ($r=0.23$, $P<0.01$), DAS28 ($r=0.18$, $P<0.05$)], but was not related to seropositivity for RF or anti-CCP, or disease severity [HAQ score, presence of erosions or EAD]. HOM levels did not relate to DMARD (including MTX) or NSAID usage but were higher prednisolone users (median 13.5mmol/l, IQR 10.7-16.8 vs. 11.1mmol/l, IQR 8.65-13.8; $Z=2.38$, $P<0.05$). Folate was higher in patients prescribed MTX ($Z = 3.45$, $P=0.001$), and correlated negatively with HOM (Spearmans rho $=-0.474$, $P<0.001$). MTHFR genotype had a major impact, with 677TT homozygotes having significantly higher HOM levels ($F=9.64$, $P<0.001$); within 677TT homozygotes, those taking MTX had non-significantly higher HOM than those who were not on MTX. In multiple regression, HOM levels associated significantly with MTHFR genotype, older age, male sex, smoking, EAD and prednisolone usage.

Conclusion: HOM is increased in RA and its levels are determined by MTHFR polymorphisms, sex, age, smoking, extra-articular disease and use of prednisolone. MTX does not significantly affect HOM, probably due to the co-prescription of folate supplements.

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Heavy Chain Hyaluronan in the Serum and Synovial Fluid of Rheumatoid Arthritis Patients as a Possible Marker of Inflammation. Hossam El-Zawawy, Mark Lauer, Vincent Hascall and Elaine Husni, Cleveland Clinic, Cleveland, OH

Purpose: Nonspecific markers of inflammation such as ESR and CRP have been used as an adjunct to the clinical assessment of disease activity in rheumatoid arthritis (RA) but are often imprecise. The synthesis of hyaluronan (HA) is increased by joint inflammation, primarily mediated by IL-1 and TNF-α as well as the amount of HA in the synovial fluid, which is increased in RA. Cells undergoing stress (injury to a knee joint) synthesize and deposit a hyaluronan matrix that is specifically recognized by inflammatory cells that are recruited into the tissue. This pro-inflammatory hyaluronan is modified by a reaction that transfers heavy chain (HC) proteins from a serum molecule named

inter-alpha-trypsin inhibitor. The heavy chain transfer is catalyzed by the TNF-α-induced protein 6, which is up-regulated in inflammation. As this only occurs in inflammatory processes, the heavy chain-hyaluronan complex (HC-HA) is a robust marker for inflammation. The purpose of this study is to test HC-HA in the serum and synovial fluid as a possible marker of inflammation in RA patients.

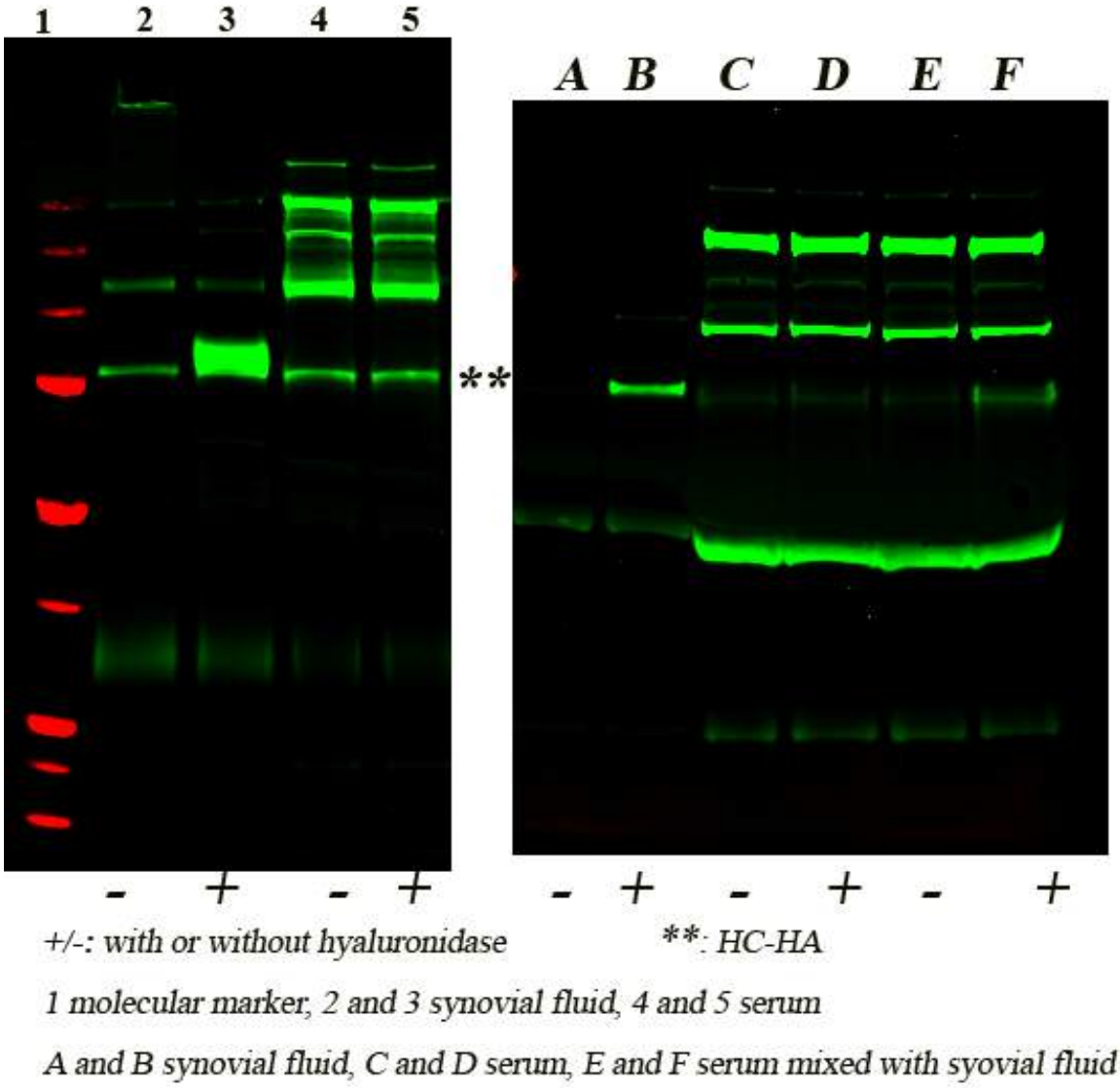
Methods: Western blot was performed on serum and synovial fluid from 7 RA patients. Approximately 25 µl of 5% serum or 1% synovial fluid was applied to each well of a 10-well SDS-PAGE gel and blotted to nitrocellulose membrane. The blot was blocked with a Li-Cor blocking buffer and probed with antibodies against IαI at 1:1000, or the simultaneous incubation of two HC antibodies at 1:200 dilution in the blocking buffer. The blots were probed with secondary antibodies at 1-15,000 dilution and imaged on an Odyssey infrared imaging system.

Western blot was done in duplicate from each sample. One of the duplicates was done after incubation of the synovial fluid or serum with SD hyaluronidase.

Results: Western blot analysis demonstrated clearly HC-HA in the synovial fluid. However in the serum, western blot did not show any HC-HA (figure, left panel).

Mixing serum and synovial fluid did not affect the reaction. HC-HA could still be detected after mixing the serum with the synovial fluid (figure, right panel).

Conclusion: The above results show that western blot was able to detect HC-HA in the synovial fluid but was unable to detect HC-HA in the serum. Mixing the synovial fluid with the serum did not affect the ability of western blot to detect HC-HA in the synovial fluid. This was done to eliminate the possibility that the serum contains inhibitory enzymes preventing the detection of HC-HA. The amount of HC-HA in the serum does not reflect the amount of HC-HA in the synovial fluid with the current technique. Experiments are underway to test the hypothesis of low sensitivity of western blot to detect “very low concentration” of the HC-HA in the serum. This will include purification and concentration of any HC-HA in the serum.



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Unexpectedly High IL-1α Levels in Cerebrospinal Fluid of RA Patients and Correlations with Fatigue Severity. Marie Westman[1], Diana Kadetoff[1], Anna Nordenstedt-Agréus[1], Caroline Gillis-Haegerstrand[2], Magnus Andersson[1], Mohsen Khademi[1], Eva Kosek[1] and Jon Lampa[1], [1]Karolinska Institute, Stockholm, Sweden, [2]Danderyds Hospital, Stockholm, Sweden

Purpose: Fatigue is common in RA patients and often cause substantial distress and reduced work capacity. There is a lack of knowledge of how fatigue is mediated, but central acting inflammatory mechanisms have been suggested in this context. In this pilot study, we investigated cerebral inflammation in RA patients and focused initially on IL-1β, because it has been implicated in sleep regulation and fatigue*.

Methods: Cerebrospinal fluid (CSF) was obtained from 14 female RA patients, 15 age-matched female patients with fibromyalgia (FM), 15 age-matched patients with multiple sclerosis (MS) in clinical remission and 12 age-matched control women without chronic pain undergoing surgery for benign gynecological conditions (before given spinal anesthesia). FM, RA patients and controls had no earlier or present

concurrent neurological disease. Mean DAS28 for RA patients was 3.6 (range 1.5 to 6.5). IL-1 levels were analyzed with ELISA (IL-1β: R&D, high sensitivity Quantikine). In RA and FM fatigue was assessed with visual analogue scale (VAS) as previously described[#] and current pain with VAS.

Results: CSF IL-1β levels was markedly elevated in RA (11.63±12.59 pg/ml) compared with FM (2.57±1.98 pg/ml), MS patients (1.23±1.86 pg/ml) and controls (0.66±1.03 pg/ml) (ANOVA $p<0.0001$; post hoc Bonferroni: $p<0.0006$; $p<0.0001$ and $p<0.0001$ respectively). There was no difference between FM, MS and control IL-1β levels. Pain was increased in FM compared to RA ($p<0.0001$), but there were no differences in fatigue between the diseases. After adjustment for age, disease activity and pain there was a significant positive correlation between RA CSF IL-1β levels and fatigue ($p<0.05$, $F=5.24$) whereas no similar correlation to fatigue was detected in FM ($p=0.23$, $F=1.6$).

Conclusion: This is to our knowledge the first evidence of increased cerebral inflammation in RA. The correlation between intrathecal IL-1β and fatigue in RA, but not in FM, supports involvement of cerebral inflammatory action in RA fatigue, and additionally suggests different mechanisms for fatigue in RA and FM.

*Krueger JM, Curr Pharm Des. 2008;14(32):3408-16

#Wolfe et al, J Rheumatol. 1996 Aug;23(8):1407-17

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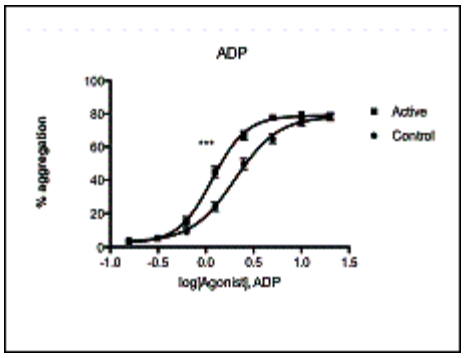
Platelet Hyper-Reactivity in Active Inflammatory Arthritis Is Unique to the ADP Pathway: a Novel Finding and Potential Therapeutic Target. Paul A. MacMullan[1], Aaron J. Peace[2], Anne Madigan[1], Anthony F. Tedesco[2], Dermot J. Kenny[2] and Geraldine M. McCarthy[1], [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, Ireland

Purpose: Patients with inflammatory arthritis (IA) have a markedly elevated risk of adverse cardiovascular events. This risk is greatest in those with poor disease control. Platelets play a crucial role in the pathogenesis of atherothrombotic events. To date, platelet function in the IA population has not been well characterised. Therefore, we decided to assess the influence of disease activity on platelet function in patients with IA.

Method: 96 patients with an established diagnosis of IA (rheumatoid, psoriatic, seronegative spondyloarthropathy) were recruited. Patients with a history of cardiovascular disease (CVD), diabetes mellitus, or receiving anti-platelet therapy were excluded. Demographic data, traditional CVD risk factors and medication use were recorded. Patients were characterised as Active disease (n =38) or Control disease (n = 58) groups respectively, based on internationally validated measures of disease activity, {comprising serological markers (ESR,CRP,fibrinogen) , patient measures (VASDA) ,evaluator global assessment, and the DAS-28 score}. Platelet function was assessed using a novel assay of platelet reactivity. Platelet aggregation to multiple concentrations of arachidonic acid, collagen, epinephrine, thrombin receptor activating peptide (TRAP), and ADP were measured simultaneously using a modification of light transmission aggregometry.

Results: The two groups (Active v Control) were similar in terms of demographics and CVD risk factors. Anti-TNFa therapy use was higher in the Control group ($p=0.004$) while NSAID use was higher in the Active group ($p=0.001$).There was a significant difference between the two groups in platelet response to ADP ($p<0.001$). Platelet aggregation in response to submaximal concentrations of ADP was increased in the Active disease group compared to the Control group. There was no difference in platelet reactivity between the groups in response to any of the other agonists.

Conclusion: Patients with active IA demonstrate enhanced platelet reactivity , unique to the ADP pathway. This potential pro-thrombotic bias may contribute to their increased cardiovascular risk.



***** p<0.001 Significantly increased platelet response to ADP in patients with active inflammatory arthritis.**

Disclosure: P. A. MacMullan, None; **A. J. Peace**, None; **A. Madigan**, None; **A. F. Tedesco**, None; **D. J. Kenny**, Health Research Board , Ireland, 2 ; **G. M. McCarthy**, None.

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Screening of Differentially Expressed Serum Proteins for Rheumatoid Arthritis by Proteomic Fingerprinting. Li Long[1], Yongzhe Li[2], Chaojun Hu[1] and Zhanguo Li[3], [1]Bejing Univ People's Hosp, Beijing, China, [2]Peking Union Medical College Hospital, Beijing, China, [3]Peking University People's Hospital, Beijing, China

Purpose: To search for proteomic patterns distinguishing rheumatoid arthritis (RA) patients from healthy controls, biomarker candidates specific for early RA, and proteins reflecting disease activity, by profiling of serum proteins using magnetic bead-based (MB) separation and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Method: Magnetic chemical affinity beads were used to differentially capture serum proteins prior to MALDI-TOF analysis. Seventy serum samples from RA cases fulfilling the American College of Rheumatology (ACR) classification criteria and 50 from healthy controls were analyzed. The samples were randomly allocated to the training set or test set to develop a pattern by means of decision tree algorithm. Nonparametric Mann-Whitney test was utilized to search for potential biomarkers for early RA. Linear correlation analysis was employed to estimate the intensity of the overexpressed peaks in relation to the level of serum C-reactive protein (CRP).

Results: The algorithm identified a pattern based on 3 peaks (m/z 2490, 5910.07 6436.73) that, in the training set, separated RA patients from healthy controls with a sensitivity and specificity of 87.5% and 96.7%, respectively. Blind test data indicated a sensitivity of 86.7% and specificity of 90%. The peaks of m/z 1014.92 and 1061.37671 were raised significantly in early RA group (disease duration<12 months) compared with those in non-early RA group (disease duration>=12 months) and healthy controls. A positive correlation was found between the intensity of peak 1770.16 and the level of serum CRP.

Conclusion: Using MB separation followed by MALDI-TOF-MS enabled rapid diagnosis of RA according to fingerprint pattern, a method which might also help to assess disease activity and identify early RA**.**

Disclosure: L. Long, None; **Y. Li**, None; **C. Hu**, None; **Z. Li**, None.

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Soluble GITR Ligand Is Extremely Elevated in Sera From RA Patients. Kazuhiro Kurasawa, Tetsuya Ohara, Satoko Arai, Takayoshi Owada, Reika Maezawa, Ryosuke Hanaoka and Takeshi Fukuda, Dokkyo Medical University, Mibu, Tochigi, Japan

Purpose: Glucocorticoid-Induced TNF-Related Protein (GITR) and its ligand, GITR ligand (GITRL), are members of the TNF receptor and TNF superfamilies, respectively. GITRL is a membrane protein and expressed on endothelial cells, dendritic cells, and some tumor cells. GITR/GITRL interaction plays important roles in immune response and inflammation, which activates regulatory effects of CD25+ CD4+

regulatory T cells and, on the contrary, stimulates inflammation. However, the role of GITR/GITRL pathway in the development of autoimmune diseases remains to be elucidated. In addition, it is unknown whether a soluble form of GITRL is produced similarly to some members of TNF family such as TNF.

The aim of this study is to determine whether there exists soluble form of GITRL (soluble GITRL) in sera from patients with rheumatic diseases. If so, to clarify the role of GITRL in the development of rheumatic diseases

Method: We developed EIA to detect soluble GITRL using a pair of antibodies against extracellular portion of GITRL. Serum samples from patients from RA (n=76), SLE(n=59), SSc (n=34), bacterial infection(n=21) and healthy controls (n=34) were tested. The soluble GITRL was examined with western blot analysis. Clinical features of patients with soluble GITRL were examined by review of medical records.

Results: Soluble GITRL was detected in sere from some patients with collagen-vascular diseases, particularly with RA .The molecular weight was approximately 15KDa. The patients with soluble GITRL levels above 0.5ng/ml (mean +3 sd of healthy controls) were 53% of RA, 2% of SLE, 18% of SSc, and 0% of infection. Interestingly, serum levels of soluble GITRL in RA were extremely elevated compared to those in other collagen-vascular diseases. Patients with soluble GITRL levels above 10ng/ml and 100ng/ml were 25% and 6.5% of RA, respectively. RA patients with extremely high levels of soluble GITRL (> 10ng/ml) were aged old and had high titers of RF, compared to those with soluble GITRL levels less than10ng/ml or with normal levels. Among RA patients with extremely high, high and normal soluble GITRL levels, no significant differences were found in disease duration, disease activity, levels of CRP and treatment

Conclusion: Soluble GITRL exists in serum of patients with collagen-vascular diseases, particularly with RA and the levels of which were extremely elevated in RA patients. GITR/GITRL system including soluble GITRL might be involved in the development of RA, although further investigations are required.

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Biomarkers in Early Rheumatoid Arthritis: Analysis of the Diagnostic Performance. Donatello Pietrapertosa, Barbara Tolusso, Silvia L. Bosello, Anna L. Fedele, Maria C. Papalia, Elisa Gremese and Gianfranco Ferraccioli, Division of Rheumatology – Catholic University of the Sacred Heart, Rome, Italy

Purpose: To test if a combination of biomarkers can increase the classification power of autoantibodies to cyclic citrullinated peptides (anti-CCP) in the diagnosis of early rheumatoid arthritis (ERA).

Method: We tested the levels of anti-CCP2 antibodies, Anti-MCV antibodies, rheumatoid factor (RF) IgM and IgA, Interleukin-6 (IL-6), ESR and CRP by ELISA in serum samples from 83 patients with ERA and 132 control subjects (80 with undifferentiated arthritis and 52 healthy controls). To evaluate the diagnostic performance of different assays, receiver operating characteristic (ROC) curves were constructed. For every parameter we obtained sensitivity and specificity along with 95% confidence interval (95% CI). Differences were tested with McNemar test.

Results: The sensitivity of the bio-markers was evaluated in a panel with cut-offs determined at 95% specificity. When individual tests were considered, sensibility for ERA was highest for the anti-CCP2 (66.7%, 95%CI: 55.3-76.8) and anti-MCV (64.6%, 95%CI: 53.0-75.0), followed by IL-6 (41.5%, 95%CI: 30.7-52.9), RF-IgM (35.1%, 95%CI: 24.5-46.8%), RF-IgA (32.5%, 95%CI: 22.2-44.1), ESR (31.9%, 95% CI: 21.4-44.0) and CRP (16.7%, 95% CI: 8.9-27.3). The difference between anti-CCP2 and anti-MCV was non significant (p=1.0), and both were significantly better than the IL-6 (p<0.01), RF-IgM (p<0.001), RF-IgA (p<0.001), ESR (p<0.001) and CRP (p<0.001).

The combination of markers (at least one of both positive) of anti-CCP2 antibodies and anti-MCV gave a sensitivity of 73.3% (95%CI: 62.7-83.0) and a specificity of 90.3% (95%CI: 84.0-94.7). The combination of anti-CCP2 antibodies and IL-6 gave a sensitivity of 79.0% (95%CI: 68.5-87.3) and a specificity of 90.4% (95%CI: 84.1-94.8). When the other marker combinations along with anti-CCP2 were considered, sensitivity for ERA ranged from 68.7% (RF-IgM) to 74.7% (ESR).

The combination of anti-MCV antibodies and IL-6 gave a sensitivity of 77.2% (95%CI: 66.4-85.9) and specificity of 89.4% (95%CI: 82.8-94.1). When the other marker combinations along with anti-MCV were considered, sensitivity for ERA ranged from 70.1% (RF-IgM) to 77.0% (ESR).

The best marker combination of anti-CCP2 and IL-6 resulted in a significantly sensitivity gain of 12.3% (p=0.001) at a minor loss in specificity of 4.6% compared with anti-CCP as the best single marker. Specificity was significantly higher for the combination of anti-MCV and IL-6 compared with anti-MCV as a single bio-marker (p=0.004).

Conclusion: The inflammation marker IL-6 in support of anti-CCP or anti-MCV has the highest classification power for the diagnosis of early RA.

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Stepwise Development of a Multi-Protein Biomarker Index of RA Disease Activity. Y. Shen[1], N. Knowlton[2], M. Turner[3], C. Sutton[4], D. Smith[4], D. Chernoff[1], L. Hesterberg[1], R. Roubenoff[5], N.A. Shadick[6], M. E. Weinblatt[6], G. Cavet[1] and M. Centola[3], [1]Crescendo Bioscience, So. San Francisco, CA, [2]NSK Statistical Solns, LLC, Oklahoma City, OK, [3]OMRF, Oklahoma City, OK, [4]Crescendo Bioscience, Oklahoma City, OK, [5]Biogen-Idec, Cambridge, MA, [6]Brigham & Women's Hosp, Boston, MA

Purpose: Studies such as TICORA, CAMERA and FinRACO suggest frequent quantitative monitoring of disease activity with resulting treatment changes improves patient outcomes. ACR and EULAR also recommend ongoing disease activity assessment. Current monitoring tools, while useful for longitudinal tracking, are suboptimal; laboratory tests such as ESR and CRP are non-specific and do not reflect the heterogeneous biology of RA, while symptom-based measures are subjective and have low reproducibility. We are developing a multi-protein biomarker index of RA disease activity using a rigorous, stepwise development program that comprehensively surveys the biological pathways underlying RA.

Method: Candidate serum protein biomarkers were selected from an extensive screen of literature, databases, and experimental data. Quantitative assays for 141 proteins were optimized for reproducibility, RF blocking, sensitivity, and dynamic range, resulting in 121 measurable proteins in RA patient serum.

Three serial studies were performed - only proteins with the strongest associations to disease activity continued to the next. The first study examined 121 proteins in 128 samples, the second 65 proteins in 320 samples, and the third 21 proteins in 255 samples. Associations between candidate biomarker levels and disease activity were assessed using univariate and multivariate statistics and a range of disease activity measures (including joint counts, DAS28ESR, DAS28CRP, CDAI and patient-reported outcomes). Major clinical covariates such as CCP status and treatment were taken into account by inclusion in statistical modeling and by analyzing patients by disease subtype.

Results: The 3 studies were progressively more enriched for proteins associated with disease activity. 8% of proteins had univariate correlations with DAS28 in the first study, 51% in the second and 60% in the third. The top 21 proteins, selected on the basis of univariate multivariate modeling, represent a diverse set of biological pathways implicated in RA pathogenesis. Statistical models with 4-11 protein biomarkers outperformed any individual biomarker at estimating disease activity. These models achieved average accuracy of 70% for assigning patients into low and high disease activity categories, and average correlations of 0.6 with DAS28 in 100 iterations of cross validation. Models developed in one cohort performed well in independent cohorts (correlation of 0.58-0.6 with DAS28).

Conclusion: Serum protein biomarkers contain biologically rich information reflecting RA disease activity. A robust, stepwise development path, using large cohorts from across the spectrum of care, increases likelihood of successfully validating a multi-marker assay. Developing a validated disease assessment biomarker in RA will enhance current measures and can provide value for patient care and outcomes.

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Prognostic Factors of Radiological Progression in Rheumatoid Arthritis: a 10-Year Observational Study. Theodora E. Markatseli[1], Yannis Alamanos[2], Paraskevi V. Voulgari[3] and Alexandros A. Drosos[4], [1]Trainee in Rheumatology, Ioannina, Greece, [2]Associate Professor of Hygiene and Epidemiology, Patras, Greece, [3]Assistant Professor of Rheumatology, Ioannina, Greece, [4]Ioannina Medical School, Ioannina, Greece

Purpose: To describe predictive factors of radiological damage at 10-year follow-up in rheumatoid arthritis (RA) patients.

Method: The disease course and outcome of 144 patients, with RA and with X-rays of the hands and the wrists available at baseline and at 5 and at 10 years, were studied, in order to identify predictive factors of radiological outcome. Radiographs were scored using Larsen's criteria. Baseline parameters were initially tested in univariate analysis, and then those presenting a statistically significant association with Larsen score at 10 years were included in a logistic regression model in order to determine relevant independent prognostic factors.

Results: A significant reduction of disease activity score for the 28 joint indices (DAS-28) was noted ($p<0.0001$), associated with a decrease of acute-phase reactants along the three time points in our cohort ($p<0.0001$). On the contrary, Larsen score was increased from 15.3 ± 11.5 at baseline to 25.9 ± 13.7 and 35 ± 17.3 at 5 and at 10 years respectively. The number of erosive joints was also increased from 1.6 ± 2.3 at baseline to 3.3 ± 2.9 and 4.8 ± 3.9 at 5 and at 10 years respectively. At 10 years, 18 (12.5%) patients had no erosions, while 126 (87.5 %) patients had at least one eroded joint and 63 (43.8%) presented with at least five eroded joints. The average annual progression rate was 2.13 ± 1.28 points/year between baseline and five years, and 1.81 ± 1.34 points/year between five and 10 years. Among the clinical and laboratory parameters at 10 years, a significant association with Larsen score was found only with rheumatoid nodules and C-reactive protein (CRP). Larsen score at 10 years was negatively correlated with grip strength. The time-average values of swollen joint count (SJC), erythrocyte sedimentation rate (ESR) and CRP over 10 years were also associated with the final Larsen score. In the univariate analysis, Larsen score at 10 years was significantly associated with baseline radiographic parameters (Larsen score and the number of erosive joints), the presence of autoantibodies [anti-cyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) of IgA and IgM isotype], and disease duration. In the logistic regression analysis Larsen score and the number of erosive joints, as well as anti-CCP antibodies presented a significant and independent association with Larsen score at 10 years.

Conclusion: Despite the clinical improvement, the radiological progression continues over the time due to the underlying inflammatory process. Baseline radiographic damage and autoantibodies constitute the main predictive factors of poor radiological outcome in long term.

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Radiographic Severity of Rheumatoid Arthritis in African-Americans: Results From the CLEAR Registry. S. Louis Bridges Jr.[1], Zenoria L. Causey[1], Paula I. Burgos[1], Laura B. Hughes[1], Maria I. Danila[1], Amalia van Everdingen[2], Stephanie Ledbetter[1], Doyt L. Conn[3], Ashutosh Tamhane[1], Andrew O. Westfall[1], Beth L. Jonas[4], Leigh Callahan[4], Edwin A. Smith[5], Richard Brasington[6], Larry W. Moreland[7], Graciela S. Alarcon[8] and Désirée M.F.M. van der Heijde[9], [1]University of Alabama, Birmingham, AL, [2]Medical Center Haaglanden, The Hague, Netherlands, [3]Emory Univ Schl of Med, Atlanta, GA, [4]University of North Carolina, Chapel Hill, NC, [5]Medical University of SC, Charleston, SC, [6]Washington Univ Schl of Med, St Louis, MO, [7]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Leiden University Medical Center, Leiden, Netherlands

Purpose: To describe radiographic changes in African-Americans with rheumatoid arthritis (RA) from the CLEAR (Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis) registry, a multicenter observational study.

Methods: RA patients, self-declared African-American were enrolled in CLEAR I (n=357), a longitudinal (disease duration <2 years) cohort from 2000 to 2005, and CLEAR II (n=418), the cross-sectional arm of the registry, from 2006 to the present. Demographic, clinical and radiographic data were obtained. Sets of hand/wrist and foot radiographs were scored for erosions; joint space narrowing (JSN), and total radiographic score using the modified Sharp/van der Heijde scoring system.

Results: Data from CLEAR I and CLEAR II were examined. For the CLEAR I cohort 294 patients had a mean radiographic score of 2.89 at the baseline visit; 32.0% showed either erosions (25.9%) or JSN (19.4%). At the 36-month visit the mean score was 5.65; 44.2% had erosions, 41.5% JSN and 55.4% had either. Among those patients without radiographic damage at baseline, 18.9% had progressed at the 36-month visit, compared to 57.1% of those with baseline damage ($p<0.0001$) and the risk ratio with baseline damage versus no baseline

damage was 3.02 (95% CI: 1.86 -4.88). For the CLEAR II cohort of 167 patients with RA of any duration, 65.3% exhibited joint erosions, 65.3% JSN and 74.8% exhibited either. The mean radiographic score was 33.42. These data are shown in Table 1.

Conclusion: This is the largest radiographic study of RA patients of African American ancestry. Damage occurs early in the disease course and it is associated with radiographic progression at 3 years of disease duration.

Table 1. Radiographic* Findings for Patients in the CLEAR I (Baseline, 36 month and 60 months) and CLEAR II (Baseline).

	Number of patients	**Sharp van der Heijde Score**	
	(%)	**Mean (SD)**	**Median (IQ 25-75))**
CLEAR I †			
Baseline (n=294)			
Joint Erosions	76 (25.9)	1.24 (3.68)	0.0 (0-1)
Joint Space Narrowing	57 (19.4)	1.65 (4.73)	0.0 (0-0)
Total Score	94 (32.0)	2.89 (7.65)	0.0 (0-2)
36 months (n=147)			
Joint Erosions	65 (44.2)	2.22 (5.72)	0.0 (0-2)
Joint Space Narrowing	61 (41.5)	3.44 (6.64)	0.0 (0-4)
Total Score	80 (54.4)	5.65 (11.14)	0.0 (0-6)
60 months (n=39)			
Joint Erosions	15 (38.5)	4.74 (12.78)	0.0 (0-4)
Joint Space Narrowing	18 (46.2)	7.87 (13.12)	0.0 (0-12)
Total Score	21 (53.8)	12.62 (24.95)	0.0 (0-16)
CLEAR II (n=167)‡			
Joint Erosions	109 (65.3)	14.68 (23.84)	4.0 (0-18)
Joint Space Narrowing	109 (65.3)	18.74 (26.48)	7.0 (0-24)
Total Score	125 (74.8)	33.42 (48.89)	11.0 (0-41)

*Sharp van der Heijde; † Follow up totals differs from baseline due to loss to follow up and patients who need to reach the time for the visits, ‡ Study enrollment ongoing**.**

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Which Subgroups Are at Higher Risk of Rapid Radiographic Progression in Early Rheumatoid Arthritis: Results From SONORA Study. Claire Bombardier[1], Maggie H. Chen[1], Xiuying Li[1], Peter K. Gregersen[2] and Désirée M.F.M. van der Heijde[3], [1]University Health Network, Toronto, ON, [2]Feinstein Institute for Medical Research, Manhasset, NY, [3]Leiden University Medical Center, Leiden, Netherlands

Purpose: Identifying patients with rheumatoid arthritis at high risk for radiographic progression is critical to making appropriate treatment decisions. Data from SONORA (study of new-onset rheumatoid arthritis) was analyzed to explore a prediction model for the high risk of radiographic progression in early rheumatoid arthritis (RA) patients.

Method: A total of 994 patients diagnosed as early RA (symptoms ≥3 and ≤12 months) by a board-certified rheumatologist across North America were recruited in this study. Hand radiographs were obtained at baseline, year 1 and year 2 and scored according to original Sharp method (range 0 to 280) in random order per patient. Radiographic progression was defined by a change of at least 3.2, 2.9 and 3.4 in the erosion score, narrowing score and total Sharp score, respectively[1]. The continuous risk factors were included in the model as categorical variables, which includes CRP (<0.6, 0.6-3 or >3mg/dl), swollen joint count (<10, 10-17, or <17), Rheumatoid factor (≤20 or >20), anti-CCP (≤20 or >20) and baseline sharp score (0, 0-5, 5-10 or >10). Univariate models were used to identify the risk factors for radiographic progression. General estimation equation (GEE) model controlling for disease activity score, baseline sharp score, CRP and anti-CCP was used as the prediction model to identify the subgroups for high risk of radiographic progression.

Results: Patients had a mean age 53 years (SD, 14.81), 72% female and 90% Caucasian with mean disease durations 170 (180) days. The Sharp Score was 5.49 (7.85), 6.38 (8.90) and 6.17 (8.65) at baseline (N=746), year 1 (n=756) and year 2 (n=567) respectively. Among these patients, radiographic progression was observed in 14.7% of the patients at year 1 and 19.4% at year 2. The multivariate GEE model with repeated binary outcomes at year 1 and 2 revealed that a subpopulation with CRP>3mg/dL, baseline sharp score >10, anti-CCP>20 are those ones at highest risk of radiographic progression for early RA patients at year 1 and 2. More details in table 1.

Conclusion: Radiographic progression of RA remains the best method of assessing structural damage associated with the disease. This model predicts the risk of radiographic progression using easily accessible clinical and laboratory variables. These identified subgroups can help guide rheumatologists in making treatment decisions for early RA patients.

Table 1:

Risk factors	Odds ratio	95% CI of OR	P-value
DAS28 (continuous)	1.21	(1.05,1.38)	0.0057
Baseline sharp score >10 vs. 0	3.53	(1.65,7.39)	0.0011
Baseline sharp score >10 vs. 0-5	2.72	(1.49,4.95)	0.0011
Baseline sharp score >10 vs. 5-10	1.43	(0.74,2.77)	0.281
CRP >3 vs. <3	1.65	(1.06,2.51)	0.03
Anti-CCP >20 vs. <20	2.67	(1.67,4.31)	<0.0001

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Wrist MRI After 2 Years Treatment of Early Aggressive RA. Veena K. Ranganath[1], Kambiz Motamedi[1], Espen A. Haavardsholm[2], Paul Maranian[3], David Elashoff[3], Fiona M. McQueen[4], Jeffrey Curtis[5], L W. Moreland[6], Stacey S. Cofield[5], Weiling Chen[1] and HE Paulus[1], [1]UCLA, Los Angeles, CA, [2]Department of Rheumatology, Oslo, Norway, [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, [4]University of Auckland, Auckland, New Zealand, [5]The University of Alabama at Birmingham, Birmingham, AL, [6]U Pittsburgh, Pittsburgh, PA

Purpose: Remission is the current goal of RA therapy, but erosive damage may progress despite meeting criteria for clinical remission. Objective: Evaluate relationship of clinical remission criteria to MRI inflammatory scores after 2 or more years of aggressive treatment of RA.

Methods: MRI with gadolinium contrast (1.5 Tesla) of the dominant wrist was obtained 0 to 33.5 months (Mean 5.4) after completing a 2-year controlled clinical trial comparing various combinations of MTX, etanercept, hydroxychloroquine, and sulfasalazine in 115 early (RA duration 4.1 ± 10.8 months) seropositive or erosive RA patients. DAS28/ESR were recorded every 12 weeks during the trial and at the time of MRI. Two experienced readers scored MRIs for tenosynovitis (T: range 0-30), synovitis (S: 0-9), bone marrow edema (BME: 0-42), and erosions (E: 0-140) using published RA MRI (RAMRIS) and tenosynovitis scoring methods; averages of the 2 scorers were used for analysis.

Results: Mean ± SD (subjects with "0" score): S 3.5 ± 1.3 (0); T 5.2 ± 2.7 (3); BME 2.6 ± 4.2 (32); E 10.6 ± 10.7 (0). Significant (Spearman) correlations at time of MRI: DAS with T: r = 0.26. Mean DAS over year 1, year 2, or years 1 and 2, and number of days of sustained DAS remission before the MRI did not correlate significantly with the MRI scores.

Description of Patients by DAS Remission and MRI Inflammatory Scores

	Never in Remission	Ever in Remission (Not Continuous)	Continuous DAS 2.4 R ≤ 1yr
Number of Patients (Total = 115)	34	46	21
DAS 2.4 Remission at time of MRI, N (% of total)	0	0	21 (18.9)
Total Months Ever in Remission (median, range)	0	5.7 (2.4, 19.2)	9.6 (2.4, 21.6)
Index wrist - swell or tender, N (% of category)	6 (19.4)	14 (33.3)	4 (19.1)
Number of Patients in MDA (% of category)	7 (20.6)	15 (35.7)	21 (100)
MRI Scores at MRI, mean/SD (# w/ 0 score)			
Tenosynovitis (T)	5.7/2.3 (1)	5.2/2.7 (1)	5.5/3.3 (1)
Synovitis (S)	3.9/1.4 (0)	3.3/1.4 (0)	3.3/0.98 (0)
Bone Marrow Edema (BME)	3.7/6.5 (8)	2.2/2.9 (14)	1.9/2.5 (7)
Erosions (E)	13.4/14.8 (0)	9.9/10.4 (0)	8.5/6.2 (0)
Composite (T + S + BME)	13.2/9.1 (0)	10.7/4.8 (0)	10.6/4.3 (0)
*p value <0.001 comparing patients never in remission compared with those with sustained remission >1yr MDA= Minimal Disease Activity, DAS<2.85			

Conclusion: After 2 years of aggressive treatment of early seropositive RA, 80% of patients had no pain/tenderness or swelling of the examined wrist, about half had MDA, and some met clinical criteria for DAS28 remission. The duration of clinical remission did not correlate with lower MRI scores. Thus, despite aggressive therapy for at least 2 years, patients were not devoid of evidence of synovitis, tenosynovitis, and bone marrow edema even among people in DAS28 remission.

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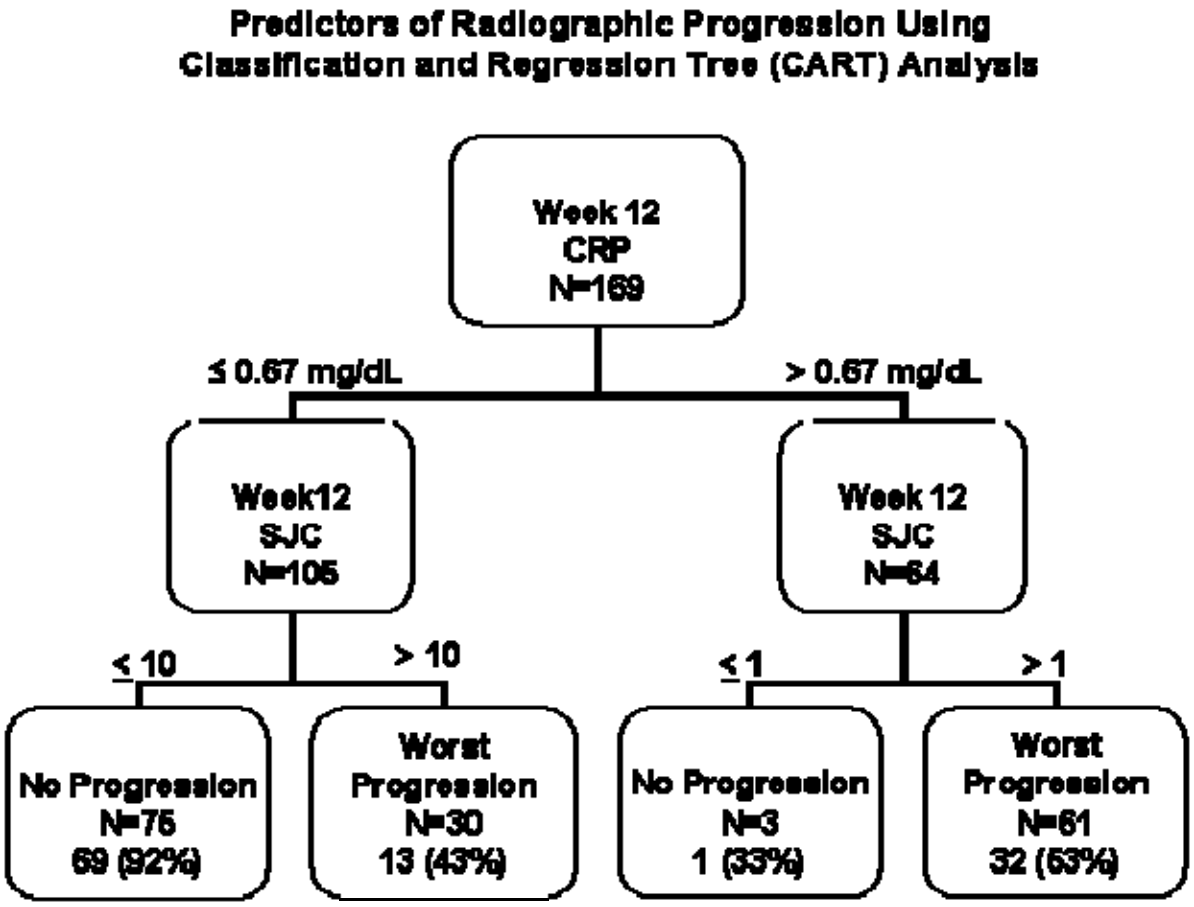
Predictors of Radiographic Progression in Rheumatoid Arthritis Patients Treated with Methotrexate. Michael E. Weinblatt[1], Edward C. Keystone[2], Marc D. Cohen[3], Bruce Freundlich[4], Juan Li[5], Yun Chon[5] and Scott Baumgartner[5], [1]Brigham and Women's Hospital, Boston, MA, [2]Professor of Medicine/University of Toronto, Toronto, ON, [3]National Jewish Medical Ctr, Denver, CO, [4]Wyeth Research, Collegeville, PA, [5]Amgen, Thousand Oaks, CA

Purpose: To identify prognostic markers associated with radiographic progression at 52 weeks in patients with rheumatoid arthritis (RA) after 12 weeks of methotrexate (MTX) therapy.

Method: The study population consisted of patients from the MTX arm of the Trial of Etanercept and Methotrexate with radiographic Patient Outcomes (TEMPO). Logistic regression analysis was used to identify possible predictors of week 52 radiographic outcome (modified total Sharp score) from clinical and laboratory assessments performed at week 12 of MTX therapy. Classification and regression tree (CART) modeling of the week 12 assessments was used to further determine the subgroups of patients with the best and worst radiographic outcomes.

Results: A total of 169 patients were analyzed. Based on logistic regression analysis, C-reactive protein (CRP) level, erythrocyte sedimentation rate, tender joint count, swollen joint count (SJC), and health assessment questionnaire scores at week 12 were significant predictors of radiographic progression at week 52 ($p < 0.05$ for each assessment). CART modeling showed that patients with CRP > 0.67 mg/dL and SJC > 1, or CRP ≤ 0.67 mg/dL and SJC > 10, at week 12 were likely to show the worst radiographic progression at week 52 (see Figure). The CART model had a sensitivity of 85%, specificity of 60%, and overall classification accuracy of 68%.

Conclusion: In patients with RA, CRP and SJC after 12 weeks of MTX therapy emerged as the best predictors of radiographic progression at week 52.



Disclosure: M. E. Weinblatt, Amgen, 5, Wyeth Pharmaceuticals, 5 ; **E. C. Keystone**, Abbott Laboratories, Amgen, AstraZeneca, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc, Novartis Pharmaceutical Corporation, Schering-Plough, UCB, Wyeth Pharmaceuticals, 2, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc., Genentech, Inc., GlaxoSmithKline, Schering-Plough, UCB, Wyeth Pharmaceuticals, 5, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Reserch and Development, Inc., Hoffmann-La Roche, Inc., Genentech, Inc., Schering-Plough, Wyeth Pharmaceuticals, 8 ; **M. D. Cohen**, Genentech., 5, Abbott , 5, UCB, 5, Wyeth , 5, Amgen, 5 ; **B. Freundlich**, Wyeth , 3 ; **J. Li**, Amgen, 3, Amgen, 1 ; **Y. Chon**, Amgen, 3, Amgen, 1 ; **S. Baumgartner**, Amgen, 3, Amgen, 1 .

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Baseline RANKL:OPG Ratio and Markers of Bone and Cartilage Degradation Predict Annual Radiological Progression Over 11 Years in Rheumatoid Arthritis. L.H.D. van Tuyl[1], A.E Voskuyl[1], M. Boers[1], P.P.M.M. Geusens[2], R. Landewé[2], B.A.C. Dijkmans[1] and W.F. Lems[3], [1]VU University Medical Center, Amsterdam, Netherlands, [2]University Hospital Maastricht, Maastricht, Netherlands, [3]VUmc, Amsterdam, Netherlands

Purpose: Traditional predictors of radiological progression in rheumatoid arthritis (RA) are mostly markers of inflammation. We investigated to what extent baseline measurements of the ratio of receptor activator of nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG) and C-terminal cross linking of type-I and type-II (CTX-I and CTX-II) in addition to traditional markers of disease severity, could predict annual radiological progression.

Method: A cohort of 155 early, active, untreated RA patients that participated in the COBRA trial was followed for 11 years. Urine was sampled at baseline and after 3 months from start of treatment and analyzed for CTX-I and CTX-II. Baseline serum samples were analyzed for RANKL and OPG. Available traditional markers of disease severity included baseline measurements of erythrocyte sedimentation rate, rheumatoid factor and baseline radiological damage. A digital database of frequent radiographs was available, scored according to the

Sharp/van der Heijde method. Individual annual progression rates were calculated and used as outcome variable. Multiple linear regression analyses identified the strongest predictors of annual radiological progression.

Results: In multivariable analyses the RANKL:OPG ratio and CTX-I or CTX-II proved to be independent predictors of annual radiological damage over 11 years. The prediction of annual radiological progression was strongest when the RANKL:OPG ratio and CTX1 or CTX2 were evaluated in the same model (36 to 39% explained variance). Adding the effect of treatment at 3 months to the baseline models improved the predictive ability of the models up to 44 to 46%.

Conclusion: Unfavorable baseline levels of the RANKL:OPG-ratio as well as CTX-I (markers of bone resorption) and CTX-II (a marker of predominantly cartilage degradation) in patients with early, active, untreated RA are strong independent predictors of rapid and persistent damage progression over 11 years follow up. Early improvement in bone markers on treatment predicts a better outcome.

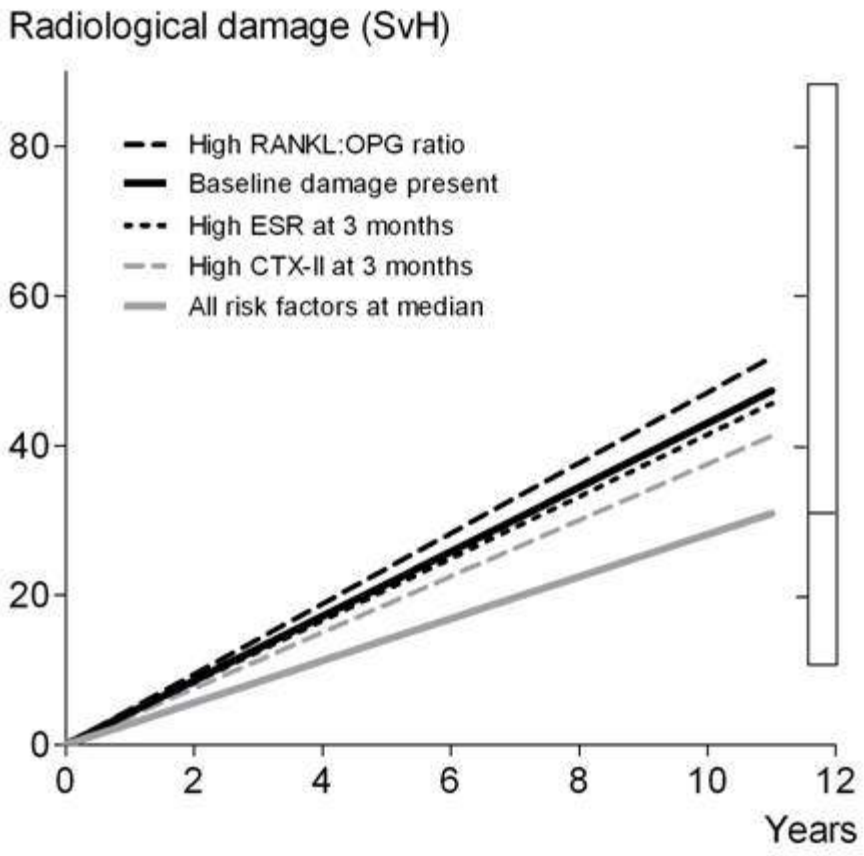

Figure 1*: Radiological progression over 11 years for patients with either an unfavourable RANKL:OPG ratio, ESR level, CTX-II level or baseline damage . This figure is created using the estimations of the model including CTX-II and the RANKL:OPG ratio, predicting 46% of variation in radiological progression determined by a high baseline RANKL:OPG ratio, high ESR at 3 months, high CTX-II at 3 months and presence of baseline damage. The graph shows the radiological progression for the model with one variable at the 90th percentile of the distribution and the other 3 variables at their median value. For example, the highest dotted line represents the radiological progression when CTX-II at 3 months and ESR at 3 months are at their median, baseline damage is absent, but the RANKL:OPG ratio is at its 90th percentile. The vertical box on the right represents the distribution from the 25th to 75th percentile of radiological damage 11 years after inclusion in the COBRA trial, if every patient would have started with zero baseline damage.*

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Identification of SNPs Associated with Severe Articular Damage in Patients with Rheumatoid Arthritis. N. Oreiro[1], J. C. Fernández-López[1], J. del Amo[2], J. Mulero[3], A. Balsa[4], R. Cáliz[5], R. Sanmartí[6], F.G. Martínez[7], D. Tejedor[2], M. Artienda[2], J.L. Andreu[3], L. Silva[3], D. Pascual-Salcedo[4], M.D. Collado[5], E. Graell[6], L. Simon[2], A. Martínez[2] and F.J. Blanco[1], [1]Complexo Hospitalario Universitario A Coruña, Coruña, Spain, [2]Progenika Biopharma S.A., Bilbao, Spain, [3]Hospital Puerta de Hierro, Madrid, Spain, [4]Hospital La Paz, Madrid, Spain, [5]Hospital Virgen de las Nieves, Granada, Spain, [6]Hospital Clinic, Barcelona, Spain, [7]Hospital Reina Sofía, Córdoba, Spain

Purpose: Rheumatoid Arthritis (RA) is an inflammatory disease with a very different course in patients. It would be very useful to identify patients at high risk of poor outcome because an early and aggressive treatment could be indicated.

Aim: To study the association of genetic polymorphisms with articular damage (erosions and articular surgery) in RA patients.

Methods: Patients from 6 rheumatology divisions were included in the study. Inclusion criteria were: a) 1987 ACR criteria for RA, b) RA should have started after 1990, c) >5 years of follow-up, d) Onset disease age >18, and e) Caucasian origin. Baseline clinical and analytical variables were collected. As main clinical endpoints, 3 radiographic patterns were defined: RX1: Space narrow and multiple erosions in hands and feet. RX2: Multiple erosions in hands and feet. RX3: Multiple erosions in hands or feet. Joint replacement information was also collected. All patients signed an informed consent. We have developed a DNA microarray that allows the simultaneous detection of 69 SNPs in 49 genes, which have been selected by they potential impact in RA, according to the published literature.

Results: In total 632 patients (465F/167M) were included. From all patients, 129 underwent prosthesis surgery, and the radiographic patterns RX1, RX2 and RX3 were present in 163, 182, and 275 RA patients respectively. Baseline number of painful joints, anti-CCP titers, ESR, RF, and CRP, were all significantly associated with the development of severe articular damage. In addition, carriers of the minor allele of 2 SNPs in SCGB1A1 and MMP-3 genes were more frequent in RA with bone erosions in hand and/or feet (Table 1). In contrast, carriers of the minor allele at 2 SNPs in PDCD1 and IL4R genes were less frequent in patients with articular damage, indicating a protective effect. The statistical analysis also showed that the frequency of homozygous for the minor allele at 2 SNPs in SLC22A4 and SCGB1A1, was higher in patients with articular prosthesis.

Table 1: Univariate analysis of 69 SNPs in 632 patients with RA: SNPs associated to articular damage

Phenotype	Rs ID	Gene	SNPs	Genotype	OR	I.C.95 %	P-value
RX1 Pattern							
	rs3741240	SCGB1A1	A587G	GA or AA	1,5	1,1-2,2	0,02
RX2 Pattern							
	rs3741240	SCGB1A1	G587A	GA or AA	1,6	1,1-2,3	0,01
	rs3025058	MMP3	113-/A	-A or AA	1,5	1,0-2,3	0,04
RX3 Pattern							
	rs2227981	PDCD1	C872T	TT	0,4	0,3-0,7	<0,01

	rs1801275	IL4R	A1969G	AG or GG	0,7	0,5-0,9	0,02
Surgery							
	rs1050152	SLC22A4	C1672T	TT	1,8	1,2-2,9	<0,01
	rs3741240	SCGB1A1	A587G	AA	1,7	1,0-2,9	0,04

Conclusion: We report the association of 5 SNPs with severe articular damage in RA patients. Genetic information, together with other baseline clinical parameters, might be useful to identify patients at high risk of highly erosive RA.

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USING VFA to Assess the Prevalence of Vertebral Fractures IN PATIENTS with RHEUMATOID ARTHRITIS: A Case Control Study. Mirieme Ghazi, Sami Kolta, Karine Briot, Simon Paternotte, Maxime Dougados and Christian Roux, Paris-Descartes University, Paris, France

Purpose: Generalized osteoporosis is a well-known complication of rheumatoid arthritis (RA). Clinical consequences of vertebral fractures (VF) in osteoporotic patients are more and more recognized. Vertebral Fracture Assessment (VFA) technology is a convenient method to assess vertebral deformities, with lower radiation and lower costs than standard X-rays.

Objective: To calculate the prevalence of vertebral fractures in female patients with RA using VFA, and to assess risk factors for VF.

Method: Consecutive patients (N= 80, 56.4± 14.7 years, mean RA duration 16 ± 10years) attending the Rheumatology Department were recruited in the study. Clinical, biological status was assessed by Erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor, health assessment questionnaire, DAS28, and duration of RA. Controls (N= 240) were randomly selected from the general population and were individually matched to each case for age. For both patients and controls, information on general health status, height, weight, smoking habits, history of fracture, and use of oral glucocorticoids, was collected. Bone mineral density was measured by DXA and osteoporosis defined as T score< -2.5 at either spine or hip. Vertebral fractures were defined using VFA during the same exam.

Results: 22.5% and 4.17% of patients and controls had a vertebral fracture respectively. Compared with controls, patients with RA had an increased risk of vertebral fracture: OR [IC 95%]: 6.7 [3.2; 13.8]. Prevalence of non vertebral fractures (low trauma) in RA was 26.25%. Prevalence of osteoporosis was 53.75% and 10.42% in patients and controls respectively. Factors associated with osteoporosis were age, use of steroids, duration of menopause, and prevalent peripheral fractures. Vertebral fractures were associated with age, duration of menopause, prevalent peripheral fractures, and prevalent arthroplasty. No other indicator of RA severity or activity was associated with presence of vertebral fractures. 48.75% patients with RA were receiving anti osteoporotic treatment. By multiple regresion, the presence of vertebral fractures was independently associated only with age (OR=1.13 [1.06; 1.22] and prevalent peripheral fractures (OR= 7.47[1.79; 31.11].

Conclusion: The prevalence of vertebral fractures is 22.5% in our population with RA. RA is a strong risk factor of such fractures (OR= 6.7). Few parameters predict these fractures in this population. Because of the consequences of these fractures, VFA should be a routine procedure in RA.

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Hand Bone Densitometry and Bone/Cartilage Markers Failed to Predict Erosion Progression at 5 Years in the Conservatively Community-Based Inceptive Vera (Very Early Arthritis) Cohort. Anne Letierce Vanlerberghe[1], Alain Daragon[2], Michel Brazier[3], Mary Jan[4], Thierry Lequerré[5], Othmane Mejjad[2], Patrick Boumier[6], Alain Gayet[7], François Tron[8], Charles Zarnitsky[9], Olivier Vittecoq[10], Patrice Fardellone[11] and Xavier Le Loët[12], [1]CHU-Hôpitaux de Rouen, France, [2]CHU Hôpitaux de Rouen, France, [3]France, [4]CHU, Rouen, France, [5]CHU Hôpitaux de Rouen, Rouen, France, [6]CHU Amiens, France, [7]CHU de Rouen-Hôpitaux de Rouen, France, [8]INSERM U 905, Rouen, [9]CH Le Havre, France, [10]Rouen, France, [11]CHU d'Amiens, France, [12]CHU Rouen - INSERM U 905, France

Purpose: Ability of bone and cartilage markers and hand bone densitometry to predict progression of structural damage at 5 years in patients with very early arthritis.

Method: Community -based- recrutment (media campaigns) of 310 adults (mean age : 51.8 years ; 68% females) with swelling of 2 or more joints persisting more than 4 weeks, evolving for less than six months (mean : 4.2 months), DMARD and steroids naïve. Then, they were conservatively treated for 5 years. Assessment was made at entry and comprised clinical data (global pain, Ritchie index and swollen joints / 44), CRP, ESR, auto antibodies rheumatoid factors (RF) by agglutination tests and IgM, IgA, IgG, isotypes by Elisa, anti-CCP II, serum pyridinoline (PYD) deoxypyridinoline (DPD), sCTX-I, Cartilage Oligométric Matrix Protéin (COMP), osteoprotegerin (OPG), RANKL, and DKK1. Hand bone densitometry by DXA was performed on both hands every year. All patients with Rheumatoid Arthritis or undifferentiated arthritis were followed but not those classified as having defined rheumatism (DR). Criterion of judgment was progression of erosion score with an increase of at least 1 unit at 5 years (measurement was done according to vdH modified erosion Sharp score by two readers).

Results: At 5 years, 140 patients were assessed (64 refused, 10 lost of follow-up; 5 death, 87 classified as DR, 4 with X ray failure) : 46 (33%) had erosion progression. With univariate analysis, there was a relationship between erosion progression and baseline value of VS (p=0.03), IgA, IgG, IgM FR (p = 0.001), anti-CCP II (p = 0.001), COMP (p= 0,02) and sCTX-I (p=0.001). But OPG, RANKL, OPG/RANKL, DKK1, PYD, DPD, CRP and bone mineral density were not associated with erosion progression. With multifactorial analysis, only anti-CCP II and IgA FR were associated with structural damage. Hand bone mineral density decreased more in the group with erosion progression during the first year, and was correlated with progression of Sharp score within the 5 years.

Conclusion: In patients with very early arthritis, conservatively treated, anti-CPP II and IgA RF are useful to identify patients with structural damage progression at 5 years. sCTX-I and COMP could be also useful, but are associated with RF. Hand bone densitometry could be used within the first year to predict structural progression at 5 years. These patients with structural damage progression could benefit from early aggressive treatment.

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Moderate Agreement On the Assessment of Rheumatoid Synovitis Among 18F-FDG-PET, Contrast-Enhanced MRI, and Clinical Examination. Noboru Hagino[1], Tetsuji Sawada[2], Miwako Takahashi[3], Harushi Mori[3], Keishi Fujio[4], Kimito Kawahata[4], Toshimitsu Momose[3], Kuni Ohtomo[3] and Kazuhiko Yamamoto[4], [1]Hospital of the University of Tokyo, Tokyo, Japan, [2]Tokyo Medical University, Shinjuku Tokyo, Japan, [3]Graduate School of Medicine, the University of Tokyo, Tokyo, Japan, [4]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Purpose: 18F-FDG PET imaging is reported to reflect active synovitis in RA, although clinical significance of 18F-FDG PET imaging in the assessment of RA activity is yet to be determined. This study was performed to assess the utility of 18F-FDG PET for visualizing active rheumatoid synovitis, comparing with clinical examinations, serological markers, and contrast-enhanced MRI of the wrist and hand.

Method: We prospectively studied 20 RA patients. Two independent rheumatologists (NH and TS) assessed each patient clinically, and calculated disease activity score that include 28-joint counts (DAS28). Serological data including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and matrix metalloproteinase-3 (MMP-3) were measured. In each patient, the knees, the wrists, the carpometacarpal (CMC) joints and the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, the elbows, and the shoulders were imaged with 18F-FDG PET. PET data were analyzed by visual interpretation of radiologists (MT and TM), and 18F-FDG uptake was quantified using the standardized uptake value (SUV).

All patients underwent gadolinium-enhanced MRI of the wrist and hand. MR-images were scored according to the OMERACT-RAMRIS scoring system.

Results: Patients are all female, with mean age 52.3 (range 37-70). Mean disease duration of RA was 9.2 years (range 1-24). Three patients used infliximab, and another 3 patients used etanercept. All other patients were on conventional DMARDs. The mean DAS28-ESR and DAS28-CRP were 4.22 and 3.41 respectively. The joints showing significant uptake of 18F-FDG corresponded moderately with swollen joints on examination with a kappa-coefficient of 0.52. The existence of synovitis of grade 2 or more in contrast-enhanced MRI also showed moderate agreement with the significant uptake of 18F-FDG (kappa coefficient 0.45). There was poor agreement with the uptake of 18F-FDG and joint tenderness. The sum of SUV didn't correlate with DAS28 or DAS28-CRP (correlation coefficient 0.49 and 0.48 respectively) but well correlated with MMP-3 (correlation coefficient 0.77). In one patient, cervical inflammation was visualized via PET imaging.

Conclusion: 18F-FDG PET imaging visualizes active synovial inflammation in RA but its findings of active synovitis only moderately correlated with those of Contrast-enhanced MRI or clinical examinations. In the patients with long-standing RA and joint deformities, 18F-FDG PET imaging can be a powerful tool to assess active rheumatoid synovitis, independently from old synovial thickening without inflammation.

Disclosure: N. Hagino, Nihon Medi-physics, 2 ; **T. Sawada**, Nihon Medi-physics, 2 ; **M. Takahashi**, Nihon Medi-physics, 2 ; **H. Mori**, Nihon Medi-physics, 2 ; **K. Fujio**, None; **K. Kawahata**, None; **T. Momose**, Medi-physics, 2 ; **K. Ohtomo**, Nihon Medi-physics, 2 ; **K. Yamamoto**, Nihon Medi-physics, 2 .

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A Prediction Rule for Disease Outcome in Patients with Undifferentiated Arthritis by MRI of the Wrists and Finger Joints and Serologic Autoantibodies: Second Report Regarding to the Utility of Plain MRI. Mami Tamai, Atsushi Kawakami, Masataka Uetani, Kazuhiko Arima, Keita Fujikawa, Naoki Iwamoto, Shin-ya Kawashiri, Junko Kita, Akitomo Okada, Tomohiro Koga, Toshiyuki Aramaki, Makoto Kamachi, Satoshi Yamasaki, Hideki Nakamura, Hiroaki Ida, Tomoki Origuchi, Kiyoshi Aoyagi and Katsumi Eguchi, Nagasaki University, Nagasaki, Japan

Purpose: We have recently reported a prediction rule for disease outcome in patients with undifferentiated arthritis (UA) by MRI of the wrists and finger joints and serologic autoantibodies in Arthritis Rheum (61; 772-778, 2009). In this report, the presence of synovitis, bone edema and bone erosion were considered by both plain and Gd-enhanced MRI. If plain MRI is enough for the consideration, a cost as well as adverse events due to Gd can be reduced. To investigate whether plain MRI of the wrists and finger joints with serologic autoantibodies at entry is equally efficient for the prediction of development of RA at 1 year, as comparison with our recent report obtaining by plain and Gd-enhanced MRI (Arthritis Rheum 2009; 61: 772-778).

Method: The patients population is exactly same as our recent report which contains 129 UA patients. Seventy-five progressed to RA at 1 year (RA group) whereas 54 did not develop in RA at 1 year (non-RA group). The presence of synovitis, bone edema and bone erosion in MRI of the wrists and finger joints of both hands, read by plain MRI, was compared with those read by both plain and Gd-enhanced MRI. We also tried to find a suitability of plain MRI-interpreted features at entry, with serologic autoantibodies, for the prediction toward RA at 1 year.

Results: As compared with the features interpreted by both plain and Gd-enhanced MRI, symmetrical synovitis as well as bone erosion interpreted by plain MRI were more frequently distributed in non-RA group though a significantly high distribution of bone edema in RA group was still found in plain MRI. Accordingly, in UA patients positive with both plain MRI-proven bone edema and anti-CCP antibodies who were considered to have progressed to RA at 1 year, PPV was still in 100% of 24 patients.

Conclusion: Even in plain MRI of the wrists and finger joints, bone edema is a RA-prone feature as compared with symmetrical synovitis and bone erosion. Plain MRI can be an alternative to Gd-enhanced MRI to examine the progression of RA among patients with UA.

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Hand Bone Mineral Density (BMD) Loss Is Significantly Associated with the Level of Disease Activity in Patients with Rheumatoid Arthritis (RA). M. Güler-Yüksel[1], N.B. Klarenbeek[1], B.A.M. Grillet[2], I. Speyer[3], T.W.J. Huizinga[1], B. A. C. Dijkmans[4], C.F. Allaart[1] and W.F. Lems[4], [1]LUMC, Leiden, Netherlands, [2]Walcheren Hospital, Vlissingen, Netherlands, [3]Bronovo hospital, Netherlands, [4]VUMC, Amsterdam, Netherlands

Purpose: To investigate the differences in changes in hand BMD after 1 year between RA patients with high and low disease activity and patients in remission, with or without anti-rheumatic drugs.

Methods: 145 patients with active early RA, dynamically treated with anti-rheumatic drugs in a DAS<2.4 steered setting in the BeSt study, were included in this study. The patients were divided in 4 groups based on disease activity level during 1 year follow-up: 1. continuous high disease activity (DAS>2.4), 2. moderate disease activity (1.6<=DAS<=2.4), 3. in remission (DAS<1.6) with anti-rheumatic drugs and 4. drug-free remission. Changes in cortical BMD in metacarpals 2-4 of both hands after 1 year were measured by digital X-ray radiogrammetry (Sectra, Sweden). Changes in BMD were divided in 3 groups: 1. accelerated BMD loss (>-0.003 gr/cm^2), 2. stable BMD (-0.003 to 0.003 gr/cm^2) and 3. gain in BMD (>-0.003 gr/cm^2).

Multivariate multinomial regression analyses were performed to examine the differences in changes in hand BMD between the 4 different disease activity groups, adjusted for age, sex, body mass index, smoking status, diagnosis duration, baseline BMD and DAS, anti-rheumatic and anti-resorptive (bisphosphonates, calcium, vitamin D and hormone replacement) treatment and presence of rheumatoid factor and anti-CCP.

Results: Patients (68% women, mean age 57 years) had at baseline a mean disease duration of 63 weeks and 3 erosions in hands and feet. The mean BMD loss in patients in remission, with or without drugs, was significantly lower than in patients with moderate or high disease activity (overall p<0.0001, table). The differences in mean BMD loss between patients in remission with and without drugs were not significant, as well as between patients with moderate and high disease activity. On patient level, patients in remission had significant less often accelerated BMD loss and more often gain in BMD than patients with disease activity (overall p=0.003, table). In multivariate analyses patients in remission had significant more often gain in BMD than patients with high disease activity with an OR (95% CI) of 7.7 (1.2-48) independent of confounders.

Conclusion: Hand BMD loss is substantially lower in RA patients in continuous remission compared to patients with continuous disease activity. Furthermore one third of the patients in remission are gaining in their hand BMD, suggesting that to stop or prevent inflammatory hand BMD loss the target of treatment should be DAS<1.6.

Table. Changes in hand BMD, in mean (SD) and divided in 3 groups, after 1 year in patients with high and low disease activity and patients in remission, with or without anti-rheumatic drugs

	Group 1. DAS>2.4	Group 2. 1.6<=DAS<=2.4	Group 3. DAS<1.6 with anti-rheumatic drugs	Group 4. Drug-free DAS<1.6
Mean (SD) changes in BMD, % of baseline BMD	-0.031 (0.042)	-0.021 (0.025)	-0.0045 (0.020)	-0.0020 (0.013)
Accelerated BMD loss (>-0.003 gr/cm^2), %	70.0	70.3	38.7	48.1
stable BMD (-0.003 to 0.003 gr/cm^2), %	24.0	18.9	29.0	14.8
gain in BMD (>-0.003 gr/cm^2), %	6.0	10.8	32.3	37.0

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Does the Age at Onset Influence the Disease Progression in Early Rheumatoid Arthritis? Lena Innala[1], Bozena Möller[2], Lotta Ljung[1], Torgny Smedby[3], Anna Södergren[1], Staffan Magnusson[4], Ewa Berglin[1], Solbritt Rantapää-Dahlqvist[1] and Solveig Wållberg-Jonsson[1], [1]Norrland University Hospital, Umeå, Sweden, [2]Sunderby Hospital, Luleå, Sweden, [3]Östersund Hospital, Östersund, Sweden, [4]Sundsvall Hospital, Sundsvall, Sweden

Purpose: Disease activity and severity contribute to mortality and comorbidity in rheumatoid arthritis (RA). Confounding factors are age at disease onset and sex. In the present study we evaluated potential differences in disease progression and treatment and related prognostic factors in patients with younger vs. later onset of RA.

Method: All patients from the 4 most northern counties of Sweden diagnosed with RA (<12 months symptoms) are consecutively included in a large survey on the progress of the disease and its co-morbidies. Up til now 700 patients have been included. The median age at disease onset was 57 years (range 18-89). All patients were followed clinically on a regular basis, blood was sampled and a survey of co-morbidities was made at inclusion and after 5 years. At regular intervals, measures of disease activity (ESR, CRP, tender joints, swollen joints, VAS pain and VAS global, DAS28, HAQ) were assessed. Disease severity (extraarticular disease, rheumatoid nodules), co-morbidities and pharmacological treatment (DMARDs, corticosteroids, biologics, NSAIDs, COX2-inhibitors) were registered. Autoantibodies (RF, ANA, ACPAs) and HLA-shared epitope were analysed. Data analyses were based on stratification of the patients in groups over/below the median age at disease onset.

Results: Patients with later-onset of RA had significantly higher ESR (36.3 vs. 26.4 mm/h, $p<0.001$), CRP (24.9 vs. 18.9 g/L, $p<0.01$), VAS global (47.8 vs. 42.9, $p<0.05$) and HAQ (1.0 vs 0.8, $p<0.001$) at baseline and significantly higher accumulated disease activity (AUC for DAS28) at 6 ($p<0.001$), 12 ($p<0.001$) and 18 months ($p<0.01$) compared to patients with younger-onset. Patients with younger-onset had significantly more often ACPAs ($p<0.01$), and were numerically more often RF and ANA positive. Presence of extraarticular disease, nodules and frequencies of HLA-shared epitope or PTPN22 T variant did not differ significantly. Patients with later-onset were significantly more often treated with corticosteroids (77.2 vs. 67.8%; $p<0.05$), significantly less treated with methotrexate (76.4 vs. 86.9%; $p<0.001$) and with biologics (9.1 vs. 19.4%, <0.01). Patients with younger-onset were treated with DMARDs earlier (within 3 months from inclusion, 93.5% vs. 84.6%; $p<0.01$).

Conclusion: Patients with onset of RA later in life appear to have higher disease activity in early disease. Despite that, they are less treated with DMARDs and more often with corticosteroids. This may have implications for the development of co-morbidities.

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Women with Early Rheumatoid Arthritis Have More Disease Activity and Functional Impairment Than Men, Although Radiographic Damage Is Similar. Jennie Ursum[1], N.B. Klarenbeek[2], Ben A.C. Dijkmans[3], T.W.J. Huizinga[4], C.F. Allaart[2] and D. van Schaardenburg[5], [1]Jan van Breemen Institute, Amsterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands, [4]LUMC, Leiden, Netherlands, [5]Jan van Breemen institute, Amsterdam, Netherlands

Purpose: Women with rheumatoid arthritis (RA) seem to have more disease activity then men with RA[1], whereas reports vary about female gender as a prognostic factor for radiographic damage[2,3]. The aim of this study was to determine whether there are gender differences in patients with early RA concerning disease activity, functional status, radiographic damage and use of medication.

Methods: Patients from the early arthritis clinic of the Jan van Breemen Institute (EAC-JBI) who fulfilled the ACR criteria for RA at baseline (1996-2007) were included, and follow-up data until a maximum of 5 years were analyzed. The annual radiographic progression rate (Sharp-van der Heijde score) per patient was determined using linear regression, while for the disease activity score (DAS) and functional status (HAQ) the weighted mean was used. The same analysis was used for the 5-year data of the two initial monotherapy groups of the BeSt study (early RA): sequential monotherapy and step-up combination therapy.

Results: Women were younger than men (mean 55 vs. 58 year; $p=0.01$ in the EAC-JBI, and 53 vs. 57; $p=0.05$ in BeSt). The annual radiographic progression of women and men was similar (in both cohorts, see table). The number of used DMARDs was higher in women than in men (medians: 2 versus 1 ($p=0.02$) in EAC-JBI en 3 versus 2 in BeSt ($p=0.007$)). In spite of this women in both cohorts had a higher

DAS (mainly caused by tender joints and general health on the visual analogue scale). In the EAC-JBI women had a significantly higher HAQ than men (p<0.001); this was not found in BeSt.

	EAC-JBI	*Follow-up duration until 5 yrs)		BeSt Study	(all patients 5 yrs follow-up)	
	Women n=464	Men n=215	p	Women n173	Men n=74	p
DAS28	3.27 (1.04)	2.79 (1.02)	0.02	-	-	-
DAS44	-	-	-	2.27 (0.75)	2.01 (0.80)	0.01
HAQ	0.69 (0.37-1.13)	0.54 (0.19-0.89)	0.0	0.58 (0.29-1.02)	0.54 (0.25-0.99)	0.49
SHS, progressionrate (b)	0.48 (0-2.28)	0.57 (0-2.79)	0.8	0.29 (0-2.12)	0.76 (0-3.33)	0.07
Number of used DMARDs	2 (1-3)	1 (1-2)	0.02	3 (2-4)	2 (1-4)	0.007

Conclusion: Women have more disease activity and use more medication than men, whereas their radiographic progression rate is similar. Functional impairment was higher in women, but only in one of the two study cohorts. The gender difference is mainly apparent in disease symptoms, with a higher burden of disease in women. References: [1] Kvien TK, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 2006; 1069:212-222. [2] Ahlmen M, Svensson B, Albertsson K, Forslind K, Hafstrom I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis 2009. [3] Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Disease activity score-28 values differ considerably depending on patient's pain perception and sex. J Rheumatol 2007;34:2382-7.

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Disease Modifying Anti-Rheumatic Drugs Taking Behavior in a Cohort of Early Rheumatoid Arthritis Patients. Impact of Inadequate Medication Taking Behavior On Clinical Outcomes and Prognosticators. Virginia Pascual-Ramos[1], Irazú Contreras-Yáñez[2], Sergio Ponce de León[3], Javier Cabiedes[2] and Marina Rull-Gabayet[2], [1]Instituto Nacional de la Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico CITY, Mexico

Purpose: current management recommendations of rheumatoid arthritis suggest use of disease modifying anti-rheumatic drugs (DMARDs) when disease activity and/or radiographic damage progression are recognized. Inadequate DMARDs taking behavior ranges in occurrence from 20 to 70% of the patients. Study's objectives were: 1.- To determine adherence and persistence with DMARDs during six months of follow-up in a cohort of early rheumatoid arthritis patients. 2.- To investigate their impact on disease outcomes. 3-. To identify prognosticators of nonadherence and nonpersistence.

Methods: patients currently attending the early arthritis Clinic (≤1 year since first symptom) and receiving at least one DMARD (N=94) were invited to participate. Ninety-three patients were enrolled and attended 4 consecutive evaluations, each 2 months apart, during which 28-joint disease activity score (DAS28) and Health Assessment Questionnaire (HAQ) were scored, comorbidities and treatment recorded and a compliance questionnaire and a drug record registry applied. Serum metotrexate was measured in 81 samples. Descriptive statistics, Student´s t and chi-squared testes and logistic regression analysis were used.

Results: at study entry, 80 (86%) patients were females, 62 (66.7%) had rheumatoid factor and patients had (mean±SD) age of 40.8±3.9 years, follow-up at the Clinic of 25±12.2 months, DAS28 of 2.1±1.2, HAQ of 0.09±0.22, and DMARDs/patient Nº of 2.5±0.9. At last evaluation, 47 (50.5%) patients were adherent, 51 (54.8%) persistent and both had more frequently DAS28-remission than their counterparts

(69.4% vs. 30.6% and 74.2% vs. 25.5%, respectively, p≤0.001) and no disability (56.9% vs. 40.3% and 65.3% vs. 34.7%, p≤0.03). Compared to methotrexate-monotherapy, regimens with >3 DMARDs had increased risk of nonadherence and nonpersistence (p≤0.02). Baseline higher DAS28 was associated to nonadherence (OR: 2.7, 95%CI: 1.56-4.56, p≤0.001) and Nº of DMARDs/patient (OR: 1.8, 95%CI: 1.04-2.96, p=0.04) and higher HAQ (OR: 16.22, 95%CI: 1.52-172.95, p=0.02) to nonpersistence. Sensitivity and specificity of the compliance questionnaire and the drug record registry to detect persistence were of 90.6% for both, and of 75% and 71.4%, respectively (serum-quantitative-methotrexate used as validation method).

Conclusion: Early RA patients with inadequate DMARDs taking behavior showed poorer clinical outcomes than their counterparts. Higher disease activity and disability, and more complex therapeutic regimens were baseline prognosticators of nonadherence and nonpersistence.

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Lifestyle and Comorbidity Risk Factors for a Poor Prognosis in Very Early Inflammatory Polyarthritis: Results From the STIVEA Trial. S.M.M. Verstappen[1], M.J. McCoy[1], C. Roberts[1], N.E. Dale[1], A.B. Hassell[2], D.P.M. Symmons[1] and STIVEA trial committee, [1]arc Epidemiology Unit, the University of Manchester, Manchester, United Kingdom, [2]National Primary Care Centre, Keele, United Kingdom

Purpose: Medical history and lifestyle factors, such as smoking and diet, may play a role in the aetiology and course of rheumatoid arthritis (RA). However, hardly any data on these factors is available among patients presenting very early in the course of inflammatory polyarthritis (IP). The objective of this study was to identify lifestyle and comorbidity predictors for a poor prognosis in patients with very early IP.

Methods: Patients included in this study were participants in the STIVEA (Steroids In Very Early Arthritis) multi-centre randomised, double blind, placebo-controlled trial. GPs were asked to refer patients with very early IP (4-11 weeks duration) to the rheumatologist. Patients were randomised to receive three IM injections of either methyl prednisolone or placebo given at one week intervals and were followed for 12 months. Assessments were monthly for six months after the first injection, and then at 1 yr. At baseline, patients were asked to complete a questionnaire covering family history, medical history, immunisations, blood transfusion, smoking (ever vs never) and a food frequency questionnaire. Women were also asked about reproductive factors and use of the oral conceptive pill. Baseline predictors of poor prognosis (i.e. the need to start SLT by 6 months or the clinical diagnosis of RA according to the physician at 1 yr) were identified applying adjusted (for treatment group) logistic regression analyses. We present Odds Ratios (OR) with 95% confidence intervals.

Results: Mean disease duration at baseline was 8 weeks. 162 of 253 patients with available SLT data filled out the questionnaire; 107/162 (66%) patients were identified as needing SLT by 6 month after inclusion. 149 of 222 with a diagnosis at one year filled out the questionnaire; 85/149 (58%) were diagnosed as having RA at 1 year. Patients who had hay fever were less likely to be diagnosed with RA at 1 yr (OR 0.33; 0.12 to 0.93, p=0.036). However, hay fever was not associated with the need for SLT. Although not significant, there was a trend for smoking to be associated with a worse outcome (OR need to start SLT 1.91; 0.97 to 3.78, p=0.063; OR diagnosis of RA 1.95; 0.99 to 3.82, p=0.052). A treatment factor interaction was also tested and was significant for smoking (p=0.035) and the diagnosis of RA (OR in placebo group 0.875; 0.32 to 2.40, p=0.795 and OR in steroid group 3.90; 1.50 to 10.13, p=0.005). Pre-menopausal women were less likely to need SLT (OR 0.38; 0.16 to 0.94, p=0.036). Diet and all other factors examined were neither associated with the need for SLT nor with a diagnosis of RA.

Conclusion: Among patients with very early IP, only a few lifestyle factors were associated with a poor prognosis.

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The Increased CC Chemokine Ligand 19 (CCL19) at Baseline Is An Independent Predictor of the 5-Year Radiographic Progression in Early Steroid and DMARD-Naive Rheumatoid Arthritis (RA) Patients. Torkell Ellingsen[1], Ib Hansen[1], Jonas Thorsen[2], Bjarne K. Møller[2], Ulrik Tarp[1], Merete L. Hetland[3], Kim Hørslev-Petersen[4] and Kristian Stengaard-Pedersen[1], [1]Rheumatology Universityhospital, Aarhus, Denmark, [2]Clinical Immunology Universityhospital, Aarhus, Denmark, [3]Rheumatology Universityhospital, Copenhagen, Denmark, [4]Rheumatology King Christian X's Hospital, Graasten, Denmark

Purpose: To measure CCL19 in plasma and the CCR7 density on circulating monocytes and CD4+ T-lymphocytes and to analyse for correlation of this chemokine system to long-term radiographic progression in early DMARD-naïve RA patients.

Method: Forty patients with less than 6 months duration sinde appearance of first swollen joint were randomized to receive intraarticular betamethasone in combination with methotrexate/cyclosporine A (MTX/CYA) or methotrexate/placebo (MTX) for 52 weeks and then followed on conventionally shaped DMARD or biological anti-rheumatic treatment..

In house CCL19 ELISA on plasma (healthy controls n=54) and density of CCR7 on monocytes and CD4+ T-lymphocytes by flow cytometry (healthy controls n=15). ELISA and flow cytometric analysis were carried out at baseline and after 52 weeks in RA patients. Radiographic progression was scored by delta total Sharp/van der Heijde score (TSS) from 0 to 5 years. At baseline the median DAS28 was median 5.1 (range 2.5-7.6), at 5 years DAS28 was 1.6 (0.96-5.2).

Results: In DMARD and steroid naive early RA patients the increased CCL19 concentration before treatment ((p=0.005) median 90 pg/mL range 31-1008pg/ml) decreased after 52 weeks of treatment (59pg/ml (31-1030pg/ml), (p=0.051)) but to the level of healthy controls ((p=0.66) (62pg/ml (31-184pg/ml)).

In a univariate analysis the CCL19 koncentration at baseline correlated to delta TSS 0-5 years (p=0.0074 ; r=0.49) but not after 1 year (p=0.70 ; r=0.06). Multiple regression analysis was performed with delta TSS 0-5 years as dependent variable and CCL19 concentration at baseline, crp-levels, anti-CCP and smoking as explanatory variables. CCL19 concentration was the only independent predictor of delta-TSS progression after 5 years (p=0.039). Crp-levels, anti-CCP and smoking at baseline did not predict radiographic progression.

Prior to treatment CCR7 density was increased on monocytes compared to healthy controls (p=0.008) and decreased to normal level after 52 weeks in both the MTX and the MTX/CYA treated group (p=0.002; p=0.02 respectively). The increased CCR7 density on CD4+ T-lymphocytes at week 0 (p=0.018) was unaffected by MTX treatment (p=0.62). The CCR7 density on monocytes and CD4+ T-lymphocytes did not correlate with radiographic progression, neither at year 1 nor at year 5.

Conclusion: In Early steroid and DMARD-naive RA patients increased CCL19 concentration in plasma at baseline was the only independent predictor of delta-TSS radiographic progression after 5 years. Crp-levels, anti-CCP and smoking did not explain radiographic progression. CCL19 in plasma and its receptor CCR7 on monocytes but not on lymphocytes decreased during DMARD treatment. The CCR7 receptor density did not correlate with radiographic progression.

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Synovial Tissue Vascularity Is Related to Outcome in Early Undifferentiated Arthritis Patients. Maria J.H. de Hair[1], Marleen G.H. van de Sande[1], Yvonne Schuller[1], Gijs P.M. van de Sande[1], Carla A. Wijbrandts[1], Danielle M. Gerlag[2] and Paul P. Tak[3], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: A subset of the early arthritis patients presenting in the outpatient clinic cannot be classified and are diagnosed as undifferentiated arthritis (UA) patients. About one third of these patients will have self-limiting disease, whereas others will progress to chronic persistent arthritis. Accurate prediction of outcome in these patients will help decision making to start disease-modifying antirheumatic drug (DMARD) treatment. As synovium is the main affected tissue in arthritis, analysis of synovial tissue (ST) might identify biomarkers that can be used to predict outcome. Aim is to evaluate the value of the expression of ST cellular and vascular markers in predicting outcome in early UA patients.

Method: Of the DMARD naive early arthritis patients (arthritis duration < 1 year) enrolled in our prospective cohort we selected the UA patients (n=43) with ST available for analysis. At baseline ST samples were obtained and clinical analysis was performed. Outcome defined as self-limiting disease (no DMARD or joint swelling in past 3 months) or persistent disease was evaluated after 2 years of follow up. Immunohistochemistry was used to evaluate the synovial cell infiltrate and vascularity. Expression of the various cellular and vascular markers was quantified by digital image analysis. Independent predictors of outcome were identified by logistic regression analysis.

Results: After 2 years of follow up 19 patients had self-limiting disease and 24 had persistent arthritis. ST expression of von Willebrand factor (vWF), a measure of vascularity, was significantly related to outcome (P=0.03) with an explained variance of 18% (R^2 according to Nagelkerke= 0.180). However, substantial overlap in expression of vWF was observed between the 2 outcome groups.

Conclusion: vWF expression is in part related to outcome in recent onset UA patients. However, outcome cannot be completely predicted by this marker alone. Therefore, identification of other markers is needed to develop a multivariate prediction model that can be used for personalised treatment decisions in UA.

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Interaction Between the PTPN22 620W Risk Allele and Tobacco and Hormonal Treatments Influence the Anti-CCP or RF Status of Rheumatoid Arthritis: Results From the ESPOIR Cohort. Carine Salliot[1], Karen Dawidowicz[2], Pascale Nicaise-Roland[2], Joelle Benessiano[2], Alain Saraux[3], Maxime Dougados[1], Sylvie Chollet-Martin[2], Olivier Meyer[2] and P. Dieudé[2], [1]Paris Descartes University, Medicine Faculty - Cochin Hospital, APHP, Paris, France, [2]Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [3]CHU de Brest, Brest, France

Background: Gene-environment interactions play a major role in the pathogenesis of rheumatoid arthritis (RA), such as *HLA-DRB1* shared epitope alleles and smoking.

Purpose: To perform a genotype-phenotype correlation in RA including gene-environment interactions between the *PTPN22* 620W risk allele and tobacco/hormonal treatments in a cohort of early arthritis.

Methods: The ESPOIR cohort included patients with at least 2 synovitis for at least 6 weeks but less than 6 months. 578 patients had RA (defined as the fulfillment of ACR criteria either at baseline, 6 or 12 month follow-up visit) and were genotyped for the *PTPN22* rs2476601 (R620W) SNP. Data regarding anti-CCP and RF status at baseline, HLADR1 and/or DR4 status, demography (age, gender, ethnicity), co-morbidities (BMI, cardiovascular diseases), exposure to tobacco and hormonal treatments (hormonal replacement treatment and/or contraceptives) were collected. Logistic regression was performed to estimate the ORs adjusted for confounding factors including gender, age, ethnicity, BMI, HLADR1 and DR4 status.

Results: At baseline, mean age was 49±12 years, 76.4% were women, 92% were Caucasian, 54% had IgM RF and 47% had anti-CCP antibodies. 56% carried HLADR1 and/or DR4 antigen and 20% carried the *PTPN22* 620W allele. 47% had ever smoked and 69.5% of women had ever received hormonal treatment.

PTPN22 620W risk allele was associated with anti-CCP positive status (11.4% vs 8.4%, OR=2.47, 1.5-4.0 95% CI, p<0.0001) and also correlated with the anti-CCP titter (Mann-Whitney test: mean 335.5 U/ml in 620W+ *vs* 278 U/ml 620W-, p<0.0001).

Gene-environment interaction study found that smoking would increase the risk for anti-CCP and RF positive RA, restricted to individuals who carried the *PTPN22* 620W risk allele. Conversely, hormonal treatment would reduce this risk for anti-CCP seropositive RA in women who carried the 620W risk allele (Tables 1 & 2).

Conclusion: *PTPN22* 620W risk allele interact with tobacco and hormonal treatment for both RF and anti-CCP status in RA population.

Table 1- *PTPN22* -environment interaction and anti-CCP status

PTPN22 620W	Smoking	Anti-CCP+ N=271	Anti-CCP- N=307	ORs (95%CI)	*P*
None	Never	106	141	1	-
Any	Never	31	26	2.47 (1.5-4.0)	*<0.0001*
None	Ever	94	121	1.25 (0.8-1.8)	*0.24*

Any	Ever	40	19	4.26 (2.0-9.1)	*<0.0001*
PTPN22 620W	Hormonal treatments	Anti-CCP+ N=199	Anti-CCP- N=241	ORs (95%CI)	*P*
None	Never	74	59	1.0	-
Any	Never	23	10	2.35 (1.3-4.3)	*0.005*
None	Ever	81	152	0.43 (0.3-0.7)	*<0.0001*
Any	Ever	21	20	1.30 (0.5-2.9)	*0.55*

Table 2- *PTPN22*-environment interaction and RF status

PTPN22 620w	Smoking	IgM RF+ N=311	IgM RF- N=267	ORs (95%CI)	*P*
None	Never	133	114	1	-
Any	Never	32	25	1.86 (1.2-2.9)	*0.009*
None	Ever	103	112	1.07 (0.7-1.5)	*0.68*
Any	Ever	43	16	3.43 (1.6-7.3)	*0.001*
PTPN22 620w	Hormonal treatments	IgM RF+ N=235	IgM RF- N=205	ORs (95%CI)	*P*
None	Never	80	53	1	-
Any	Never	24	9	1.81 (1.0-3.2)	*0.04*
None	Ever	107	126	0.58 (0.4-0.9)	*0.01*
Any	Ever	24	17	1.32 (0.6-3.0)	*0.51*

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A Predictive Algorithm Combining Routine Assessment and Power Doppler Ultrasonography for the Development of Rheumatoid Arthritis From An Early-Onset Undifferentiated Arthritis. Fausto Salaffi[1], Alessandro Ciapetti[1], Stefania Gasparini[1], Emilio Filippucci[1], Marina Carotti[2] and Walter Grassi[1], [1]Department of Molecular Pathology and Innovative Therapies, Università Politecnica delle Marche, Jesi, Ancona, Italy, [2]Department of Radiology, Università Politecnica delle Marche, Ancona, Italy

Purpose: The ability to predict the development of rheumatoid arthritis (RA) in patients with an early-onset undifferentiated arthritis (UA) is highly required if the remission or an adequate response to the treatment are the main goal. The statement of purpose was to develop a predictive algorithm combining clinical variables, serological biomarkers and power Doppler ultrasonography (PDUS) for the progression from an early-onset UA to RA in daily rheumatological practice.

Method: A predictive algorithm was developed after a 12 months study of 149 adult patients with a recent-onset UA and a clinical involvement of the hands. The combination of five routine assessment variables (sex, symptoms duration, morning stiffness, anti-citrulline antibodies and IgM-rheumatoid factor) and PDUS findings was investigated. Logistic regression analysis was performed to identify the independent factors for the development of RA and global predictive score was calculated. The area under the ROC curve (AUC) was used to evaluate the diagnostic performance of the algorithm and a cut off point, maximizing both sensitivity (SE) and specificity (SP), was selected. The post-test probability (post-TP) was evaluated using the Fagan's nomogram.

Results: During the follow up period, 62 patients (41.6%) developed a RA. The score of the global predictive algorithm ranged from 0 to 10, being a higher score indicative of a higher risk to develop RA. The algorithm demonstrated excellent discriminative ability, with an AUC of 0.951 [SE 0.019; 95% interval of confidence (CI) from 0.903 to 0.980]. With the optimal cut-off point of 5 SE was 93.6% (95% CI from 80.1% to 96.3%), SP was 89.9% (95% CI from 81.3% to 95.1%) and positive likelihood ratio (LR+) was 9.39. If a threshold of 7 was applied a higher value of SP (98.1%) was obtained, but SE (58.1%) decreased (LR+ of 31.02). The post-TP value of the two different cut-off points mentioned above were 66% and 87%, respectively.

Conclusion: Our predictive algorithm, which include PDUS assessment, revealed an excellent discriminative ability for assessing the likelihood of development of RA. Further studies are required to confirm the results and to tailor a therapeutic approach in patients with an early-onset UA, according to the values of the predictive algorithm proposed in the present study.

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Low Educational Level, Family History of RA and Early Disability Are Associated with Moderate to Severe Disability at 1 Year of Follow-up in Patients with Early RA: Results From the ESPOIR Cohort. Carine Salliot[1], Claire Bombardier[2], Valérie Devauchelle[3], Cedric Lukas[4], Alain Saraux[5], Bernard Combe[6] and Maxime Dougados[7], [1]Cochin Universitary Hospital, Descartes University, APHP, Paris, France, [2]University Health Network, Toronto, ON, [3]CHU Brest, Brest, France, [4]Lapeyronie hospital, Montpellier, France, [5]CHU de Brest, Brest, France, [6]Immuno-Rheumatologie, Hospital Lapeyronie, Montpellier, France, [7]University of Paris V, Cochin Hospital, Paris, France

Purpose: To assess baseline characteristics as associated factors with disability after 1 year of follow-up in a cohort of early arthritis.

Method: The ESPOIR cohort is a multicenter French cohort of patients suffering of at least 2 synovitis for at least 6 weeks but less than 6 months. 579 patients had a diagnosis of RA at 1 year of follow-up (defined as the fulfillment of ACR criteria either at baseline or at 6 or 12month follow-up visit). Data regarding the disease characteristics (clinical, biological, radiological and immunological features), demography (age, gender), socio economy (educational level, family monthly income), family history of RA, comorbidities (smoking status, BMI, cardiovascular disease) were collected at baseline and assessed as associated factors with moderate to severe disability at 1 year (HAQ score $\geq$ 1/3), using univariate and multivariate analyses.

Results: At Baseline, mean age was 49±12 years, 76.4% were women, 48% had IgM Rheumatoid factors (RF) and 54% had anti-CCP antibodies. The mean DAS28 score was 5,3 ±1,2, HAQ score was 1,0 ± 0,7 and the mean modified Sharp score was 6.2 ±8.1. 90% of the patients received at least 1 DMARD during the first year of follow-up. At 1 year, 143 patients had a HAQ score of at least 1 and 436 experienced a low disability.

Logistic regressions were performed with adjustments for several confounding factors (such as gender, age, DAS28 score at baseline, presence of erosion at baseline and treatments received).

Low educational level (compulsory school only), family history of RA and the level of disability at baseline were significantly associated with moderate to severe disability at 1 year (Table). The patients who stopped their trainee after the compulsory school lived more frequently in a rural area ($p<0.000$), had a low monthly income ($p<0.000$), a higher consumption of tobacco ($p=0.05$) and a longer disease duration before the inclusion in the cohort ($p=0.004$)

The presence of RF, anti-CCP, smoking and structural damage at baseline were not associated with disability at 1 year.

Conclusion: In the ESPOIR cohort, early disability was associated with low educational level (compulsory school only), family history of RA and the level of disability at baseline.

At Baseline	**Adjusted ORs for HAQ score ≥1 at 1 year (95% Confidence Interval), *p* values**
Compulsory school only	1.8 (1.1-3.0), p=0.02
Family history of RA	2.6 (1.4-5.0), p=0.003
HAQ score at baseline	
0 to 0.5	1.0 (Reference)
0.5 to 1	3.4 (1.3-9.1), p=0.01
1 to 2	11.8 (4.6-30.4), p<0.0001
≥ 2	21.4 (7.1-64.5), p<0.0001

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The Relationship Between Synovial Lymphocyte Aggregates and Diagnosis and Outcome After Follow up in Early Arthritis Patients.

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Background: Synovial lymphocyte infiltration is one of the characteristics of inflammatory joint diseases. Different synovial lymphocyte infiltration patterns, ranging from diffuse infiltration to follicular aggregates that resemble lymphoid germinal centers, can be observed. Germinal center formation has been proposed to play a role in promoting self perpetuating inflammation both by stimulating the humoral immune response to autoantigens and by contributing to T-cell responses and cytokine production. Synovial lymphocyte infiltration patterns have previously been suggested to be a stable feature in time and patient specific. Therefore, lymphocyte infiltration patterns might be of use for patient subclassification and prediction of outcome.

Purpose: To investigate the lymphocyte infiltration pattern in early undifferentiated arthritis patients and its relationship to outcome.

Methods: We analyzed the presence of lymphoid aggregates in synovial tissue (ST) samples from 37 DMARD naive early undifferentiated arthritis (UA) patients (disease duration < 1 year). Patients were selected from our early arthritis cohort based on the diagnosis UA and the availability of ST at baseline. Patients were followed for 2 years to allow confirmation of the diagnosis according to established classification criteria. Furthermore, patients were classified at 2 years as self-limiting, persistent or persistent erosive disease. The presence of lymphocyte aggregates was assessed on anti-CD3-stained sections. Aggregates were counted and graded by size (1-3) (Arthritis Rheum. 2008;58:1582-9). The presence and size of lymphoid aggregates at baseline was compared between the different outcome groups using the Chi^2 test.

Results: After 2 years of follow up 9 patients (24%) fulfilled ACR criteria for rheumatoid arthritis (RA). Furthermore, 16 (43%) patients had self-limiting disease, 14 (38%) persistent disease and 7 (19%) patients had persistent erosive disease. Interestingly, the presence or size of aggregates at baseline was not predictive of the diagnosis RA; there was no difference between patients with RA (34% any aggregate, 22% ≥grade 2) or non-RA (54% any aggregate, 36% ≥grade 2) after 2 years of follow up. Moreover, no difference in presence of aggregates at

baseline was observed between patients with self-limiting (62% any, 31% ≥ grade 2) versus persistent (36% any, 29% ≥grade 2) or erosive disease (43% any, 43% ≥grade 2).

Conclusion: The presence of lymphocyte aggregates at baseline is not specific for RA and not related to outcome in early arthritis patients.

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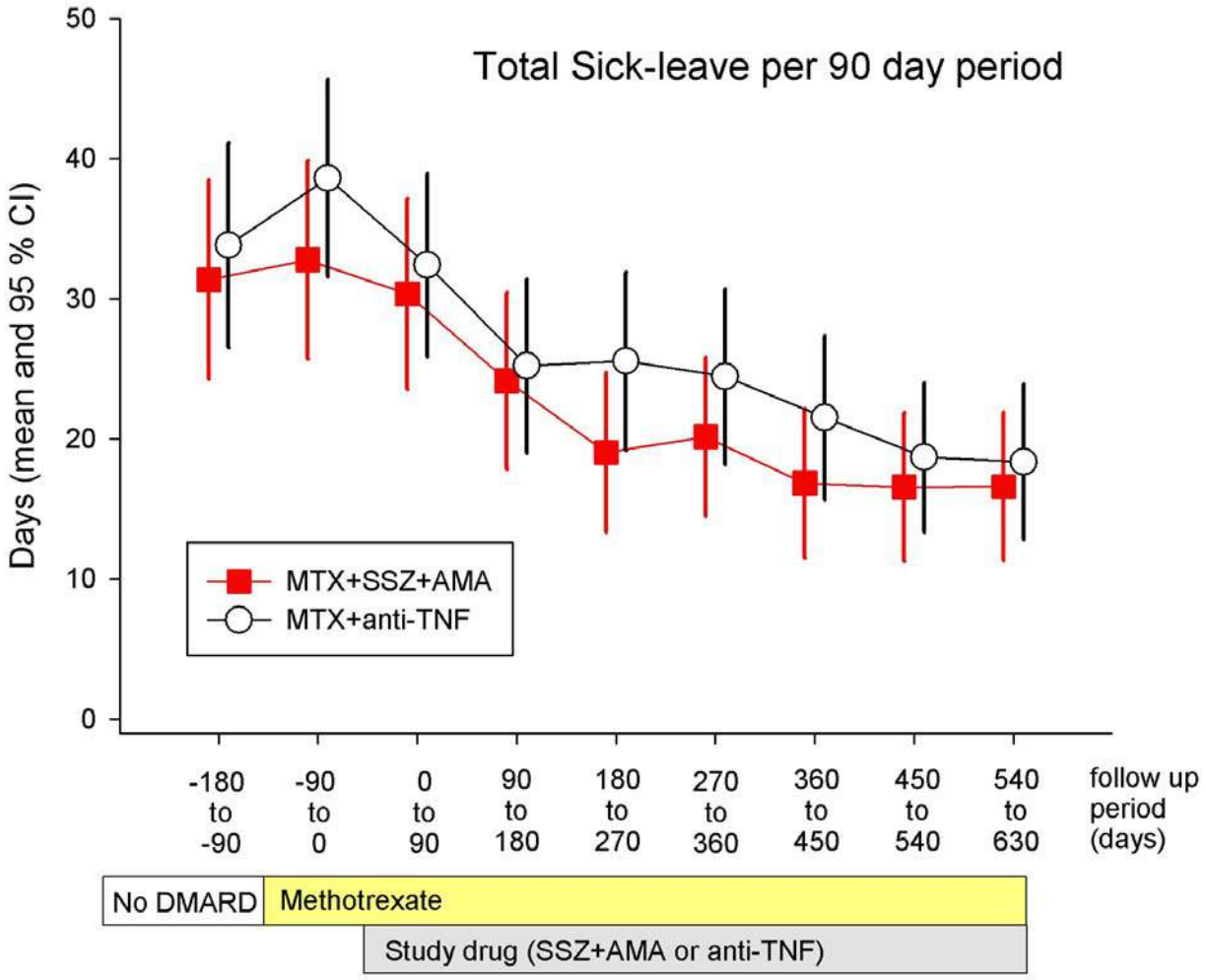
Early Combination Therapy in RA Patients Improves Work Capacity: Results From the SWEFOT Clinical Trial. Sofia Ernestam[1], Johan Bratt[1], Ingemar Petersson[2], Ronald F. Van Vollenhoven[3] and P. Geborek[4], [1]Karolinska University Hospital, Stockholm, Sweden, [2]Lund University, Department of Clinical Sciences, Lund, Lund, Sweden, [3]The Karolinska Institute, Stockholm, Sweden, [4]Lund University, Department of Clinical Sciences, Lund, Sweden

Purpose: In Sweden historically approximately 30% of RA patients are on sick leave/disability pension at their 1st visit to a rheumatologic specialist with no return to working capacity. Similar results have recently been reported from the multinational QUEST study. The SWEFOT study, recruiting patients in an observational open "real life" setting with a randomized procedure from 2003 to 2005, studied early pharmacologic intervention in RA patients with insufficient response to 3-4 months methotrexate (MTX). This part of the investigation included health economic measures such as sick leave to see if early and more aggressive pharmacological intervention could improve work capacity in RA patients.

Method: 258 early RA patients who had not achieved DAS28≤3.2 after 3-4 months treatment with MTX were included in an open, randomized, controlled trial. In arm A (n=130) sulfasalazine and hydroxychloroquine was added and in arm B (n=128), infliximab was added. The Eular good response at 12 months based on intention-to-treat for all randomized patients has been presented previously and showed arm B to be superior to arm A (39% vs. 25%, $p<0.02$). Full time and part time sick leave was computed into total sick leave per 3 month period for patients with working capacity. Last observation carried forward technique was used for dropouts and missing values.

Results: In both groups a similar and steady decrease in sick leave was observed over a two-year period with start after the randomization at 3 months (Figure 1). Mean (SD) total sick leave in days/ 3 months decreased from 32,7 (39,8) and 38,6 (39,3) at baseline to 16,6 (30,1) and 18,3 (31,3) at 2 years for group A and B, respectively. Only one patient progressed to disability pension during the two-year study. In group A 5 patients were on disability pension for other reasons than RA prior to study start and 22 had age pension. The corresponding figures for group B were 7 and 16.

Conclusion: In early RA patients with only partial response to MTX, addition of aggressive pharmacological treatment improve work capacity. No obvious differences in sick leave were found between the treatment strategies.



Disclosure: S. Ernestam, Schering-Plough, 3 ; **J. Bratt**, None; **I. Petersson**, None; **R. F. Van Vollenhoven**, Abbott Immunology Pharmaceuticals, 2, Roche Pharmaceuticals, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2 ; **P. Geborek**, None.

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The Clinical Course, Outcomes, and Treatment of Early Inflammatory Arthritis: Results From CATCH (Canadian Early Arthritis Cohort). W. Katchamart[1], Gilles Boire[2], Janet Pope[3], C. Haraoui[4], Carol A. Hitchon[5], Shahin Jamal[6], Jc Thorne[7], Vivian P. Bykerk[8] and Near, [1]Mount Sinai Hospital, Toronto, ON, [2]Centre hospitalier universitaire de Sherbrooke, Sherbrooke, [3]St Joseph Health Care, London, ON, [4]Institut de Rhumatolgie de Montreal, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]St. Michael's Hospital, Toronto, [7]Newmarket, [8]Mt Sinai Hospital, Toronto, ON

Purpose: To investigate the clinical course, outcomes, and treatments of early inflammatory arthritis (EIA) over time comparing between patients in different disease activity states at presentation

Methods: Patients were recruited to CATCH, a Canadian, multicenter, prospective, observational study of EIA, according to these criteria: >16 years old, symptoms for 6-52 weeks, and ≥2 swollen joints or 1 swollen MCP/PIP joint and ≥1 of: + rheumatoid factor, anti-CCP, morning stiffness > 45 min, a response to NSAIDs, or painful MTP joint squeeze test. Treatment consisted of initial DMARDs based on patient and rheumatologist' discretion to reach a goal of remission. Patients were assessed at baseline, every 3 months for 1st year and every 6 months thereafter. Patients were eligible in this analysis if they had completed DAS28 data at baseline and one year of follow-up.

Results: A total of 234 patients had completed one year of follow-up. At baseline, the proportion of patients who had high (HAD), moderate (MDA), low disease activity (LDA) and were in remission was 52%(121), 35%(83), 6%(15), and 6%(15), respectively. Patients with HAD, MDA, and LDA significantly improved over the time of follow up ($p<0.0001$), while patients presenting with remission had an increased mean disease activity over 1-year of follow-up (mean change of DAS28 ± SD at 3 month 0.5 ± 0.55, 6 month 0.35 ± 1.03, 9 month 0.23 ± 0.73, and 1 year 0.12 ± 0.94 with $p <0.0001$). Patients with baseline LDA (20%) and remission (33%) had a significant higher proportion of clinical progression compared to patients presenting with HAD (2%) or MDA (12%). Patients presenting with remission significantly received less aggressive treatments with MTX, parenteral MTX, and DMARD combinations. They also received a delayed MTX treatment compared to HDA group (53% vs.16%, p 0.006).

Conclusion: In this early arthritis cohort, a significant number of patients presented with very low disease activity. One-third had progressive disease within 1 year despite DMARD treatment. Patients with mild inflammatory arthritis who have a poor prognosis need to be identified early so that more aggressive treatment can be started at the outset.

Disclosure: W. Katchamart, None; **G. Boire**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **J. Pope**, None; **C. Haraoui**, None; **C. A. Hitchon**, Wyeth Pharmaceuticals, 2, Amgen, 2 ; **S. Jamal**, None; **J. Thorne**, None; **V. P. Bykerk**, Amgen, 2, Wyeth Pharmaceuticals, 2 .

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Tendinitic Involvement Can Precede the Development of Synovial Inflammation in Anti-CCP Positive Patients: Results of US Examination at An Early Arthritis Clinic. Pierluigi Macchioni[1], Mariagrazia Catanoso[1], Luigi Boiardi[1], Irene Modesto[1], Luca Magnani[1], Giuseppe Germanò[1], Sabrina Frigelli[1], Alessandra Ghinoi[1], Giovanna Restuccia[2] and Carlo Salvarani[3], [1]Arcispedale S.Maria Nuova, Reggio Emilia, Italy, [2]Arcispedale S.Maria Nuova, Italy, [3]Arcispedale S Maria Nuova, Reggio Emilia, Italy

Purpose: We describe a form of rheumatic disease characterized by early tendinitic involvement with the presence of anti-CCP antibody and good outcome.

Method: We have evaluated the record of 355 patients seen in 36 months at our early arthritis clinic. All the afferring out-patients were evaluated for clinical and laboratory parameters according to a standardized form which include all the core sets variables of ACR response criteria, the calculation of DAS28 and the determination of serum anti-CCP and RF. All the patients had wrists, hands and feet US examination performed at the same time visit and X-ray hands and feet examination.. **Results:** Eighteen patients (F15 pts/M3 pts, mean age 51+14y, mean disease duration 16+6wks) who presented at rheumatological examination sign and symptoms of peripheral joint involvement (morning stiffness, pain and swollen joints) did not have at US evaluation articular synovitis but only tenosynovitis and/or tendonitis. The distribution of US tendon involvement was : 5 patients wrist flexor (right/left/bilateral 5/4/4), 8 pts wrist extensor (r/l/b 5/7/4), 14 pts digital flexor (r/l/b 12/14/12), 9 pts digital extensor (r/l/b 8/9/8). The most frequent US localization of tendon inflammation was at metacarpal-phalangeal level (15 pts). Fourteen patients had high level of anti-CCP antibody (mean values 306+389 U/ml) and 12 were RF positive. Mean baseline values were : ESR 29.7±18.9 mm/1st h, CRP 0.69±1.1 mg/dl, HAQ 0.76±0.58, DAS28 4.27±0.82, (1 pt low DAS, 3 pts high DAS, 14 patients medium DAS). None of the patients presented joint erosions at X-ray baseline examination.

Because of isolated tendon inflammation none of the patients received any DMARDs and were treated only with AINS and/or low steroid daily dose. After a mean follow-up of 15±7 months 7 patients are in remission without treatment, 8 patients developed synovial joint inflammation (4-8 months later) and were treated with standard MTX weekly dose with good outcome (4 pts remission, one pt LDA, 3 medium disease activity). Only two patients developed radiological erosions. At the last US examination (after 15±7 m) tendonitis/tenosynovitis was still present in 8 pts, 5 pts presented synovial inflammation and 5 had complete US resolution.

Conclusion: US examination is useful for the recognition of an isolated tendinitic involvement in anti-CCP positive patients. The form seems to have a good clinical outcome.

Disclosure: P. Macchioni, None; **M. Catanoso**, None; **L. Boiardi**, None; **I. Modesto**, None; **L. Magnani**, None; **G. Germanò**, None; **S. Frigelli**, None; **A. Ghinoi**, None; **G. Restuccia**, None; **C. Salvarani**, None.

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Association of Rheumatoid Arthritis (RA)-Related Autoimmunity and Joint Findings in Unaffected at-Risk Populations. J. R. Kolfenbach[1], K. D. Deane[1], L. A. Derber[1], C. O'Donnell[1], M.H. Weisman[2], J.H. Buckner[3], T. R. Mikuls[4], James R. O'Dell[4], P.K. Gregersen[5], R. M. Keating[6], J.M. Norris[7] and V. M. Holers[1], [1]U Colo Denver, Aurora, CO, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Benaroya Rsch Ini., Seattle, WA, [4]U Nebraska, Omaha, NE, [5]Feinstein Insititute Med Rsch, Manhasset, NY, [6]U Chicago, Oak Park, IL, [7]U Colo Denver

Purpose: The presence of RA-related autoantibodies prior to diagnosis suggests that there is a pre-clinical period in RA. Prospective analysis of *pre-diagnosis RA* may allow for a more complete understanding of early disease pathogenesis. We have established prospective cohorts with subjects at potentially higher risk for RA based on genetic risk factors, with intent to examine RA-related autoimmunity in these populations. The purpose of our current analysis was to identify RA-related autoantibodies within these populations and to examine potential associations with clinical endpoints such as joint disease and systemic inflammation.

Methods: We have created a prospective cohort of first-degree relatives (FDRs) of probands with RA as part of the SERA study (Studies of the Etiology of RA). FDRs *without RA* by ACR criteria are evaluated during a clinical research visit where joint examination and laboratory data are independently obtained. Identical analysis is performed on a second at-risk DR4-enriched population containing parents of children with high risk HLA alleles and/or Type I diabetes (DAISY parents, Diabetes and AutoImmunity Study of the Young). Prevalence of high-risk genetic markers was compared between these cohorts and the general population using control data from the North American Rheumatoid Arthritis Consortium (NARAC). Association analysis was performed by chi-square and Fisher's exact testing.

Results: Data from 1058 FDRs and 627 DAISY parents was analyzed. Prevalence of the shared epitope (SE) (≥1 allele) was higher in the FDR and DAISY cohorts than the general population (55%, 51.6%, and 43% respectively; $p < 0.01$). Prevalence of the PTPN22 polymorphism (≥1 allele) was higher in FDRs than the general population (20% vs. 15.9%; $p < 0.05$). One or more autoantibodies were detected in 15.9% of FDRs and 14.2% of DAISY parents. RF-IgM positivity in FDRs was associated with ≥ 1 tender joint on exam (OR 2.50, 95% CI 1.27-4.89) and elevated CRP (OR 5.31, 95% CI 1.45-19.52). In DAISY parents, RF-IgM was associated with ≥ 1 swollen joint (OR 4.22, 95% CI 1.80-9.93).

Conclusion: Autoantibodies in these at-risk populations are associated with joint swelling and tenderness as well as elevated CRP. Follow-up of subjects with very early signs of clinical disease will be valuable to further understanding the factors associated with transition to a phenotype that meets full ACR or other classification criteria. In addition, these findings support the utility of further prospective analysis of at-risk populations in the study of RA development prior to clinical diagnosis.

Disclosure: J. R. Kolfenbach, None; **K. D. Deane**, None; **L. A. Derber**, None; **C. O'Donnell**, None; **M. H. Weisman**, None; **J. H. Buckner**, None; **T. R. Mikuls**, None; **J. R. O'Dell**, None; **P. K. Gregersen**, None; **R. M. Keating**, None; **J. M. Norris**, None; **V. M. Holers**, None.

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Clinical Factors That Predict Erosion-Free Status in Rheumatoid Arthritis. Katherine P. Liao[1], Michael E. Weinblatt[1], Jing Cui[1], Hiroshi Yoshioka[2], Christine Iannaccone[1], Lori Chibnik[1], Bing Lu[3], Jonathan S. Coblyn[1], Nancy A. Shadick[1] and Daniel H. Solomon[3], [1]Brigham & Women's Hosp, Boston, MA, [2]Brigham & Women's Hosp, Boston, [3]Brigham & Women's Hospital, Boston, MA

Purpose: Subsets of rheumatoid arthritis (RA) patients remain erosion-free despite years of disease. Our objective was to characterize this group of RA patients and identify the significant predictors for remaining erosion-free.

Methods: Our study was conducted using data from a prospective observational cohort of RA patients recruited from an outpatient practice of an academic medical center. We included patients with bilateral hand radiographs obtained at recruitment and at 2 yr follow-up whose radiographs had been formally assessed with Sharp scores. The primary outcome was erosion-free status at recruitment and at 2 yr follow-up. We assessed the following characteristics at recruitment: age at RA onset, gender, RA disease duration, DAS28, CRP, tender/swollen joint counts, MDHAQ, smoking status, methotrexate use, anti-TNF use, and the presence of the HLA-shared epitope (SE). Our primary analysis was conducted on subjects with RA duration <10 years to mitigate confounding by secular trends in care. We conducted a

univariate analysis to identify potential predictors. Variables with p<0.20 were selected for the multivariable logistic regression model; significant predictors for erosion-free disease were selected using forward/backward selection. A secondary analysis was conducted on a dataset from the same cohort matched by RA duration.

Results: 222 subjects in our cohort had RA duration < 10 years: 38% were erosion-free at recruitment and 2 year follow-up; 46% of these patients were anti-CCP+ of which 61% were HLA-SE+. 70% of erosion-free patients had an RA duration ≥ 2 years with a mean of 3.7 yrs (SD 3.1) at the time of recruitment. The mean RA duration for patients with erosions either at recruitment or follow-up was 4.7 yrs (SD 3.1). There was no significant difference in baseline methotrexate or anti-TNF use between the two groups in the unadjusted analysis. In our multivariable-adjusted analysis significant predictors of remaining erosion-free were younger age at onset, male gender and shorter RA duration (Table 1). Anti-CCP status was not a significant predictor for erosion-free status. Secondary analyses on a dataset matched by RA duration supported these findings.

Conclusion: In our cohort, the absence of anti-CCP was not a significant factor in predicting erosion-free disease; 46% of individuals who were erosion-free at recruitment and at two year follow-up were anti-CCP+, of which 61% were HLA-SE+. Clinical factors independently predicting remaining erosion free were younger age, male gender and shorter RA duration.

Table 1. Predictors of erosion-free disease in patients with disease duration < 10 years.

Description	Multivariable adjusted (OR)*	p-value	Significant predictors (OR)	p-value
Age at onset (per 5 yrs)	0.81	0.002	0.82	0.0005
Male gender	3.1	0.007	2.9	0.004
Disease duration (per yr)	0.93	0.16	0.89	0.019
Anti-CCP negative	1.5	0.26	-	
SE (1 vs 0 copy)	0.78	0.45	-	
SE (2 vs 0 copies)	0.44	0.08	-	

* Variables with p<0.20 from unadjusted analysis were tested in the adjusted models

Disclosure: K. P. Liao, None; **M. E. Weinblatt**, Biogen/Idec, Crescendo, 2, Biogen/Idec, Crescendo, 5 ; **J. Cui**, Crescendo Biosciences, 2, Biogen Idec, 2 ; **H. Yoshioka**, None; **C. Iannaccone**, None; **L. Chibnik**, None; **B. Lu**, None; **J. S. Coblyn**, None; **N. A. Shadick**, bristol myers squibb foundation, 2, Amgen, 2, crescendo biosciences, 2, Biogen Idec, 2 ; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 .

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The Association Between Focal Bone Loss (erosions) and Generalized Bone Loss (osteoporosis) in Rheumatoid Arthritis. Allen P. Anandarajah[1], Muhammad El-Taha[2], Cheng Peng[2], Jeffrey D. Greenberg[3] and Christopher Ritchlin[4], [1]Univ of Rochester Med Ctr, Rochester, NY, [2]University of Southern Maine, [3]New York University School of Medicine, Millburn, NJ, [4]University of Rochester Medical Center, Rochester, NY

Background: Local and systemic bone loss, that manifest as erosions and osteoporosis respectively, are hallmark findings in rheumatoid arthritis (RA). Relatively little is known, however, about the relationship between these two forms of bone loss.

Purpose: To determine if there is an association between focal bone loss (erosions) and generalized bone loss (osteoporosis) in patients with rheumatoid arthritis.

Method: Patients with RA were selected from the Consortium of Rheumatology Researchers of North America (CORRONA) database. CORRONA is the largest independent database in North America and collects clinical data, from physicians and patients. Multiple logistic regression models were constructed to assess the association between the two key variables, presence or absence of erosions and T-scores in

patients with RA. Adjustment was made for use of steroids, gender, methotrexate, status of using other disease modifying agents, biologics (categorical variables) and weight, age, body mass index (BMI) and disease index (continuous variables).

Results: A total of 16,978 patients with RA were identified in the database. Information on erosions was available in 3898 subjects of which 2085 reported no erosions and 1813 reported the presence of erosions. Values were missing in 13,080. Patients with erosions were significantly younger (mean age 46.9) and had a lower body mass index (BMI) than subjects without erosions (mean age 49.6) ($p<0.0001$ for both). Those with erosions were significantly more likely to have a positive anti-CCP antibody ($p=0.0001$) and have higher disease activity scores (DAS-28) (0.0008) than those without erosions. Additionally the multivariate model revealed that T-scores for the lumbar spine and hips were also significantly lower in RA patients with erosions compared to patients without erosions ($p=0.0002$ and <0.0001 respectively). A significantly larger proportion of patients with erosions were on anti-TNF therapy and osteoporosis medications compared with those without erosions ($p<0.0001$ and 0.0003).

Conclusion: RA patients with erosions were younger, more likely to have an anti-CCP antibody and have more active disease as measured by the DAS-28, compared to subjects without erosions. Interestingly patients with erosions also had a lower BMI compared with RA patients without erosions. The presence of bone erosions in patients with RA was significantly associated with lower T-scores at the lumbar spine and hips. These data suggest a relationship between localized and generalized bone loss in patients with RA.

Disclosure: A. P. Anandarajah, None; **M. El-Taha**, None; **C. Peng**, None; **J. D. Greenberg**, Corrona, 5 ; **C. Ritchlin**, None.

ACR Poster Session A

Rheumatoid Arthritis Treatment: Steroids, Methotrexate, and Novel Targets

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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A Phase 2 Study to Assess the Efficacy and Safety of Maraviroc, a CCR-5 Antagonist in the Treatment of Rheumatoid Arthritis. D. Fleishaker[1], X. Wang[2], S. Menon[2], Bernhardt G. Zeiher[3] and T.C. Stock[2], [1]Pfizer, Inc., Chesterfield, MO, [2]Pfizer, Inc., New London, CT, [3]Pfizer Global Research and Development, New London, CT

Purpose: Maraviroc (MVC) is an antagonist of the human chemokine receptor 5 (CCR5) and has been approved for use in treatment of patients infected with the CCR5-tropic human immunodeficiency virus, Type-1 (HIV). Presence of a nonfunctional receptor of the CCR-5 gene resulting from a 32-base pair deletion has been associated with a reduced incidence and severity of rheumatoid arthritis (RA). Levels of the CCR-5 receptors ligands, RANTES, MIP-1α, MIP-1β are also increased in synovial fluid of RA subjects. Maraviroc 300 mg BID was investigated in this study to determine whether CCR-5 antagonism would prove safe and effective in the treatment of RA patients on background methotrexate (MTX).

Method: This study was divided into two components: Safety/PK (data not shown) and Proof-of-Concept (POC). The Safety/PK component enrolled 16 subjects and demonstrated that MVC 300 mg BID was well tolerated and there was no drug-drug interaction with MTX. The POC component was a randomized, multi-center, double-blind, placebo-controlled, parallel group study. Subjects with active RA, receiving stable weekly MTX (≥ 10 mg and ≤25 mg) for at least 12 weeks were eligible for enrollment if they had at least 6 tender and swollen joints and CRP ≥7.0 mg/L. Subjects were randomized 2:1 to MVC or placebo treatment for 12 weeks and the primary endpoint was ACR20 response. Subjects on background biologic therapy, other oral DMARDs (except antimalarials) and those homozygous for the CCR5Δ32 mutation were excluded from entry.

Results: The study was terminated at the time of a planned interim analysis for futility. 110 subjects were enrolled: 77 (MVC 300 mg BID) and 33 (placebo BID) with similar demographic features across both treatment groups. There was no significant difference between MVC and placebo in ACR20 responder rate utilizing the full analysis set (MVC: 27.27% vs. placebo: 18.18%; p value=0.155); ACR50 and ACR70 were not different. Components of the ACR response, including CRP were not changed. MVC was safe and well tolerated with the majority of AEs mild to moderate in nature. The most common all causality AEs in the MVC-treated group were constipation (7.8%), nausea (5.2%), fatigue (5.2%), urinary tract infection (3.9%) and respiratory tract infection (2.9%) compared to placebo. There were no clinically

significant findings in vital signs, ECG measurements or clinical laboratories including transaminases. There were no SAEs reported in the treated population.

Conclusion: Selective antagonism of CCR-5 using MVC failed to improve the signs and symptoms of RA in subjects with active disease on background MTX. Treatment with MVC was safe and well tolerated in RA subjects over 12 weeks. No impact in transaminases was noted in subjects receiving MVC vs. placebo despite background MTX use in this population.

Disclosure: D. Fleishaker, Pfizer Inc, 3, Pfizer, 1 ; **X. Wang**, Pfizer Inc, 3 ; **S. Menon**, Pfizer Inc, 3 ; **B. G. Zeiher**, Pfizer, Inc, 3 ; **T. C. Stock**, Pfizer Inc, 3, Pfizer Inc, 1 .

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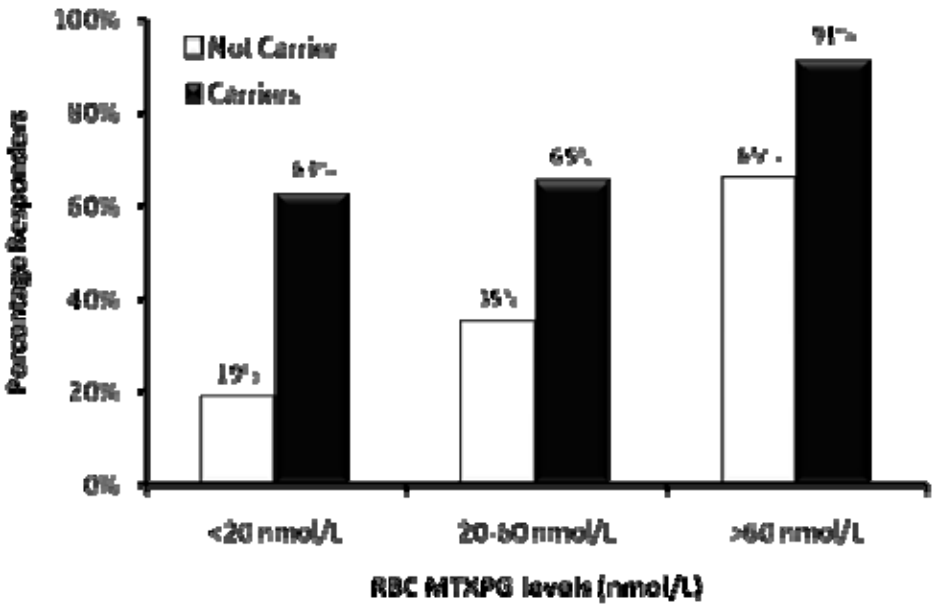
High-Order Epistatic Interactions Between Folate and Adenosine Biological Systems Affect Methotrexate Efficacy in Rheumatoid Arthritis. Thierry Dervieux[1], Judith Wessels[2], Tahar van der Straaten[2], Jason Moore[3], Nadia Penrod[3], Henk-Jan Guchelaar[2] and Joel M. Kremer[4], [1]Cypress Bioscience, San Diego, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Dartmouth-Hitchcock Medical Center, Lebanon, [4]Albany Medical College, Albany, NY

Purpose: No single definitive predisposing genetic marker has emerged as pivotal to the efficacy of Methotrexate (MTX) in rheumatoid arthritis (RA). In this study, we sought to establish that discrete non-linear gene-gene interactions (epistasis) involving multiple low-penetrance single nucleotide polymorphisms in folate, purine and pyrimidine pathways may materialize as combinations modulating MTX effects.

Method: A total of 255 patients treated with low dose MTX were enrolled in a multicentred study at 3 sites. Efficacy to MTX was assessed using the EULAR response criteria or a physician's assessment of patient's response visual analogue scale. A total of 14 single nucleotide polymorphisms were measured together with erythrocyte MTX polyglutamate concentrations (MTXPGs). Detection of non-linear gene-gene interactions was performed using Multifactor Dimensionality Reduction (MDR), a method delineating and deciphering complex interactions among gene networks. MDR reduces the n-dimensions corresponding to the n-genotypes into one dimension by combining high and low predisposing genotypes of efficacy into two separate groups depending on whether they are more common in patients presenting with response or not. The robustness and significance of the model was tested through cross validation consistency (CVC, 10-fold) and 1000-fold permutation testing.

Results: MDR analysis revealed that efficacy (53% responders) was associated with high order epistatic interactions among variants in Inosine Triphosphate Pyrophosphatase (C94A), Amino-Imidazole Carboxamide Ribonucleotide Transformylase (C347G) and Reduced Folate Carrier (G80A) genes. Testing accuracy was 0.638 and CVC was 10/10 (permutation testing $p<0.001$). Significance was achieved independently at all sites ($p<0.05$). Carriers of a predisposing genotype combination were 3.8-fold more likely to respond to MTX than those without (CI95%: 2.2-6.8; $p<0.001$). Sensitivity was 64.7%, specificity was 67.2 % and accuracy was 65.9%. Greater response rates were achieved at low levels of MTXPGs (<20nmol/L) in the presence of predisposing genotype combinations versus in their absence (63% vs. 19% responders) ($p<0.001$). However, the increase of MTXPGs from low to high levels produced greater rates of improvements in the absence of predisposing genotype combinations, (OR: 8.1, CI95%: 2.4-31.8; $p<0.001$) than in their presence (OR= 3.6; CI95%: 1.1-12.5; $p<0.001$). At high MTXPG levels achieved (i.e. >60nmol/L) a convergence in response rates was observed (65% vs. 91% responders), thereby indicating that the disadvantage in the absence of predisposing genotype combinations was reduced as function of increasing MTXPG levels.



Conclusion: These hypothesis generating data indicate that epistatic interactions in folate and purine pathways selectively modulate the effects of MTX in RA.

Disclosure: T. Dervieux, Cypress Bioscience, 3 ; **J. Wessels**, None; **T. van der Straaten**, None; **J. Moore**, Cypress Bioscience, 5 ; **N. Penrod**, None; **H. J. Guchelaar**, None; **J. M. Kremer**, None.

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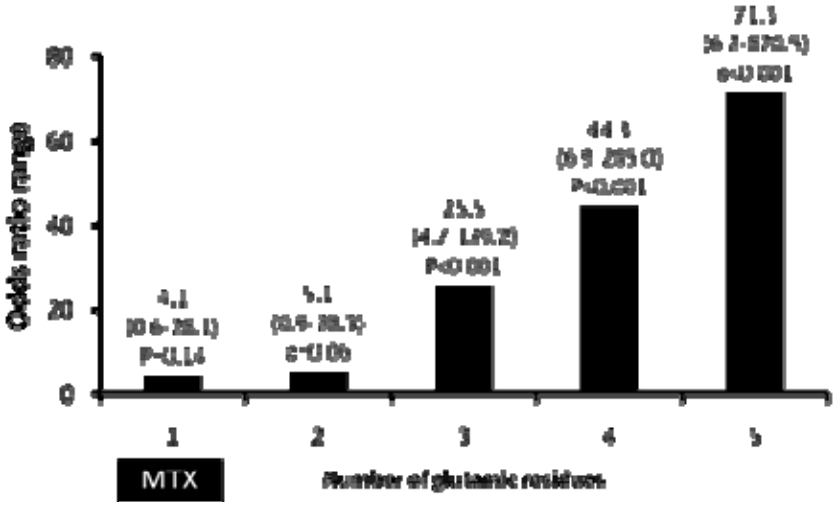
The Sequential Addition of Glutamic Residues On Methotrexate Selectively Potentiates the Efficacy of This Prodrug in Rheumatoid Arthritis. Thierry Dervieux[1], Rong Zablocki[1] and Joel M. Kremer[2], [1]Cypress Bioscience, San Diego, CA, [2]Albany Medical College, Albany, NY

Purpose: Methotrexate (MTX) is an antifolate prodrug activated to MTX polyglutamates (MTXPGs) through a Folylpolyglutamate Synthase mediated sequential addition of glutamic residues added to MTX. In vitro, this process selectively enhances the inhibition of Aminoimidazole Carboxamide Ribonucleotide (AICAR) Transformylase (PNAS 15:4881-5 1985), a *de novo* purine biosynthesis enzyme whose inhibition results in the release of adenosine, a potent anti-inflammatory agent. A relationship between an increasing number of glutamic residues on MTX and its anti-inflammatory/therapeutic effects in rheumatoid arthritis (RA) has yet to be established.

Method: A total of 256 patients treated with low dose MTX for at least three months were enrolled in a multicentred study at 3 sites. MTX efficacy was assessed using the EULAR response criteria or a physician's assessment of patient's response to MTX visual analogue scale as previously described (Arthritis Rheum. 2004 50:2766-74). Red cells MTXPGs concentrations were measured using liquid chromatography with post column photo-oxidation technique (limit of detection 2 nmol/L). Statistical analysis consisted of logistic regression with dose and MTXPGs as independent variables.

Results: There was a large interpatient variability in MTX dosing (median 15 mg/week, range 5-25mg) and MTXPG accumulation. A total of 53% patients were responders. MTXPG levels (median, [range]) were $MTXPG_1$: 23 nmol/L (<2-157), $MTXPG_2$: 19 nmol/L (<2-72), $MTXPG_3$: 37 nmol/L (<2-132), $MTXPG_4$: 8 nmol/L (<2-83) and $MTXPG_5$: <2 nmol/L (<2-51). Poor efficacy was associated with higher dosage administered ($p<0.01$). Long chains $MTXPG_3$ represented 38% of total MTXPGs while very long chains $MTXPG_5$ accounted for only 2.4% of total MTXPGs. Short chains MTXPG ($MTXPG_{1-2}$) were not significantly associated with efficacy ($p>0.06$; Figure). In contrast, the increase in $MTXPG_3$ levels from undetectable levels to 132 nmol/L was associated with a 25.5-fold (CI95%: 4.7-139.2) higher likelihood of response to MTX ($p<0.001$). Further addition of glutamic residues appeared to enhance the efficacy of MTX as an increase in $MTXPG_5$ levels from undetectable levels to 51 nmol/L resulted in a 71.3 fold higher likelihood of response (CI95%: 6.2-820.5; $p<0.001$; Figure).



Conclusion: We have demonstrated for the first time that the sequential addition of glutamic residues on MTX selectively potentiates the efficacy of this prodrug in patients with RA. These in vivo data are consistent with in vitro findings establishing that the increasing number of glutamic residues on MTX produces several fold greater inhibition of AICAR Transformylase, and lends further indirect evidence that AICAR accumulation mediates MTX's anti-inflammatory effects through the release of adenosine.

Disclosure: T. Dervieux, Cypress Bioscience, 3 ; **R. Zablocki**, Cypress Bioscience, 3 ; **J. M. Kremer**, None.

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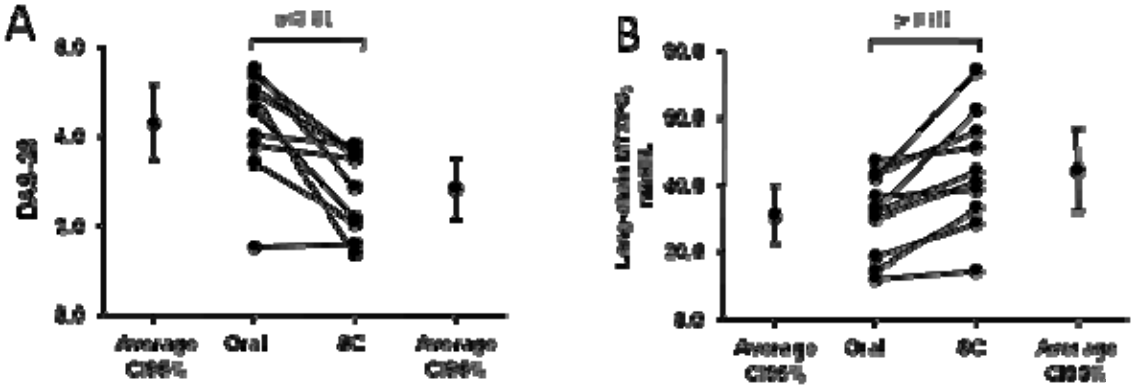
Switching From Oral to Parenteral Methotrexate Administration Produces Clinical Improvements through Selective Accumulation of Long-Chains Methotrexate Polyglutamates. Joel M. Kremer[1], Rong Zablocki[2] and Thierry Dervieux[2], [1]Albany Medical College, Albany, NY, [2]Cypress Bioscience, San Diego, CA

Purpose: Methotrexate (MTX) is effective in rheumatoid arthritis (RA), yet large interpatient variability in MTX absorption and activation to MTX polyglutamates (MTXPGs) often preclude the achievement of appropriate exposure to maximize antiarthritic effects. We evaluated the effects of switching from oral to parenteral MTX on disease activity and MTXPG accumulation in patients with RA.

Method: A total of 10 patients with RA taking oral MTX (dose 17.7±0.8 mg; average±SEM) for 27±3.0 weeks and presenting with a disease activity score (DAS28) of 4.3±0.4 were switched from oral to parenteral administration of MTX to control disease activity. In 4 patients, parenteral administration was also associated with an increase in MTX dose (final average dose 19.0±0.8 mg). At the time of the following visit (average 8.7±1.4 weeks later) DAS28 was determined together with MTXPG levels. Physicians were blinded to MTXPG concentrations. The intrapatient variability in RBC MTXPG levels was assessed in a total of 25 patients receiving a stable oral dose of MTX (range 7.5 to 20 mg/week) for at least 6-weeks. RBC MTXPG levels were determined twice, with the first determination made after 27 weeks (median) therapy (range 13-40 weeks) and the second determination made after 36 weeks (median) therapy (range 21-49 weeks). Long-chains RBC $MTXPG_3$ were measured using liquid chromatography and the change in DAS28 and MTXPG levels between visits were assessed using Wilcoxon paired test or regression analysis.

Results: The intrapatient variability (assessed using the coefficient of variation, CV) was low for MTXPG (median CV=10%) levels when patients were under a stable dose of oral MTX. The Figure (panel A) indicates that switching from oral to parenteral administration of MTX was associated with significant reduction in disease activity (median change -31%; p=0.004). In one patient the decrease in disease activity was only evident after 19 weeks of parenteral MTX. The change in MTX dosage was not associated with reduction in disease activity (p=0.39). In contrast, median percentage increase in RBC MTXPGs levels before and after parental switch was 37% (range 6%-123%) (p=0.002; panel B). The percentage change in the disease activity score was associated with the absolute change in MTXPGs levels (R^2=0.50; p=0.022) thereby indicating that parenteral administration of MTX produced greater antiarthritic effects through greater accumulation of MTXPGs.



Conclusion: These data suggest that switching from oral to parenteral MTX administration produces clinical improvements through selective accumulation of long-chains MTXPGs and are consistent with the observation that parenteral administration is significantly more effective than oral administration (Arthritis Rheum. 2008 58:73-81).

Disclosure: J. M. Kremer, None; **R. Zablocki**, Cypress Bioscience, 3 ; **T. Dervieux**, Cypress Bioscience, 3 .

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MEDI5117: A Human High Affinity Anti-IL-6 Monoclonal Antibody with Enhanced Serum Half-Life in Development for the Treatment of Inflammation and Rheumatological Diseases. Jacques Moisan[1], Raffaella Faggioni[2], Meina Liang[2], Michael A. Bowen[1], Amy K. Schneider[2], Rozanne Y.W. Lee[2], Inna Vainshtein[2], T. Scott Manetz[1], Lolke de Haan[3], LuAnn McKinney[1], Laura Richman[1], Rob Woods[1], William Dall'Acqua[1], Donna K. Finch[3], Philip R. Mallinder[4], S. Cruwys[4], Steven Lane[3], Matthew Sleeman[3], Lorin K. Roskos[1], Herren Wu[1], Bahija Jallal[1], Anthony J. Coyle[1], Roland Kolbeck[1] and Michael Fung[1], [1]MedImmune LLC, Gaithersburg, MD, [2]MedImmune LLC, Hayward, CA, [3]MedImmune Ltd, Cambridge, United Kingdom, [4]AstraZeneca R&D Charnwood, Loughborough, United Kingdom

Purpose: IL-6 is a pleiotropic pro-inflammatory cytokine linked to the pathogenesis of numerous inflammatory conditions, such as rheumatoid arthritis, lupus, Crohn's disease and cancer.

Method: Here we report the generation and characterization of an affinity-optimized human anti-IL-6 monoclonal antibody IgG1 (MEDI5117) which incorporates YTE Fc modification to extend its plasma half-life.

Result: This modification does not alter the biological potency and specificity of MEDI5117 in comparison with its parent mAb. MEDI5117 binds to recombinant human IL-6 with high affinity in ELISA, consistent with the results from KinExa assays for affinity constant determination (KD < 1 pM). MEDI5117 exhibits potent neutralizing activity against recombinant human IL-6-induced TF-1 cell proliferation (IC50 = 5.2 pM) *in vitro* via inhibition of productive engagement of IL-6 with membrane-bound IL-6Rα (classical signaling mechanism). In addition, MEDI5117 also displays high neutralizing activities (IC50 = 1.2 nM) against native human IL-6-induced VEGF production by fibroblast-like synoviocytes from rheumatoid arthritis patients in the presence of exogenous recombinant soluble IL-6Rα (trans-signaling mechanism). In both assays, MEDI5117 shows similar or slightly better anti-IL-6 neutralizing actvities as compared to a benchmark anti-IL-6 monoclonal antibody (CNTO-136). Mutagenesis studies of human IL-6 show that MEDI5117 binds to an epitope on IL-6 known to be responsible for IL-6Rα interaction. In a pharmacokinetic and pharmacodynamic study in cynomolgus monkeys, MEDI5117 shows approximately 3 fold longer plasma half-life than the parent mAb when given by iv (28 vs 8.5 days) and sc (27 vs 9.1 days) administrations.

Conclusion: Together, our data demonstrate that MEDI5117 is a potent anti-IL-6 human monoclonal antibody with superior pharmacokinetic properties. Therefore, MEDI5117 is an attractive candidate for development to treat IL-6-mediated inflammation, autoimmune diseases, and cancer.

Disclosure: J. Moisan, Medimmune, 3, Astra Zeneca, 1 ; **R. Faggioni**, MedImmune, 3 ; **M. Liang**, Medimmune, 3 ; **M. A. Bowen**, Medimmune, 3 ; **A. K. Schneider**, None; **R. Y. W. Lee**, None; **I. Vainshtein**, None; **T. S. Manetz**, MedImmune, 3, MedImmune, 1 ; **L. de Haan**, None; **L. McKinney**, Medimmune,

3, Astra Zeneca, 1 ; **L. Richman**, MedImmune, 3 ; **R. Woods**, MedImmune, 3 ; **W. Dall'Acqua**, MedImmune, 3 ; **D. K. Finch**, MedImmune Ltd, UK, 3 ; **P. R. Mallinder**, AstraZeneca, 3 ; **S. Cruwys**, AstraZeneca, 3 ; **S. Lane**, Medimmune Ltd, 3 ; **M. Sleeman**, MedImmune, 3 ; **L. K. Roskos**, Medimmune, 1, Medimmune, 3 ; **H. Wu**, Medimmune, 3 ; **B. Jallal**, MedImmune, 3 ; **A. J. Coyle**, medimmune, 1 ; **R. Kolbeck**, MedImmune, LLC, 3 ; **M. Fung**, MedImmune, LLC, 3 .

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Hypothalamus-Pituitary-Adrenal (HPA)-Axis Function in Rheumatoid Arthritis (RA) Patients Treated with Either Standard or Modified-Release Prednisone. Rieke Alten[1], Gisela Doering[2], Stephan Witte[3], Rainer H. Straub[4], Maurizio E. Cutolo[5], Erika Gromnica-Ihle[6] and Frank Buttgereit[7], [1]Schlosspark-Klinik, Berlin, Germany, [2]Merck KGaA, Darmstadt, Germany, [3]Nitec Pharma GmbH, Mannheim, Germany, [4]University Hospital Regensburg, Regensburg, Germany, [5]University of Genova, Genova, Italy, [6]Berlin, Germany, [7]Charite University Med-Berlin, Berlin, Germany

Purpose: Glucocorticoids (GCs) are effective anti-inflammatory and immunosuppressive drugs for the treatment of rheumatic diseases. Prednisone chronotherapy of RA with a modified-release (MR) tablet, allowing drug release during the rising flank of the circadian cortisol cycle is a novel approach to improve GC therapy. In the CAPRA1 study, the MR formulation was more effective than an identical dose of the immediate release (IR) prednisone administered in the morning (1). As part of this study, we investigated the effects of the two formulations on the HPA axis.

Methods: A total of 32 Corticotropin-Releasing-Hormone (CRH) tests were performed in patients treated with IR prednisone (5.3 mg; 0.82) and 30 tests in patients treated with MR prednisone (5.6 mg; 1.56) during the 12-month study (mean daily dose; SD). Changes of cortisol were assessed and compared to individual patients' efficacy and safety data.

Results: At baseline the increase (mean, SD; highest of two post-injection assessments) of serum cortisol after the injection of corticorelin was 5.5 (4.37) µg/dL in patients on IR prednisone (n=21) and 5.3 (4.07) µg/dL on MR prednisone (n=22) at the end of the study. Normal / suppressed / no response-reactions were similarly frequent in both treatments. Switching from IR to MR prednisone did not influence responses, nor did treatment up to 12 months with MR prednisone. No adverse events indicating an impairment of the HPA-axis such as signs and symptoms of Addison's disease or adrenal crisis were detected during the course of the study.

Conclusion: No differences were seen between the treatments regarding influence on HPA-axis function. Since MR prednisone has been shown to reduce duration of morning stiffness better than IR prednisone, we conclude that chronotherapy with this novel drug improves the risk-benefit ratio of long-term low-dose GC treatment in patients with RA

(1) Buttgereit et al. Lancet 2008; 371:205-214

Disclosure: R. Alten, None; **G. Doering**, Merck KGaA, 1, NitcPharma AG, 3 ; **S. Witte**, Nitec Pharma GmbH, 3, Nitec Pharma AG, 1 ; **R. H. Straub**, None; **M. E. Cutolo**, None; **E. Gromnica-Ihle**, None; **F. Buttgereit**, Merck Pharma GmbH, 2, Merck Pharma GmbH, 5, Merck Pharma GmbH, 8, Nitec Pharma AG, 2, Nitec Pharma AG, 5, Nitec Pharma AG, 8 .

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Sustained Safety and Efficacy of TRU-015 with Continued Retreatment of Rheumatoid Arthritis Subjects Following a Phase 2B Study. S. Stromatt[1], V. Chopiak[2], L. Dvoretskiy[3], G. Koshukova[4], E. Nasonov[5], V. Povoroznyuk[6], M. Stanislavchuk[7] and P. Leith[1], [1]Trubion Pharmaceuticals, Seattle, WA, [2]Lviv Reg Clin Hosp, Lviv, Ukraine, [3]Moscow Med Acad, Moscow, Russia, [4]Republic Hosp Semashko, Simpheropol, Ukraine, [5]Institute of Rheumatology, Moscow, Russia, [6]Institute of Gerontolgy, Kiev, [7]Vinnytsia Nat Med Univ, Vinnytsia, Ukraine

Background: In a Phase 2b double-blind, placebo-controlled randomized clinical trial, 276 subjects with active rheumatoid arthritis received a single infusion of placebo, 200, 400, 800 or 1600mg of TRU-015, a CD20-directed small modular immunopharmaceutical (SMIP ™) protein. Improvement in rheumatoid arthritis disease activity was observed in the 800mg and 1600mg dose groups at 24 weeks. Subjects were eligible to enter an open label retreatment phase and receive 800mg of TRU-015 at 24 week intervals. Further improvement in disease activity was observed after the first retreatment (R1). Data from the second retreatment (R2) are now reported.

Purpose: To evaluate the safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK) and clinical activity of repeat doses of TRU-015.

Method: All subjects were evaluated for safety. PK parameters were calculated from serum concentration data analyzed by ELISA, and PD, measured by B-cell depletion, was evaluated using CD19+ cell counts. Efficacy assessments were performed on RF+ subjects and included ACR responses (20/50/70) and improvement in DAS28 measured in relationship to baseline values.

Results: 226 subjects (94% of 240 subjects from R1) received R2. Retreatment infusions were generally well tolerated; no subjects experienced a serious adverse event on the day of infusion. 7 subjects (3%) experienced SAEs during the second retreatment period, similar to the incidence observed in the initial double blind phase of the study (placebo 2%, 800mg group 4%) and first retreatment (4%). Subjects treated with 800mg in the initial treatment, R1, and R2 demonstrated comparable PD and PK parameters after each treatment. At 24 weeks after R2, this group achieved ACR 20, 50 and 70 response rates of 72%, 39%, and 21%, respectively, which were similar to the response rates after R1 (70%, 40% and 23%, respectively). Numeric reductions of DAS28, HAQ, and CRP seen at the end of the double-blind treatment period and first retreatment period were maintained or continued to improve during the second retreatment period.

Conclusion: Repeat administration with TRU-015 is generally well tolerated, exhibits pharmacodynamic and pharmacokinetic profiles comparable to initial treatment, and results in sustained improvement in rheumatoid arthritis disease activity.

Disclosure: S. Stromatt, Trubion, 3 ; **V. Chopiak**, None; **L. Dvoretskiy**, None; **G. Koshukova**, None; **E. Nasonov**, None; **V. Povoroznyuk**, None; **M. Stanislavchuk**, None; **P. Leith**, Trubion, 3 .

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Corticosteroids Increase Risk for Acute Myocardial Infarction in Rheumatoid Arthritis: The Effects of Careful Modeling of Cumulative Exposure. J. Antonio Avina-Zubieta[1], Michal Abrahamowicz[2], Hyon K. Choi[1], M. Mushfiqur Rahman[1], Marie Pierre Sylvestre[3], John M. Esdaile[1] and Diane Lacaille[1], [1]Arthritis Research Centre of Canada / University of British Columbia, Vancouver, BC, [2]McGill University, Montreal, QC, [3]Samuel Lunenfeld Research Institute., Toronto, ON

Purpose: To determine the effect of corticosteroids (CS) on the risk of acute myocardial infarction (AMI) in rheumatoid arthritis (RA).

Methods: We assembled a retrospective longitudinal cohort of all incident RA cases from Jan 1997 to Dec 2001 followed until March 2006 using administrative data. We excluded cases with prior CS use or AMI at baseline. CS exposure was defined as any dispensed prescription for oral CS during follow up. We used 4 exposure measures to assess the impact of CS on the risk of AMI (Table 1). We used propensity scores (PS) to control for the observed differences between CS users and non users on 12 covariates (age, gender, hypertension, diabetes, angina, hypercholesterolemia, use of other cardiovascular drugs, COPD, Charlson's index, physician responsible of care, and # of medical visits per year), and included them as covariates in the final model because of residual imbalance within PS quintiles. The primary outcome was time to the first AMI event during the study period (hospitalizations or death from AMI). To account for possible cumulative effects of CS use, we used a novel time-dependent Cox model that considers dose and timing of CS exposure. Thus, at any point during the follow-up, cumulative dose is calculated as a weighted mean of past doses, with higher weights assigned to more recent doses (Model 4). We used a 6 months exposure time window for the weighting function (models 3-5). Methotrexate (MTX), NSAID's, and Cox-2 inhibitors use were represented as time-dependent covariates.

Results: 6,981 RA cases provided 42,792 person-years of follow up. Of these 2,789 (40%) were CS users. There were 248 incident AMI events (4 %) during the follow up. CS increased the risk of AMI in all models (Table 1). In each model CS exposure is represented by a different time-dependent covariate. To explore the importance of dose vs duration of use, we included 2 time-dependent exposure measures (Model 5). Weighted cumulative duration of use was not associated with AMI, but current dose was. MTX and care by rheumatologist showed statistically significant protective effects for AMI (HR from **0.42 to 0.44** and **0.48 to 0.53,** respectively in all models).

Conclusion: CS exposure in people with RA is independently associated with a higher risk of AMI, with a 2% increase in risk per 1 mg increase in the mean daily prednisone dose, regardless of the duration of use. Careful modeling of CS exposure history may enhance the understanding of the mechanisms underlying their adverse effects. MTX use and care by rheumatologist were associated with decreased risk of AMI

Model	Exposure measurement	Hazard Ratio (95% CI)			
		Unadjusted	P value	Adjusted	P Value
1	Current use (yes/no)	2.14 (1.49 – 3.08)	0.0001	1.60 (1.08 - 2.43)	0.02
2	Current dose (mg)	1.03 (1.02 - 1.04)	0.0001	1.01 (1.01 – 1.02)	0.001
3	Cumulative duration (month)	1.33 (1.17 – 1.52)	0.0001	1.21 (1.04 – 1.41)	0.01
4	Cumulative dose (per g)	1.01 (1.01 – 1.02)	0.0002	1.01 (1.004 – 1.018)	0.001
5	Current dose +	1.02 (1.01 – 1.04	0.01	1.02 (1.002 – 1.038)	0.03
	cumulative duration	1.25 (1.08 – 1.45)	0.003	1.13 (0.95 – 1.34)	0.15

Disclosure: J. A. Avina-Zubieta, None; **M. Abrahamowicz**, None; **H. K. Choi**, None; **M. M. Rahman**, None; **M. P. Sylvestre**, None; **J. M. Esdaile**, None; **D. Lacaille**, None.

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Characterization of a Potent and Neutralizing Fully Human Anti CD44 Antibody PF 03475952. Herbert A. Runnels[1], Gregory L. Weber[1], Jing Min[1], Elizabeth Kudlacz[2], James Zobel[1], Carol Donovan[2], Mark Thiede[2], Jun Zhang[1], Robbin Alpert[2], Michelle Salafia[2], Douglas Burdette[3], Rosonald Bell[2], Jean Beebe[2] and Xu Xu[2], [1]Pfizer Global Research and Development, Chesterfield, MO, [2]Pfizer Global Research and Development, Groton, CT, [3]Pfizer Global Research and Development, Ann Arbor

Purpose: CD44 is a cell adhesion molecule believed to play a critical role in T cell and monocyte infiltration in the inflammatory process. The reduction of CD44 expression or its ability to properly interact with its key ligand hyaluronic acid (HA) inhibits migration and subsequent activation of cells within sites of inflammation such as synovial tissue and is expected to decrease production of pro-inflammatory cytokines such as TNF-a, IL-6, and IL-1b in the synovium. The genetic knock-out of CD44 expression in mice resulted in a decreased incidence and severity of disease in a mouse arthritis model.

Method: We developed PF-03475952 which is a fully human IgG_2 anti-CD44 monoclonal antibody (mAb).

Results: Binding of PF-03475952 to CD44 inhibits binding of HA, induces loss of CD44 from the cell surface, and inhibits LPS-induced cytokine release from various leukocytes. PF-03475952 also passed a series of safety pharmacology assays designed to assess the risk of the mAb to bind Fc receptors, activate complement, stimulate cytokine release from human whole blood and stimulate cytokine release from peripheral blood mononuclear cells using platebound stimuli. The latter assay was designed specifically to mitigate the cytokine storm potential as seen with TGN1412 (the immunostimulatory CD28 superagonist mAb) and utilized a TGN1412-like mAb as a positive control. PF-03475952 exhibits high affinity binding to both human and cynomolgus monkey CD44, but does not cross-react with rodent CD44. Thus, supporting the rationale of anti-CD44 therapy, a surrogate, rat anti-mouse CD44 mAb (IM7) was utilized to demonstrate a dose-dependent decrease of disease incidence and severity in a mouse collagen-induced arthritis model. Importantly, efficacy was correlated with ≥ 50% loss (measured at 24h post final dose) of cell surface CD44 on circulating cells, which provided a pharmcodynamic marker for both monkey studies and human clinical trials. Loss of CD44 expression on $CD3^+$ lymphocytes was monitored following a single dose in cynomolgus monkeys. The recovery of CD44 expression was found to be dose-dependent. PF-03475952 doses of 1, 10 and 100 mg/kg reduced CD44 expression below 50% for 218, 373 and >504 h, respectively.

Conclusion: Targeting of CD44 is a unique mechanism of action in the treatment of inflammatory diseases and is expected to reduce joint damage induced by inflammatory mediators resulting in disease modification in inflammatory diseases such as RA.

Disclosure: H. A. Runnels, Pfizer Inc, 3 ; **G. L. Weber**, Pfizer Inc, 3, Pfizer Inc, 1 ; **J. Min**, Pfizer Inc, 3 ; **E. Kudlacz**, Pfizer Inc, 3 ; **J. Zobel**, Pfizer Inc, 3 ; **C. Donovan**, Pfizer Inc, 3 ; **M. Thiede**, Pfizer Inc, 3 ; **J. Zhang**, None; **R. Alpert**, Pfizer Inc, 3 ; **M. Salafia**, Pfizer Inc., 3 ; **D. Burdette**, None; **R. Bell**, None; **J. Beebe**, Pfizer Inc, 3 ; **X. Xu**, Pfizer Inc, 3 .

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Tetracycline Antibiotics for Treating Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. M. H. Q. Adwan, Wycombe hospital, High Wycombe, United Kingdom

Background: Tetracycline antibiotics have been used in Rheumatoid arthritis (RA) since the late 1940s. Animal and in vitro studies have shown them to modify the inflammatory process in various ways unrelated to their antimicrobial activities. These include effects on matrix metalloproteinases, Nitric oxide, phospholipase A_2, inflammatory cytokines, immunomodulatory and anti-oxidant effect, as well as effects on angiogenesis, apoptosis, MAP kinases, TGF beta and poly (ADP-ribose) polymerase-1.

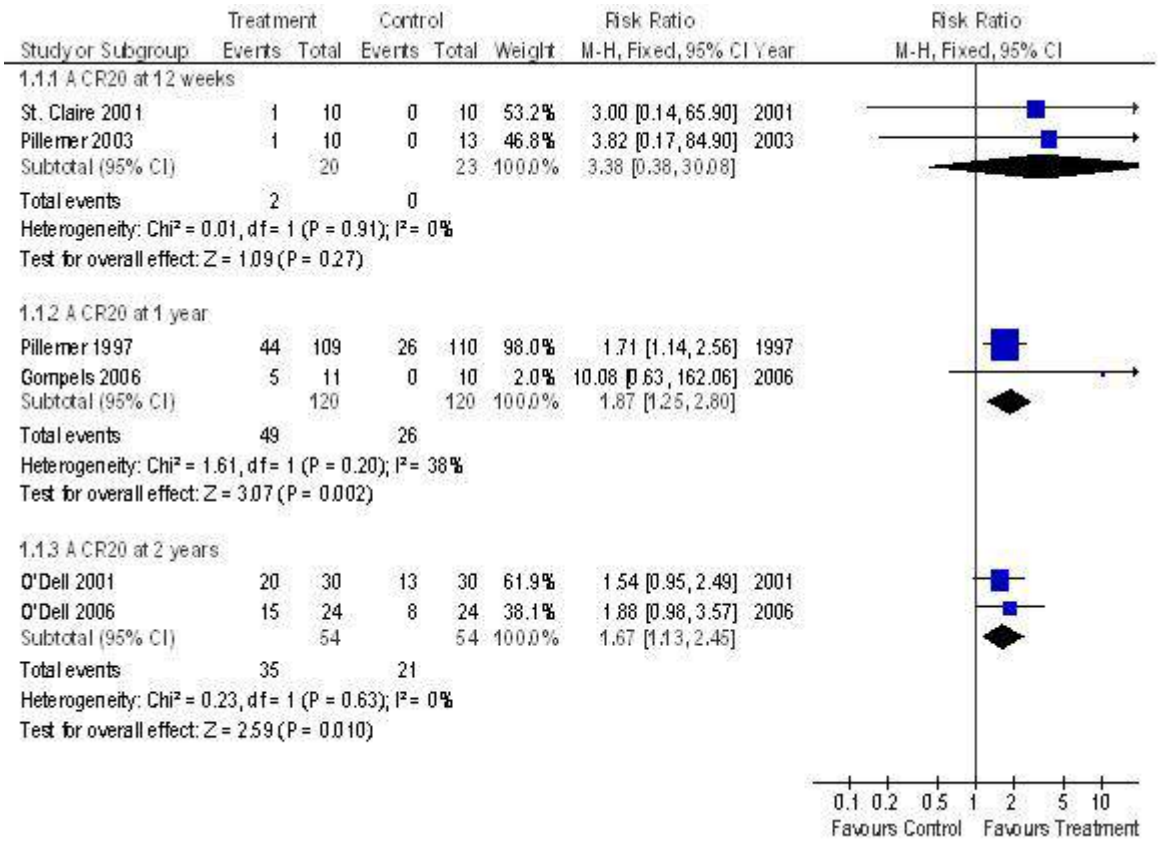
Purpose: To investigate the effectiveness of tetracycline antibiotics in controlling disease activity in RA.

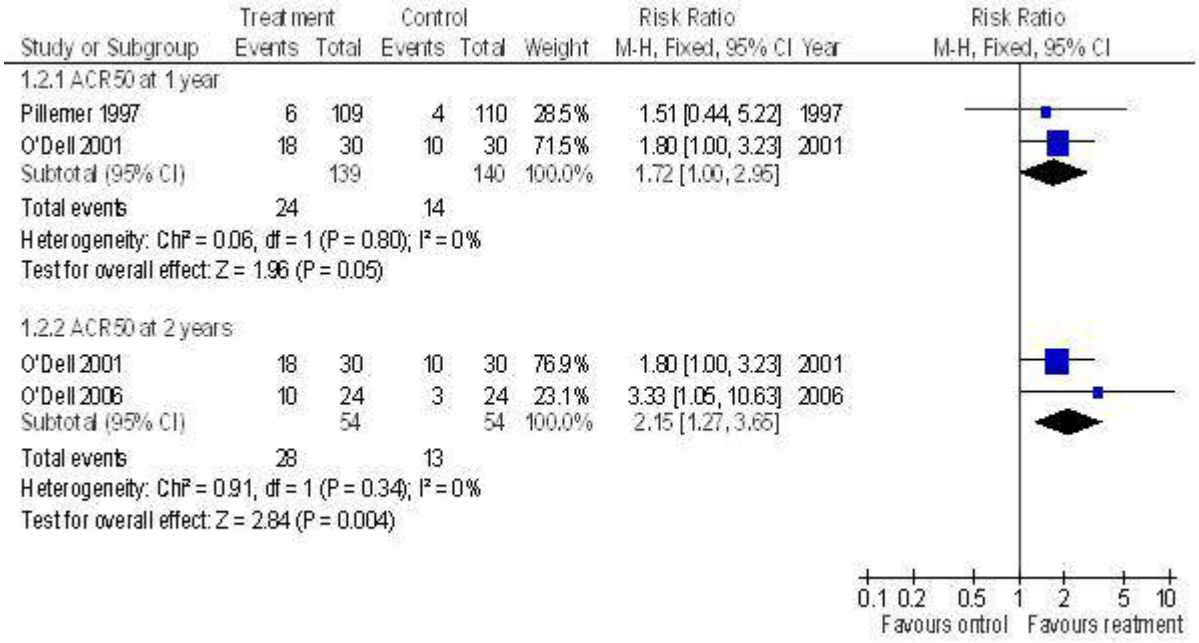
Methods: The following databases were searched: Medline (1950 to January week 3 2009), The Cochrane Central Register of Controlled Trials (Issue I, 2009) and Embase (1966-2008) for randomised controlled trials (RCTs) investigating the use of tetracycline antibiotics in RA. In addition, the reference lists of included studies were also searched.

All RCTs comparing tetracycline antibiotics to placebo or other disease modifying drugs were included. Data were collected on a pre-designed form. Methodological quality was assessed using the Cochrane 'risk of bias' tool. Outcome measures included ACR20, 50 and 70, components of the ACR core set, radiological changes and adverse effects. Continuous data were reported as weighted mean difference (WMD). Dichotomous data were reported as relative risk (RR).

Results: The search yielded 268 studies, of which 11 studies, including 562 patients, were included in the meta-analysis. The meta-analysis showed a significant improvement in the proportion of patients achieving ACR20 and ACR50 at one and two years compared to placebo or conventional treatment (RR: ACR20 1.87 at 1 year and 1.67 at 2 years, ACR50 1.72 at 1 year and 2.15 at 2 years) . There was no effect on radiological change. Total withdrawals and withdrawals due to lack of efficacy were significantly less for tetracyclines. Withdrawals due to adverse events were more in the antibiotic group than the control group (RR 2.28). But individual adverse effects were not different between treatment and control. The quality of evidence was low to moderate due to the small size of available studies.

Conclusion: Tetracycline antibiotics may be potentially effective and reasonably safe in rheumatoid arthritis.


Treatment
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
1.1.1 ACR20 at 12 weeks
St. Claire 2001 1 10 0 10 53.2% 3.00 [0.14, 65.90] 2001
Pillemer 2003 1 10 0 13 46.8% 3.82 [0.17, 84.90] 2003
Subtotal (95% CI) 20 23 100.0% 3.38 [0.38, 30.08]
Total events 2 0
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.27)
1.1.2 ACR20 at 1 year
Pillemer 1997 44 109 26 110 98.0% 1.71 [1.14, 2.56] 1997
Gompels 2006 5 11 0 10 2.0% 10.08 [0.63, 162.06] 2006
Subtotal (95% CI) 120 120 100.0% 1.87 [1.25, 2.80]
Total events 49 26
Heterogeneity: Chi² = 1.61, df = 1 (P = 0.20); I² = 38%
Test for overall effect: Z = 3.07 (P = 0.002)
1.1.3 ACR20 at 2 years
O'Dell 2001 20 30 13 30 61.9% 1.54 [0.95, 2.49] 2001
O'Dell 2006 15 24 8 24 38.1% 1.88 [0.98, 3.57] 2006
Subtotal (95% CI) 54 54 100.0% 1.67 [1.13, 2.45]
Total events 35 21
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.59 (P = 0.010)
0.1 0.2 0.5 1 2 5 10
Favours Control Favours Treatment


Treatment
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
1.2.1 ACR50 at 1 year
Pillemer 1997 6 109 4 110 28.5% 1.51 [0.44, 5.22] 1997
O'Dell 2001 18 30 10 30 71.5% 1.80 [1.00, 3.23] 2001
Subtotal (95% CI) 139 140 100.0% 1.72 [1.00, 2.95]
Total events 24 14
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)
1.2.2 ACR50 at 2 years
O'Dell 2001 18 30 10 30 76.9% 1.80 [1.00, 3.23] 2001
O'Dell 2006 10 24 3 24 23.1% 3.33 [1.05, 10.63] 2006
Subtotal (95% CI) 54 54 100.0% 2.15 [1.27, 3.65]
Total events 28 13
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.004)
0.1 0.2 0.5 1 2 5 10
Favours ontrol Favours reatment

Disclosure: M. H. Q. Adwan, None.

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Functional Polymorphisms within the Folate Pathway Predict Red Blood Cell Folate Concentrations but Are Not Associated with Methotrexate Response in RA. Lisa Stamp[1], J.L. O'Donnell[2], PT Chapman[3], M. Zhang[4], C. Frampton[5], M. Barclay[4], M. Kennedy[5] and R. Roberts[5], [1]University of Otago, Dunedin, New Zealand, [2]Canterbury Health Laboratories, Christchurch, [3]Christchurch Hospital, New Zealand, [4]Christchurch Hospital, Christchurch, New Zealand, [5]University of Otago, Christchurch, New Zealand

Purpose: It is currently not possible to predict which RA patients will achieve adequate control of disease activity with MTX, nor who will develop adverse effects. The aims of this study were to determine whether polymorphisms of genes encoding enzymes in the folate pathway were associated with MTX efficacy and/or toxicity and red blood cell (RBC) folate concentrations.

Method: A cross-sectional study of 200 RA patients on long-term oral MTX was undertaken. Disease activity was assessed by SJC, TJC, CRP, and DAS28. Low disease activity was defined as DAS28≤3.2. A standardised questionnaire regarding common MTX adverse effects was completed. 13 genes encoding enzymes within the folate pathway previously shown to have an effect on gene expression or function were examined (ABCB1, AMPD1, SLC19A1, MTHFR1298, MTHFR677, MTRR, MTR, MTHFD1, ABCC2, ATIC, ITPA, SHMT and TYMS).

Results: Of the 200 patients, an ESR was not obtained in 8 patients and one patient refused to have DNA sampled leaving 191 for analysis. 72.7% were female and mean age was 60.5 years (18-84 years). Mean duration of RA was 10.4 years (0.25 – 53years). 25.1% of patients had rheumatoid nodules, 62.8% radiographic erosions, 80.6% were RF positive and 76.3% anti-CCP positive. There was no significant association between any of the SNPs examined and SJC, TJC, pain VAS, patient global or physician global scores, or DAS28. Similarly there was no association between any of the SNPs and the low and high disease activity groups. There was a weak association between the presence of any CNS adverse effects and AMPD1 (p=0.04) and between the presence of any GI adverse effects and MTHFD1 (p=0.03). RBC folate concentration was significantly higher in patients with high disease activity compared to low disease activity (mean ± SEM: 786.9 ± 31.2nmol/L vs 664.2 ± 27.4 nmol/L, p=0.002). There was a significant association between RBC folate concentrations and MTHFR 677C>T (p=0.002), MTRR (p=<0.0001), MTHFD1 1958 (p=0.001) and SHMT (p=0.01). There was a dose response relationship between genotype and RBC folate concentrations for MTHFR 677C>T, MTRR, and SHMT. Despite this there was no association between the presence of these SNPs and low disease activity after controlling for RBC folate concentrations.

Conclusion: Polymorphisms for genes in the folate pathway were found to be associated with RBC folate concentrations, and less disease activity was seen in patients with lower RBC folate concentrations. Despite this, no relationship was found between folate pathway gene polymorphisms and response to MTX.

Disclosure: L. Stamp, WYETH, 6 ; **J. L. O'Donnell**, None; **P. Chapman**, None; **M. Zhang**, None; **C. Frampton**, None; **M. Barclay**, None; **M. Kennedy**, None; **R. Roberts**, None.

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Safety, Pharmacokinetics, and Pharmacodynamics of PD-0360324, AHuman Monoclonal Antibody to Monocyte/Macrophage Colony Stimulating Factor, in Healthy Volunteers. Seth Sadis, Arnab Mukherjee, Stephen Olson, Melba Dokmanovich, Robert Maher, Chun-Hua Cai, Vu Le, Megan Crawford, Ronald Fedechko, Lloyd Whitfield, Thomas Stock, Marie-Pierre Hellio le Graverand Gastineau and Bernhardt Zeiher, Pfizer, Inc., New London, CT

Purpose: The monocyte/macrophage cell lineage is required for innate immunity but may also contribute to the pathology of human disease by promoting chronic inflammation. We examined the safety, pharmacokinetics (PK), and pharmacodymanics (PD) of PD-0360324, a novel neutralizing human monoclonal antibody against monocyte/macrophage colony stimulating factor (M-CSF).

Method: Six groups of healthy volunteer subjects received a single intravenous infusion of PD-0360324 or placebo at escalating doses of 3, 10, 30, 100, and 300 mg. The sixth cohort repeated evaluation of the 100 mg dose in an in-patient setting to minimize the influence of lifestyle factors on clinical and laboratory assessments. Safety evaluations and sample collection for PK and PD analyses occurred on days 1, 2, 3, 4, 7, and 14 post-infusion with additional monthly visits to follow PD-0360324 concentrations until below the limit of quantitation.

Results: Forty-eight subjects were enrolled (age 21-55 years). Serum PD-0360324 concentrations increased with escalating doses. The extent of systemic exposure, AUC(0-∞), increased in a greater than dose-proportional manner over the dose range of 3-300 mg. Single doses of PD-0360324 led to rapid dose-dependent suppression of $CD14^{+}CD16^{+}$ monocytes and urinary n-telopeptide of cross-linked collagen I, a marker of bone resorption. Adverse events (AE) were mild to moderate in severity. The most common treatment emergent AEs included headache, elevated blood creatine kinase (CK), upper respiratory tract infection, nasal congestion, oropharyngeal pain, and fatigue. Clinical observations at the highest evaluated dose that were considered potentially dose-limiting included non-pitting edema of the peri-orbital tissue (2 subjects), marked asymptomatic elevation of CK and myoglobinemia (1 subject), and CK elevations of 2.0 to 13.2× ULN (5 subjects). Subjects receiving ≥30 mg of PD-0360324 demonstrated reversible dose-related increases in serum CK and in aspartate transaminase (AST). No subject manifested detectable anti-drug antibody titers.

Conclusion: PD-0360324 exhibited a nonlinear PK profile associated with rapid suppression of PD markers and was generally well tolerated. Because M-CSF regulates the homeostasis of certain tissue macrophage populations, the observed dose-related elevations in CK and AST may reflect the drug's effect on liver macrophages (Kupffer cells), which remove short-lived serum enzymes from the blood. Inhibition of M-CSF is predicted to suppress generalized and focal bone loss and may have less acute infection risk relative to cytokine directed therapies. The safety and efficacy profile of PD-0360324 will be investigated further in a multi-dose study in patients with rheumatoid arthritis.

Disclosure: S. Sadis, Pfizer Inc, 3 ; **A. Mukherjee**, Pfizer Inc, 3 ; **S. Olson**, None; **M. Dokmanovich**, Pfizer Inc, 3 ; **R. Maher**, Pfizer Inc, 3 ; **C. H. Cai**, Pfizer Inc, 3 ; **V. Le**, Pfizer Inc, 3 ; **M. Crawford**, Pfizer Inc, 3 ; **R. Fedechko**, Pfizer Inc, 3 ; **L. Whitfield**, Pfizer, 1 ; **T. Stock**, Pfizer Inc, 3 ; **M. P. Hellio le Graverand Gastineau**, Pfizer Inc, 3 ; **B. Zeiher**, Pfizer, Inc, 3 .

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Prednisone Chronotherapy of Rheumatoid Arthritis: Sustained Efficacy of A Novel Modified-Release Formulation Over 12 Months.

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Purpose: Glucocorticoids (GCs), although not free of side effects, are effective drugs for the treatment of rheumatic diseases due to their anti-inflammatory and immunosuppressive effects. It was hypothesized that the timing of GC administration adapted to the circadian rhythms of endogenous cortisol and the typical morning symptoms of RA might improve the risk-benefit ratio. A modified release (MR) tablet has been developed that releases prednisone 4 hours after ingestion. If taken at bedtime, drug release occurs during the night resulting in peak plasma levels in the early morning. The superiority of the MR prednisone tablet over immediate-release (IR) prednisone was shown in a clinical study in patients with RA who were pre-treated with GCs and DMARDs (Lancet 2008; 371: 205-14). Sustained efficacy and safety were followed up in a 9-month open trial.

Method: Prednisone doses during the study (<10 mg/day) were equivalent to pre-study doses. The primary outcome measure was duration of morning stiffness (MS). Secondary endpoints included interleukin-6 (IL-6) as well as RA disease activity and adverse events.

Results: 288 patients were randomized to study treatments (144 per group, mean age 55 yrs, mean disease duration approx. 10 years). During the 3-month double-blind phase, the mean relative reduction of MS duration was significantly higher with MR prednisone than with IR prednisone (p=0.045). 249 patients of the 251 who had completed the double-blind study continued on MR prednisone. Treatment periods on MR prednisone were 12 months in 104 and 9 months in 115 patients, respectively. After 12 months of treatment, the mean relative reduction of morning stiffness was 55 % and 45 % in the patients with 9 months of MR treatment. In addition, after 9 and 12 months a reduction by one count in the DAS 28 as well as a reduction of intensity of pain by 13 or 11 mm on the 100mm-VAS scale, respectively, was observed. Median reductions in IL-6 were about 50% in both groups. At the end of the study, 37 % of the patients achieved improvement according to the ACR20 criteria. The incidence of adverse events was low throughout the study and in line with published data for low dose GC treatment of RA.

Conclusion: Low-dose prednisone chronotherapy of RA via the new MR tablet provides greater efficacy than conventional immediate-release prednisone. The effects on RA symptoms and the favorable safety profile of low dose MR prednisone therapy persist on long-term treatment of RA for at least 12 months.

Disclosure: F. Buttgereit, Merck Pharma GmbH, 2, Merck Pharma GmbH, 5, Merck Pharma GmbH, 8, Nitec Pharma AG, 2, Nitec Pharma AG, 5, Nitec Pharma AG, 8 ; **G. Doering**, NitecPharma AG, Reinach, Switzerland, 5, Merck KGaA, 1 ; **C. Knauer**, Nitec Pharma AG, 1, Nitec Pharma GmbH, 3 ; **S. Witte**, Nitec Pharma AG, 1, Nitec Pharma GmbH, 3 ; **J. Szechinski**, None; **R. Alten**, Merck Pharma GmbH, 5, Merck Pharma GmbH, 8, Nitec Pharma GmbH, 5 .

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Benefit of Continuing Treatment Beyond 12 Weeks in Patients with Rheumatoid Arthritis Treated with Tocilizumab and DMARDs Who Had Previous Inadequate Responses to DMARDs or TNF Inhibitors. Edward C. Keystone[1], A. John[2] and K. Wong[3], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Roche, Nutley, NJ, [3]Everest Clinical Research Services Inc, Markham, ON

Purpose: Some patients (pts) with rheumatoid arthritis (RA) achieve rapid responses to treatment with biologic agents, but those who do not respond early may still reach clinical responses if treatment is continued. The objective of this post hoc analysis was to assess the midterm course of pts with no or limited responses to treatment with tocilizumab (TCZ) and DMARDs, including methotrexate (MTX), at wk 12.

Method: This analysis was performed using data from pts who participated in 4 phase 3 clinical trials and who had previous inadequate responses to DMARDs (DMARD-IR; pooled data from OPTION, TOWARD, and LITHE) or tumor necrosis factor-α inhibitors (TNFi-IR, RADIATE). Pts were treated for 24 wks with TCZ (4 mg/kg or 8 mg/kg) and DMARDs/MTX. Proportions of nonresponders (NR) in various disease activity parameters (ACR20/50/70, LDAS [DAS28 ≤3.2], DAS28 remission [<2.6]) at wk 12 but who achieved the respective responses at wk 24 (responders [R]) were determined.

Results: The analysis included 2018 DMARD-IR pts and 331 TNFi-IR pts (Table). Response rates at wk 12 for ACR20/50/70, LDAS, and DAS28 remission were numerically higher for pts in the DMARD-IR and TNFi-IR populations who were randomly assigned to TCZ 8 mg/kg than to TCZ 4 mg/kg. Of DMARD-IR pts, more in the TCZ 8 mg/kg (33%) than in the TCZ 4 mg/kg (25%) group who were ACR20 NR at wk 12 responded by wk 24. Similarly, of TNFi-IR pts, more in the TCZ 8 mg/kg (27%) than the TCZ 4 mg/kg (10%) group who were ACR20 NR at wk 12 responded by wk 24. High-level responses became more apparent after 24 wks of TCZ treatment for pts who had not achieved the respective level of responses at wk 12, with absolute response rates numerically higher for pts in the TCZ 8 mg/kg group than in the TCZ 4 mg/kg group.

Conclusion: Results of this analysis indicated that substantial proportions of DMARD-IR and TNFi-IR pts who do not respond to 12 wks of treatment with TCZ and DMARDs achieve responses if treatment is continued for 24 wks. In the more difficult to treat TNFi-IR population, nearly 30% of pts who do not achieve ACR20 or LDAS after 12 wks of treatment with TCZ 8 mg/kg and DMARDs will reach the respective responses by wk 24 if treatment is continued. Clinicians should be aware that some pts require more than 12 wks of TCZ treatment to achieve clinical benefit.

	DMARD-IR n = 2018		TNFi-IR n = 331	
	TCZ 8mg/kg + DMARDs/MTX n = 1406	TCZ 4mg/kg + MTX n = 612	TCZ 8mg/kg + MTX n = 170	TCZ 4mg/kg + MTX n = 161
Week 12 responders, %				
ACR20/50/70	55/27/11	51/23/8	44/23/8	39/14/2
LDAS/DAS28 remission	33/22	18/8	26/14	8/3
Week 12 nonresponders who were responders at week 24 % (n/n)				
ACR20 NR to ACR20	33 (213/637)	25 (73/297)	27 (26/96)	10 (10/98)
ACR 50 NR to ACR50	23 (238/1021)	16 (74/470)	15 (20/131)	11 (15/139)
ACR 70 NR to ACR70	13 (157/1246)	7 (42/562)	6 (10/156)	4 (7/157)
LDAS NR to LDAS	26 (229/883)	17 (81/476)	29 (31/107)	7 (9/131)
DAS28 NR to DAS28	17 (177/1020)	9 (48/532)	19 (24/124)	2 (3/139)
Week 24 responders who were nonresponders at week 12, % (n/n)				
ACR20 NR to ACR20	26 (213/832)	24 (73/304)	31 (26/85)	20 (10/49)
ACR 50 NR to ACR50	46 (238/520)	44 (74/167)	41 (20/49)	56 (15/27)
ACR 70 NR to ACR70	60 (157/260)	60 (42/70)	48 (10/21)	88 (7/8)
LDAS NR to LDAS	42 (229/547)	57 (81/143)	52 (31/60)	64 (9/14)
DAS28 NR to DAS28	50 (177/357)	65 (48/74)	69 (24/35)	50 (3/6)

Disclosure: E. C. Keystone, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals ; **A. John**, Roche Pharmaceuticals, 3 ; **K. Wong**, Roche Pharmaceuticals, 9 .

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Benefit of Continuing Treatment Beyond 12 Weeks in Patients with Rheumatoid Arthritis Who Were Treated with Tocilizumab or Methotrexate Monotherapy. Edward C. Keystone[1], A. John[2] and K. Wong[3], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Roche, Nutley, NJ, [3]Everest Clinical Research Services Inc, Markham, ON

Purpose: Some patients with rheumatoid arthritis (RA) achieve rapid responses to treatment with biologic agents, but those who do not respond early may still achieve clinically important disease control if treatment is continued. The objective of this post hoc analysis was to determine the proportions of patients with active RA who achieved ACR responses, LDAS, and DAS28 remission at week 24, if they were nonresponders at week 12, having continued tocilizumab (TCZ) or methotrexate (MTX) monotherapy.

Method: Post hoc analysis was performed using data from patients who participated in the phase 3 clinical trial, AMBITION. Patients included in the trial had not been treated with MTX within 6 months before randomization and had not discontinued MTX treatment because of lack of clinical response or occurrence of clinically important adverse events. Patients were treated for 24 weeks with TCZ 8 mg/kg every 4 weeks or with an initial dose of MTX 7.5 mg/week, titrated up to 20 mg/week within 8 weeks, for 24 weeks. The proportions of patients who were ACR20/50/70, LDAS (DAS28 ≤3.2), and DAS28 remission (<2.6) nonresponders (NRs) at week 12 but who achieved the respective responses at week 24 (Rs) were determined.

Results: Table. The analysis included 286 patients who had been randomly assigned to TCZ 8 mg/kg and 284 patients who had been randomly assigned to MTX (week 8 mean dose, 17 mg/week). Of patients treated with TCZ who were ACR20 NRs at week 12, 40% achieved ACR20 at week 24. Thus, of patients who achieved ACR20 at week 24, 23% achieved it between weeks 12 and 24. Higher level responses became more apparent after 24 weeks of TCZ treatment for patients who were week 12 NRs. For example, of patients treated with TCZ who achieved ACR70 at week 24, 49% achieved it between weeks 12 and 24. Numerically higher proportions of week 24 Rs treated with MTX than of those treated with TCZ were late responders and achieved clinical responses between weeks 12 and 24.

Conclusion: Results of this analysis indicate that continuing TCZ treatment beyond 12 weeks is important because substantial proportions of patients who do not achieve clinical responses by week 12 will achieve them by week 24.

	Monotherapy			
	TCZ 8 mg/kg n = 286		MTX n = 284	
	Week 12 NRs to week 24 Rs, % (n/n)	Week 24 Rs who were week 12 NRs, % (n/n)	Week 12 NRs to week 24 Rs, % (n/n)	Week 24 Rs who were week 12 NRs, % (n/n)
ACR20 NR to ACR20	40 (46/115)	23 (46/200)	29 (44/152)	30 (44/149)
ACR50 NR to ACR50	27 (47/176)	37 (47/126)	23 (52/224)	55 (52/95)
ACR50 NR to ACR70	12 (21/176)	26 (21/80)	8 (18/224)	42 (18/43)
ACR70 NR to ACR70	16 (39/237)	49 (39/80)	12 (32/263)	74 (32/43)
LDAS NR to LDAS	24 (39/165)	35 (39/113)	11 (25/234)	52 (25/48)
DAS28 NR to DAS28	20 (40/201)	48 (40/84)	8 (19/248)	63 (19/30)

Disclosure: E. C. Keystone, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 9 ; **A. John**, Roche , 3 ; **K. Wong**, Roche Pharmaceuticals, 9 .

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Interim Results of the TAMARA Study – Effectiveness and Safety of the Interleukin-6 (IL-6) Receptor Antagonist Tocilizumab After 4 and 24 Weeks in Patients with Active Rheumatoid Arthritis (RA). Andrea Rubbert-Roth[1], Juergen Braun[2], Eugen Feist[3], Herbert L. Kellner[4] and Gerd R. Burmester[5], [1]University of Cologne, Cologne, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Charite University Hospital, Berlin, Germany, [4]Munchen, [5]Charite - University Medicine, Berlin, Germany

Purpose: The IL-6 receptor antagonist tocilizumab was shown to be a safe and effective treatment option for RA-patients with intolerance or inadequate response to conventional DMARDs (1, 2, 3, 4) as well as TNF-blockers in clinical trials (5). This study was performed to assess the effectiveness and safety of tocilizumab in a setting close to real-life medical care.

Method: TAMARA is a German multi-center, open-label, non-controlled Phase IIIb study over 24 weeks with one treatment arm of tocilizumab 8 mg/kg iv q4w. A total of 293 adult RA patients with inadequate response to conventional and/or biological DMARDs were enrolled at 70 sites. Primary endpoint is the proportion of patients achieving a DAS28 "low disease" (defined as ≤3.2) at Week24. Secondary endpoints include further DAS assessments, ACR responses, changes in CDAI, acute phase reactants, HAQ-DI, SF-36, FACIT fatigue scale, prognostic values of several baseline variables in terms of treatment outcome, and adverse events experience including adverse events of special interest according to the risk management plan.

Results: In this week 4 interim analysis, data of 218 patients (75% of women, mean age 55 years, 39% previously on TNF-blockers) were evaluated. As a relevant result, tocilizumab reduced disease activity and improved quality of life and fatigue in patients with RA after 4 weeks (Table 1). The mean CRP level was completely normalized already after 1 week. In 40 patients 49 SAEs were reported as of 1st June 2009. The most often reported SAEs were respiratory tract infections (n=11) followed by increased liver enzymes (n=6). No fatal event was reported so far.

Conclusion: Treatment with tocilizumab achieves rapid improvement of signs and symptoms of RA in a setting mimic real-life medical care. The favorable safety profile of Tocilizumab could be confirmed in this ongoing study. No unexpected or new safety issues were observed.

Table: Results of the Week 4 analyses

Variable	Baseline	Week 4	Change
DAS28	7.5 ± 1.1	4.9 ± 1.5	-2.6 ± 1.3 (N=122)
CRP (mg/L)	23.4 ± 42.8	4.8 ± 13.4	-18.5 ± 41.2 (N=169)

HAQ-DI	1.48 ±0,64	1.14 ± 0,67	-0.33 ± 0.47 (N=217)
FACIT-F (fatigue)	29.2 ± 11.4	35.4 ± 3.0	6.2 ± 9.4 (N=216)

Note: Values are given as mean and standard deviation; N depicts the number of underlying observations for the calculation of changes

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Disclosure: A. Rubbert-Roth, None; **J. Braun**, Roche Pharmaceuticals, 2 ; **E. Feist**, Roche Pharmaceuticals, 8 ; **H. L. Kellner**, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 2 ; **G. R. Burmester**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8 .

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Long-Term Efficacy of Tocilizumab in Rheumatoid Arthritis for up to 3.5 Years. J. S. Smolen[1], J. J. Gomez-Reino[2], C. Davies[3], E. Alecock[3], Andrea Rubbert-Roth[4] and Paul Emery[5], [1]Medical University of Vienna, Vienna, Austria, [2]H. Clinico Universitario de Santiago, Santiago de Compostela, Spain, [3]Roche, Welwyn, United Kingdom, [4]University of Cologne, Cologne, Germany, [5]University of Leeds, Leeds, United Kingdom

Purpose: Efficacy and safety of tocilizumab (TCZ) in rheumatoid arthritis (RA) pts have been shown for up to 1 y in phase 3 trials and for up to 2.5 y in long-term extension studies. Efficacy data for up to 3.5 y are reported here.

Method: The analysis includes all pts who received ≥1 dose of TCZ in the randomized controlled studies OPTION, AMBITION, RADIATE, and TOWARD or in the long-term, open-label extension studies GROWTH95 and GROWTH96 (pts from the 4 randomized studies transitioned into GROWTH95 and GROWTH96). Also included are all pts who received ≥1 dose of TCZ in the 2-y controlled (with a 3-y follow-up) phase 3 study, LITHE. Pts were analyzed in 3 groups: inadequate responders to DMARDs (DMARD-IR), anti-TNF-IR pts, and monotherapy pts who never failed MTX (AMBITION). Outcomes, including ACR50/70, DAS28 remission rate (DAS28 ≤2.6), and low disease activity score (LDAS; DAS28 ≤3.2), were assessed every 12 wks from initial TCZ exposure to the cutoff date (Feb 6, 2009). Data are shown for a maximum of 180 wks, after which pt numbers were too low to draw conclusions. High clinical hurdles were examined, such as proportions of pts with HAQ-DI=0, ≤1 SJC, and ≤1 TJC at 96 wks. Pts who withdrew from treatment were categorized as missing for all time points thereafter. Pts with insufficient data at a given time point were excluded from analysis for that time point only.

Results: A total of 3986 pts were included. By the cutoff date, approximately 4% had discontinued due to insufficient therapeutic response and approximately 14% due to safety (including intercurrent illness). Efficacy of TCZ in DMARD-IR pts was demonstrated by increased numbers of pts who achieved ACR50 and ACR70 up to wks 72 and 96, respectively, and who achieved maintenance of ACR70 for 24 consecutive wks, LDAS, and DAS28 remission up to wk 72. Thereafter, proportions increased further or were maintained with continued TCZ up to wk 180 (Table). In anti-TNF-IR and monotherapy pts, the proportions achieving these end points increased or were maintained with continued TCZ treatment (not shown). At 96 wks, proportions in the DMARD-IR, anti-TNF-IR, and monotherapy groups with HAQ=0 were 15%, 8%, and 23%, respectively; the proportions with ≤1 SJC were 46%, 34%, and 55%, respectively; and the proportions with ≤1 TJC were 37%, 23%, and 35%, respectively.

Conclusion: Efficacy of TCZ was demonstrated during long-term treatment of RA pts, as indicated by increasing numbers and/or proportions of pts achieving outcomes. These data support TCZ as an effective, long-term treatment option in pts who are DMARD-IR or anti-TNF-IR or who have not failed MTX.

Week	0	24	48	72	96	120	144	168	180
No. pts with valid assessment	2904	2693	2429	2284	2173	1822	1257	602	363
ACR50, % (n)	—	35 (929)	45 (1085)	51 (1156)	53 (1157)	58 (1050)	59 (738)	64 (387)	67 (242)
ACR70, % (n)	—	16 (423)	24 (580)	30 (687)	31 (683)	36 (650)	38 (478)	46 (275)	46 (168)
No. pts with valid assessment	—	—	2350	2358	2220	1977	1436	779	480
ACR70 maintained for 24 consecutive wks, % (n)	—	—	8 (192)	14 (326)	16 (360)	19 (383)	21 (306)	22 (169)	22 (103)
No. pts with valid assessment	2889	2658	2385	2231	2104	1754	1211	571	344
LDAS, % (n)	2 (50)	43 (1137)	54 (1293)	62 (1380)	65 (1365)	69 (1212)	70 (848)	73 (414)	74 (256)
DAS28 remission, % (n)	1 (22)	27 (722)	40 (954)	47 (1050)	50 (1046)	54 (940)	56 (681)	58 (330)	62 (214)

Note: Data from DMARD-IR pts shown.

Disclosure: J. S. Smolen, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 2 ; **J. J. Gomez-Reino**, Roche Pharmaceuticals, Schering Plough, , 5, Roche Pharmaceuticals, Schering Plough, Bristol Meyers Squibb, , 8 ; **C. Davies**, Roche Pharmaceuticals, 3 ; **E. Alecock**, Roche Pharmaceuticals, 3 ; **A. Rubbert-Roth**, None; **P. Emery**, Amgen, 5, Schering-Plough, 5, Centocor, Inc., 5, Bristol-Myers Squibb, 5, Roche Pharmaceuticals, 5 .

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A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MDX-1100, A Fully Human Anti-CXCL10 Monoclonal Antibody, in Combination with Methotrexate (MTX) in Patients with Rheumatoid Arthritis (RA). M. Yellin[1], I. Paliienko[2], A. Balanescu[3], V. Vizir[4], S. Ter-Vartanian[5], J. Tian[1], X. Zhu[1], G. Ignatenko[6] and R. Chirieac[7], [1]Medarex Inc, Bloomsbury, NJ, [2]Bogomolets National Medical University, Kyiv, Ukraine, [3]Sf. Maria Hospital, Bucharest, Romania, [4]Zaporizhya State Medical University, Zaporizhya, Ukraine, [5]Kyiv Central Municipal Clinical Hospital, Kyiv, Ukraine, [6]M. Gorky Donetsk National Medical University, Donetsk, Ukraine, [7]Iasi Rehabilitation Clinical Hospital, Iasi, Romania

Purpose: CXCL10 (IP-10) is a chemokine that promotes directed migration of activated T cells and monocytes by binding to the cell surface receptor CXCR3. Both CXCL10 and CXCR3 are abundantly expressed in rheumatoid arthritis synovium and may play a role in disease pathogenesis. MDX-1100 neutralizes CXCL10 and has been well tolerated in Phase 1 studies. This study evaluated the efficacy and safety of repeat dosing of MDX-1100 in patients with RA who had an inadequate response to methotrexate.

Method: 70 patients with active RA (≥ 6 tender and ≥ 6 swollen joints) on stable doses of MTX (10 to 25 mg weekly) were randomized to receive every other week intravenous doses of either placebo (n=35) or MDX-1100 10 mg/kg (n=35) x 6. The primary endpoint was the ACR20 response rate at Day 85. Patients were followed for safety to study Day 141.

Results: The MDX-1100 and placebo cohorts were well balanced with respect to mean age, sex, disease duration, baseline corticosteroid and MTX doses, and rheumatoid factor (RF) status. All but one subject was anti-TNF treatment naïve and all subjects were white. At Day 85 the ACR20 response rate was significantly higher for MDX-1100 treated patients than for placebo treated patients (54% versus 17%; p-value = 0.0024). The ACR20 response rate showed a statistically significant separation between MDX-1100 and placebo treatment at every time point from Day 43 through Day 85. The ACR50 and ACR70 response rates at Day 85 were numerically higher in the MDX-1100 cohort but did not achieve statistical significance between the 2 cohorts: 9% versus 3% for ACR50 and 3% versus 0% for ACR70. Overall, 51.4% (n=18) of MDX-1100 treated patients and 30.3% (n=10) of placebo treated patients experienced at least 1 adverse event (AE). With 2 exceptions, AEs were mild or moderate in severity (Grade 1 or 2). One patient in the MDX-1100 cohort experienced a grade 3 infusion reaction (bronchospasm) and one patient in the placebo cohort died suddenly, presumably of cardiac causes. The MDX-1100 infusion was

generally well tolerated and did not require pre-medication. The infection rate was similar between the MDX-1100 and placebo cohorts (8.6% vs. 12.1%).

Conclusion: MDX-1100 was well tolerated and associated with a statistically significant increase in ACR20 responses compared to placebo. These results demonstrate that the CXCL10-CXCR3 pathway plays important roles in RA pathogenesis and provide rationale for the continued development of MDX-1100.

Disclosure: M. Yellin, Medarex, Inc, 3 ; **I. Paliienko**, None; **A. Balanescu**, None; **V. Vizir**, None; **S. Ter-Vartanian**, None; **J. Tian**, Medarex, Inc, 3 ; **X. Zhu**, Medarex, 3 ; **G. Ignatenko**, None; **R. Chirieac**, None.

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LY2439821, a Novel Anti-IL-17 Mab: Safety, Tolerability and Efficacy in Patients with RA On Background DMARDs. MC Genovese[1], F. Van den Bosch[2], SA Roberson[3], S. Bojin[4], M. Biagini[5], P. Ryan[6] and J. Sloan-Lancaster[3], [1]Stanford U, Palo Alto, CA, [2]Univ Hosp, Ghent, Belgium, [3]Eli Lilly, Indianapolis, IN, [4]County Hospital, Covasna, Romania, [5]County Hospital, Bacau, Romania, [6]Nucleus Network, Melbourne, Australia

Purpose: LY2439821 (LY) is an anti-IL-17 antibody that neutralizes the biologic activity of IL-17, a key cytokine in RA pathogenesis.

Method: This was an early phase clinical study to investigate the safety, tolerability, PK, and evidence of efficacy of LY in pts with RA taking at least one DMARD. The study was a randomized, placebo (PBO)-controlled, double-blind study, conducted in 2 parts. The study had dual primary endpoints: safety after single and multiple dosing, and efficacy after multiple dosing. Part A was an initial single dose escalation evaluating safety, which was used to enable multiple dosing. In Part B, 4 treatment groups were dosed IV in parallel every 2 wks for 8 wks (5 treatments per pt), at 0.2, 0.6, or 2.0 mg/kg of LY or PBO, and were evaluated for an additional 8 weeks. The primary efficacy endpoint was the DAS28 at Wk 10.

Results: In Part B, mean baseline characteristics were similar between groups. Mean baseline findings include : age 54.4 to 59.6 yrs; disease duration 6.1 to 10.9 yrs; DAS28 5.8 to 6.1; CRP 1.80 to 2.47 mg/dL; ESR 61.0 to 69.1 mm/hr; Tender Joint Counts (28) 15.7 to 18.2; Swollen Joint Count (28) 11.8 to 13.7; HAQ-DI 1.4 to 1.8. 77 pts were randomized to PBO (18), or LY at 0.2 mg/kg (19), 0.6 mg/kg (20), or 2.0 mg/kg (20). Multiple administrations of LY improved the signs and symptoms of RA (Table). Statistical differences in the mean change from baseline in DAS28 (each dose level compared to PBO) and ACR20 responses (0.2 mg/kg and all LY groups compared to PBO) were detected as early as 1 week after the first dose. At Week 10, statistical differences in the mean change from baseline in DAS28 were detected between the 0.2, 2.0 mg/kg, and all LY combined groups vs. PBO. There were no deaths. Three LY pts (1 at 0.6 and 2 at 2.0 mg/kg) were discontinued from study drug treatment due to AEs, and 1 LY pt was discontinued due to pre-treatment laboratory abnormalities discovered after administration of the first dose. There was 1 reported SAE (skin ulcer in a 0.6 mg/kg pt), classified as unrelated to study drug. No serious infections or malignancies were noted. The incidence of AEs was generally similar between groups.

	PBO	LY 0.2 mg/kg	LY 0.6 mg/kg	LY 2.0 mg/kg
Week 2				
DAS28	-0.5	-1.1*	-1.0*	-1.2*
ACR20 (%)	0	26.3*	30.0*	45.0*
ACR50 (%)	0	5.3	5.0	5.0
ACR70 (%)	0	0	0	0
Week 10				
DAS28	-1.7	-2.3*	-2.2	-2.4*

ACR20 (%)	55.6	73.7	70.0	90.0*
ACR50 (%)	16.7	42.1	40.0	35.0
ACR70 (%)	5.6	26.3	20.0	25.0

NOTE: DAS28 values represent change from baseline.

* Significant at the 0.05 level compared to placebo.

Week refers to number of weeks on active treatment.

Conclusion: IL-17 is a novel cytokine target. IV administrations of LY improved the signs and symptoms of RA early during treatment and confirms the rationale for targeting IL-17. In addition, LY was well-tolerated.

Disclosure: M. Genovese, Eli Lilly, 5 ; **F. Van den Bosch**, None; **S. Roberson**, Eli Lilly, 1, Eli Lilly, 3 ; **S. Bojin**, None; **M. Biagini**, None; **P. Ryan**, None; **J. Sloan-Lancaster**, Eli Lilly, 3, Eli Lilly, 1 .

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Efficacy and Safety of Baminercept in the Treatment of Rheumatoid Arthritis (RA) - Preliminary Results of the Phase 2B Study in the DMARD-IR Population. John D. Isaacs[1], Mark C. Genovese[2], Paul Emery[3], Morton A. Scheinberg[4], Aj Spindler[5], Charlotte Newman[6], Megan L. Weaver[6], Jeff Browning[6], John O'Gorman[6], Matt Cravets[7], David Hagerty[7], Evan M. Beckman[6] and Ajay Nirula[7], [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Stanford University, Palo Alto, CA, [3]University of Leeds, Leeds, United Kingdom, [4]Center for Clinical Immunology, Sao Paulo SP, [5]Universidad Nacional Tucumán, Tucuman, Argentina, [6]Biogen Idec, Cambridge, MA, [7]Biogen Idec, San Diego, CA

Purpose: The TNF-family lymphotoxin beta receptor (LTBR), present on monocytes and dendritic cells, has been implicated in formation of ectopic organized lymphoid tissues at sites of inflammation. The efficacy and safety of Baminercept, a LTBR-IgG_1 fusion protein, were evaluated in patients with moderate/severe RA with an inadequate response to non-biologic DMARD therapy.

Methods: A blinded, randomized, placebo-controlled, multicenter, Phase 2B trial was performed in patients with moderate/severe RA and inadequate response to non-biologic DMARD therapy, including methotrexate. Patients continued their stable MTX dose and received subcutaneous injections of Baminercept (5mg, 70mg, or 200 mg every other week, 70mg or 200 mg monthly, or placebo for 14 weeks). The primary endpoint was the proportion of subjects with an ACR50 response at Week 14. Secondary efficacy endpoints included ACR20 and ACR70 responses and change from baseline DAS28 at Week 14. Exploratory endpoints included the effect of Baminercept on peripheral blood lymphocyte counts.

Results: 391 subjects were randomized in the study. Treatment groups had similar baseline (BL) demographics and disease activity. Treatment with Baminercept did not result in improvement of ACR 50 (primary endpoint) or secondary endpoints of ACR 20, ACR 70, or change from baseline DAS scores (Table 1). Analysis of individual ACR core parameters showed no significant differences between drug and placebo. Baminercept was overall well tolerated and had comparable rates to placebo for adverse events, serious adverse events, and infections (Table 1). Treatment with Baminercept resulted in a dose-dependent increase in total blood lymphocytes from baseline by Week 2 (Table 1), suggesting effective targeting of the LT-beta pathway. Table 1: Preliminary Efficacy (week 14) and Safety Results in DMARD-IR study.

	Placebo	10 mg mthly	70 mg mthly	140 mg mthly	200 mg mthly	400 mg mthly
Number of patients	79	78	39	39	78	78
ACR50 (% pts)	11	14	8	18	14	10
ACR20	32	36	36	38	40	33

(% pts)						
ACR70 (% pts)	4	4	3	10	8	6
Chg in DAS28 – mean from baseline	-0.91	-0.99	-0.75	-1.23	-1.23	-0.85
Adverse Events (%)	56	53	59	62	58	54
Serious Adverse Events (%)	5	1	13	3	4	3
Infections (%)	22	26	21	28	28	26
Pct chg from baseline in blood total lymphocyte count at Week 2– mean (SD)	15.3 (35.6)	14.3 (28.3)	23.0 (42.4)	35.8* (48.4)	34.9* (30.7)	37.5* (43.5)
* = p-value < 0.01 for comparison versus placebo (post-hoc analysis)						

Conclusion: Baminercept did not exhibit efficacy in patients with RA refractory to oral DMARDs. The drug was overall well tolerated and remains a candidate for clinical study in other autoimmune diseases.

Disclosure: J. D. Isaacs, Biogen Idec, 2 ; **M. C. Genovese**, Biogen-idec, 2 ; **P. Emery**, Biogen Idec, 5 ; **M. A. Scheinberg**, None; **A. Spindler**, None; **C. Newman**, Biogen Idec, 3 ; **M. L. Weaver**, Biogen Idec, 3, Biogen Idec, 1 ; **J. Browning**, Biogen Idec, 3 ; **J. O'Gorman**, Biogen Idec, 3 ; **M. Cravets**, Biogen Idec, 1, Biogen Idec, 3 ; **D. Hagerty**, Biogen Idec, 3 ; **E. M. Beckman**, Biogen Idec, 3 ; **A. Nirula**, Biogen Idec, 3 .

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Efficacy and Safety of Baminercept in the Treatment of Rheumatoid Arthritis (RA) – Results of the Phase 2B Study in the TNF-IR Population. M.C. Genovese[1], Maria W. Greenwald[2], Jeff A. Alloway[3], Andrew R. Baldassare[4], Walter Chase[5], Charlotte Newman[6], Megan L. Weaver[6], Jeff Browning[6], Jaya Goyal[6], John O'Gorman[6], Matt Cravets[7], Evan M. Beckman[6] and Ajay Nirula[7], [1]Stanford U, Palo Alto, CA, [2]Desert Medical Advances, Palm Desert, CA, [3]Greenville, NC, [4]St Louis University, St Louis, MO, [5]Austin, TX, [6]Biogen Idec, Cambridge, MA, [7]Biogen Idec, San Diego, CA

Purpose: The TNF-family lymphotoxon beta receptor (LTBR), present on monocytes and dendritic cells, has been implicated in the formation of ectopic organized lymphoid tissues at sites of inflammation. The efficacy and safety of Baminercept, a LTBR-IgG_1 fusion protein, were evaluated in patients with moderate/severe RA with an inadequate response to anti-TNF therapy.

Methods: A blinded, randomized, placebo-controlled, multicenter, Phase 2B trial was performed in patients with moderate/severe RA and inadequate response to ≥1 TNF blocker. Patients were randomized 2:1 to either receive subcutaneous injections of Baminercept (200 mg every other week) or placebo for 14 weeks followed by 12 weeks of observation. The primary endpoint was the proportion of subjects with an ACR50 response at Week 14. Secondary efficacy endpoints included ACR20 and ACR70 responses and change from baseline DAS 28.

Results: 114 subjects were dosed in the study. Both treatment groups had similar baseline (BL) demographics and disease activity. Treatment with Baminercept did not result in improvement of the primary endpoint ACR 50 scores relative to the placebo group at week 14 (11% vs 5%, p=0.3340). Similarly, no significant changes were seen in the Baminercept group relative to placebo for secondary endpoints of ACR 20 (14% vs 13%), ACR 70 (1% vs 3%), or change from baseline DAS scores (-0.64 vs -0.67). Analysis of individual ACR core parameters showed no significant differences between drug and placebo. Baminercept was overall well tolerated and had comparable rates to placebo for adverse events (72% vs 61%) and infections (30% vs 21%); however more serious adverse events (7% vs 0%) were noted.

Exploratory analyses provided evidence strongly suggestive of LTBR pathway inhibition. Baminercept triggered a notable increase in total blood lymphocytes, with percentage changes from baseline at Week 2 (mean ±SD) as follows: placebo (2.2±29.3) and Baminercept (30.9±32.6) (post-hoc $p < 0.0001$). Additionally, reductions of approximately 50% were seen for Baminercept-treated subjects at Week 14 in serum levels of CXCL13, a chemokine regulated by LTBR signaling. Favorable clinical trends were noted at week 6 (subset of subjects) for Baminercept relative to placebo for serum lipid levels, including mean percentage changes from baseline in LDL (-5.3% vs +2.2 %) and HDL (+6.6% vs -1.0%).

Conclusion: Baminercept did not exhibit measurable efficacy in patients with RA refractory to TNF inhibitors. However given its unique mechanism of action, it remains a candidate for clinical study in other autoimmune diseases.

Disclosure: M. C. Genovese, Biogen-Idec, 9, Biogen-Idec, 5 ; **M. W. Greenwald**, Biogen Idec, 2 ; **J. A. Alloway**, Biogen Idec, 9 ; **A. R. Baldassare**, Biogen Idec, 9 ; **W. Chase**, None; **C. Newman**, Biogen Idec, 3 ; **M. L. Weaver**, Biogen Idec, 1, Biogen Idec, 3 ; **J. Browning**, Biogen Idec, 3 ; **J. Goyal**, Biogen Idec Inc, 3 ; **J. O'Gorman**, Biogen Idec, 3 ; **M. Cravets**, Biogen Idec, 1, Biogen Idec, 3 ; **E. M. Beckman**, Biogen Idec, 3 ; **A. Nirula**, Biogen Idec, 3

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Effects of the Oral JAK Inhibitor CP-690,550 (CP) On Pain, Physical Functioning (PF), Fatigue, and Health-Related Quality of Life (HRQoL) in Patients (pts) with Active Rheumatoid Arthritis (RA). G.V. Wallenstein[1], S. Cohen[2], M. Cutolo[3], D. Gruben[1], K.S. Kanik[1], J.M. Kremer[4], E.B. Lee[5], B. Wilkinson[1], S.H Zwillich[1] and J. Frain[6], [1]Pfizer Inc, New London, CT, [2]Metroplex Clinical Research Centre, Dallas, TX, [3]University of Genoa, Genoa, Italy, [4]Albany Medical College and the Center for Rheumatology, Albany, NY, [5]Seoul National University College of Medicine, Seoul, South Korea, [6]Complete Medical Communications, Macclesfield, United Kingdom

Purpose: To compare effects on pain, PF, fatigue, and HRQoL of (Study 1025) CP v placebo (PBO) for the treatment of active RA in pts with inadequate response to stable background MTX, and of (Study 1035) CP or adalimumab (ADA) monotherapy v PBO for the treatment of RA in pts with inadequate response to DMARDS.

Methods: Data are from two 6-month, double-blind, PBO-controlled Phase 2B studies. Pts with ≥6 tender and ≥6 swollen joints and evidence of inflammation were randomized to: (Study 1025) CP dosed 1, 3, 5, 10, 15 mg BID, or 20 mg QD or PBO; and (Study 1035) CP dosed 1, 3, 5, 10, 15 mg BID, or ADA 40 mg sc QOW, or PBO. Pts receiving CP 1, 3 mg BID, 20 mg QD, or PBO with < 20% reduction from baseline in tender/swollen joint counts at Week 12 were reassigned to CP 5 mg BID.

Results: In Study 1025 507 pts were randomized and received study drug. Significant improvements in pain at Week 2 and PF at Week 12 occurred for several CP groups (Table 1). Pts from the CP groups also showed significant improvements in several domains of the SF-36 at Week 12 ($p < .05$ for PF, Bodily Pain (BP), Vitality (VT), and Mental Health).

In Study 1035 384 pts were randomized and received drug. Pain and PF improved significantly for pts in several CP groups by Week 2 (Table 1). Pts from the CP groups also showed significant improvements in domains of the SF-36 at Week 12 ($p < .05$ for PF, Role Physical, BP, General Health, and VT). Finally, pts from the 10 and 15 mg groups showed significant improvement in fatigue (FACIT-F) by Week 2 ($p < .05$).

								CP - 20 mg		
			CP - 1 mg	**CP - 3 mg**	**CP - 5 mg**	**CP - 10 mg**	**CP - 15 mg**	**QD**	**ADA**	**PBO**
Study	Pain	2	-9.5	-11.0	-10.8	-15.3*	-17.7**	-18.8*	-	-4.6
1025		12	-23.2*	-24.4**	-25.8**	-24.0*	-24.0**	-29.7**	-	-10.3
		24	-36.1	-33.2	-29.9	-28.5	-31.0	-37.0	-	-21.1
	HAQ-	2	-0.15	-0.23	-0.23	-0.18	-0.24	-0.23	-	-0.05
	DI	12	-0.37*	-0.48**	-0.51**	-0.37**	-0.45**	-0.58**	-	-0.10
		24	-.60	-.53	-.61	-.47	-.53	-.66	-	-.37
Study	Pain	2	-6.0	-16.0*	-16.3*	-19.8**	-23.1**	-	-16.4*	-5.1

1035		12	-11.6	-16.0	-31.1**	-34.5**	-35.3**	-	-23.3	-13.7
		24	-9.8	-23.7	-32.8	-39.7	-37.8	-	-31.5	-22.3
	HAQ-	2	-0.13	-0.25*	-0.16	-0.27*	-0.36**	-	-0.21	-0.04
	DI	12	-0.30	-0.42	-0.43*	-0.63**	-0.81**	-	-0.32	-0.24
		24	-.58	-.53	-.45	-.63	-.82	-	-.53	-.41

Table 1 – Mean change scores for the Pain VAS and HAQ-DI. ($p < .05$*, $p < .01$** relative to PBO) Week 24 means are from groups without reassignment.

Conclusion: Pts receiving CP in combination with MTX or as monotherapy showed rapid and sustained improvement in pain, PF, fatigue, and HRQoL.

Disclosure: G. V. Wallenstein, Pfizer Inc, 3 ; **S. Cohen**, Pfizer Inc, Amgen, Wyeth, Proctor and Gamble, Genentech, Biogen-Idec/Roche, 2, Genentech/Roche/Amgen/Biogen-Idec, 5 ; **M. Cutolo**, None; **D. Gruben**, Pfizer Inc, 3 ; **K. S. Kanik**, Pfizer Inc., 3 ; **J. M. Kremer**, BMS, Pfizer, UCB, Wyeth, 5, Abbott, Amgen, BMS, Centocor, HGS, Pfizer, Roche, UCB, 2 ; **E. B. Lee**, None; **B. Wilkinson**, Pfizer Inc, 3 ; **S. H. Zwillich**, Pfizer Inc, 3 ; **J. Frain**, None.

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Relationship of Tocilizumab Dose and Neutrophil Counts. Peter N. Morcos[1], Xiaoping Zhang[1], Susan Grange[2] and Christophe Schmitt[2], [1]Roche, Nutley, NJ, [2]Roche, Basel, Switzerland

Purpose: Tocilizumab (TCZ) is a humanized IL-6 receptor inhibitor that has demonstrated not only significant improvements in the signs and symptoms of moderate–to-severe rheumatoid arthritis (RA) but also inhibition in the progression of structural joint damage (LITHE Study). In the controlled clinical trials, decreases in neutrophils below 1 x 10^9/ L was observed in 3.4% of patients on TCZ 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. The purpose is to examine the relationship of TCZ dose and neutrophil counts to provide guidance for the management of neutropenia in patients on TCZ therapy.

Methods: In study BP19461, subjects received placebo (N=39), 2 (N=5), 10 (N=36), 20 (N=41) and 28 mg/kg (N=5) TCZ intravenous infusion. In another study, WP18633, 23 patients with RA received 10 mg/kg TCZ infusion. Neutrophil counts were determined from screening until follow up visit.

Results: In healthy subjects, following TCZ infusion, mean neutrophil counts decreased at 2 to 28 mg/kg doses. Median time (T_{min}) to reach mean minimum neutrophil counts (NTT_{min}) was 3 to 5 days (Figure 1). Although not pronounced, there was a trend toward a decrease in mean NTT_{min} with increased dose. The time required for recovery to normal ranges of neutrophil counts was dose dependent (Table 1). Although there was an increase in the observed incidence of markedly low neutrophil counts with increasing dose, there was no dose relationship in the observed incidence of adverse events, specifically the incidence of infections. In patients with RA, patients demonstrated a similar pattern of absolute neutrophil counts following TCZ administration.

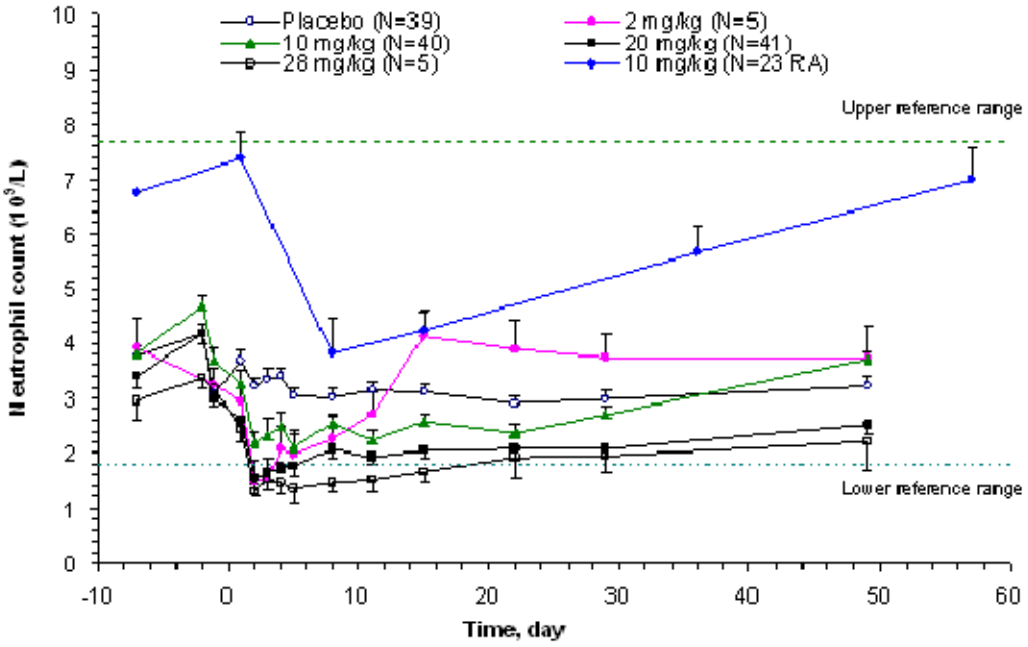
Table 1. Mean (± SD) neutrophil counts (x10^9/L) at baseline, nadir and follow-up in healthy subjects

Dose, mg/kg	Placebo	2	10	20	28
N	39	5	36	41	5
Mean ±SD NTTmin x10^9/L,day	2.43 ±0.64	1.39± 0.86	1.48± 0.79	1.28± 0.64	1.01± 0.10
Median Tmin	11	3	4	3	5

Recovery to Baseline (days)	-	14	39	49	70*

*extrapolated from available data

Figure 1. Mean neutrophil counts over time following single dose TCZ infusion from 2 to 28 mg/kg



Conclusion: In healthy subjects administered TCZ in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to the nadir 3 to 5 days following TCZ administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA patients demonstrated a similar pattern following TCZ administration.

Disclosure: P. N. Morcos, Roche Pharmaceuticals, 3 ; **X. Zhang**, Roche Pharmaceuticals, 3 ; **S. Grange**, Roche Pharmaceuticals, 3 ; **C. Schmitt**, Roche Pharmaceuticals, 3 .

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Evaluation of Safety, Pharmacokinetics and Pharmacodynamics of a Selective Glucocorticoid Receptor Modulator (SGRM) in Healthy Volunteers. Thomas Stock[1], Dona Fleishaker[1], Arnab Mukherjee[2], Vu Le[2], Jian Xu[2] and Bernhardt Zeiher[2], [1]Pfizer, Inc., Chesterfield, MO, [2]Pfizer, Inc., New London, CT

Purpose: SGRMs were identified preclinically using in vitro and in vivo assays. Compounds that displayed anti-inflammatory activity similar to glucocorticoids (e.g., prednisone) but lesser inhibition of bone formation in animal models were further evaluated in humans. PF-00251802 (C-A), and its phosphate ester pro-drug, PF-04171327 (C-B), were evaluated in separate Phase 1 single-dose studies in healthy volunteers to characterize safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of glucorticoid receptor (GR) agonism.

Method: Single C-A doses (0.3 to 300 mg), and single C-B doses (1 to 300 mg) were evaluated in separate randomized, placebo-controlled, investigator- and subject-blinded clinical studies in 27 and 18 subjects, respectively, using partial cross-over designs. A washout period of 14 days was allowed between dosing. Serial blood samples and safety parameters were collected up to 7 days post-dose for PK, biomarker and safety assessments. C-A plasma concentration, complete blood count with differential, plasma osteocalcin (OC), plasma cortisol, and urinary

N-terminal cross-linking telopeptide of type-1 collagen (uNTX-1) were measured. C-A plasma concentrations were linked to biomarker responses using PK-PD models for estimation of potency (IC50) and maximal effect (Imax). Selectivity of C-A was assessed by model-based comparison to biomarker effects of prednisolone (P), the active metabolite of prednisone, from a previous study.

Results: C-A plasma concentrations increased proportionately with increasing doses of C-A and C-B. C-A PK was similar following equivalent doses of C-A and its pro-drug, C-B, which was not absorbed systemically. Dose-dependent biomarker effects consistent with GR-mediated pharmacology were observed, including cortisol and OC suppression, lymphopenia, eosinopenia, and neutrophilia. The duration of effect was substantially longer than that of P, likely due to the longer elimination half-life and GR binding affinity (Kd) of C-A (24 hr and 0.061 nM, respectively) compared to P (3 hr and 1.3 nM, respectively). The relative potency of C-A for OC suppression versus effects on other markers (cortisol suppression, neutrophilia) was lower compared to P. The Imax for C-A effect on OC was half that of P, but Imax on cortisol and neutrophils was similar to P. PK-PD model-based evaluations indicated that C-A doses up to 10 mg QD would provide OC suppression less than or equal to that of 5 mg QD prednisone, and cortisol suppression and neutrophilia similar to or greater than that of 20 mg QD prednisone. Both compounds were generally well tolerated, with dose limiting nausea and emesis occurring in some subjects at doses greater than 150 and 300 mg for C-A and C-B, respectively. There were no serious or severe adverse events.

Conclusion: Compared to prednisone, C-A was shown to have less impact on OC, a biomarker of adverse effects on bone, with similar effects on other biomarkers of glucocorticoid activity.

Disclosure: T. Stock, Pfizer Inc, 3 ; **D. Fleishaker**, Pfizer Inc, 3, Pfizer, 1 ; **A. Mukherjee**, Pfizer, Inc, 3 ; **V. Le**, Pfizer Inc, 3 ; **J. Xu**, Pfizer, Inc, 3 ; **B. Zeiher**, Pfizer, Inc, 3 .

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Preliminary Results of a Phase I Clinical Trial of Intra-Articular Administration of ARG098, A Novel Anti-Fas IgM Mab, in RA.

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Purpose: Activated inflammatory cells including synoviocytes, lymphocytes and macrophages are primary cellular factors which activate inflammation in the joints of rheumatoid arthritis (RA) patients. They contribute to disease progression by producing local inflammatory cytokines. Selective removal of these inflammatory cells directly from inside the joint could represent an innovative therapeutic approach. ARG098 is a novel agonistic anti-Fas IgM mAb which binds to Fas molecule and is in vitro capable of inducing apoptosis in synoviocytes and infiltrating lymphocytes in synovial tissue. Here we demonstrate that ARG098 can be a novel local therapeutics for RA showing clinical benefit as well as safety profile in the clinical phase I study with RA patients in Europe.

Method: This is an open-label dose-escalation study of a single intra-articular administration of ARG098 in patients with RA having safety and tolerability as primary endpoints, and efficacy assessment and pharmacokinetic determination as secondary endpoints. The study included 7 cohorts, each consisting of 6 patients. One mL of formulated ARG098 was administered to the target knee. Safety was assessed by monitoring general findings, serum level of anti-ARG098 antibody and laboratory test over 8 weeks post-administration. Efficacy was assessed by VAS including target knee pain, global efficacy assessment by patient and physician, tender and swollen joint count including target knee, effusion, thickness and erosion by ultrasonography (US) and MRI.

Results: Thirty three RA patients (28 females and 8 males between 37 and 78 years) with knee active synovitis were enrolled for receiving 10 ng/knee through 3 μg/knee. Safety and tolerability were observed in all dosage. Preliminary efficacies were evaluated in 24 patients after injection of 10 ng, 30 ng, 100 ng and 300 ng/knee. Average decrease in VAS scale of pain in the target knee at week 1, 2, 4 and 8 post-administration compared with baseline was 49.5%, 55.1%, 60.7% and 51.8%, respectively. Ten of 23 patients showed high response with more than 80% of decrease in VAS scale of pain at week 4. Around 60% of patients experienced clinical benefit in the target knee including resolution of tenderness and swelling through week 1 to 8. Average of DAS28 of total patients showed slight decrease and in the group of patients with high response, obvious improvement of DAS28 was observed. Tendency of beneficial change was observed by US and MRI analysis.

Conclusion: This is the first report to indicate that an anti-Fas IgM mAb (ARG098) induces improvement of local symptoms and reduction of disease activity in patients with RA.In addition, ARG098 is well-tolerated and has an acceptable safety profile as a local therapeutics in RA.

Disclosure: T. Appelboom, Argenes, Inc., 5 ; **H. Mann**, None; **L. Senolt**, None; **D. Suchy**, None; **P. Nemec**, None; **J. Rolova**, None; **M. Matucci Cerinic**, None.

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Effect and Mechanism of Jak Inhibitor as a Possible New Anti-Rheumatic Drug: Analysis From in Vitro and SCID-HuRAg Mouse.
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Purpose: Janus kinase 3 (Jak3) is a tyrosine kinase necessary for lymphocyte differentiation and proliferation, and homozygous deficiency is a cause of severe combined immunodifficiency. Because of its specific expression on hematopoietic cells, inhibitors of Jak 3 have been expected to be immunosuppresive. Recent clinical trials of a Jak3 inhibitor CP-690,550 for rheumatoid arthritis (RA) has been conducted, showing efficacy and acceptable safety. However, CP-690,550 has been shown to possess inhibitory effects not only on Jak3 but also Jak1 and Jak2, both in vitro and in vivo. Thus, it is now considered as a Jak inhibitor. The effects of Jak inhibitors (CP-690,550 and PF-956980) on functions of lymphocytes and synovial cells in vitro and SCID-HuRAg model mouse were assessed in the current study.

Method: Synovium and cartilage from RA patients undergoing joint replacement was implanted into SCID mice (SCID-HuRAg) and Jak-inhibitors (CP-690,550) were administrated via osmotic mini-pump. Serological and histological examinations were performed using the SCID-HuRAg model. Synovial fibroblasts were obtained from RA synovium (RASFs) and were used during passage 2 to 6. RASFs were stimulated with LPS, IL-1, IL-6 or IL-17 under the presence of Jak-inhibitor (CP-690,550). CD4 T cells were negatively purified from RA patients, stimulated with IL-1, IL-6 or IL-23 and were evaluated for the effects of Jak-inhibitor (PF-956980). ,CP690,550 and PF956980 was provided by Pfizer.

Results: CP-690,550 decreased human IL-6, IL-8, and MMP-3 levels in SCID-huRAg mice sera in a concentration-dependent manner. The main source of IL-6 and MMP-3 is known to be synovial frbroblasts. However, CP-690,550 only marginally affected production and proliferation of RASFs. On the other hand, PF-956980 dose-dependently inhibited production of IL-17 and IFN-γ as well as proliferation of peripheral CD4 T cells from peripheral blood.

Conclusion: Recently, CP-690,550 has been described to possess inhibitory effect not only on Jak3 but also on Jak1 and Jak2 and other kinases as well. However, CP-690,550 did not show any effects on RASFs which do not express Jak3, whereas PF-956980 inhibited CD4 T cell proliferation and cytokine production. Our result suggests that CP-690,550 acts on immune cells mainly on CD4 T cells mainly through Jak3 and regulates proliferation and certain cytokine production of CD4 T cells.

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Are the Switch to Subcutaneous Administration of MTX or the Addition of Cyclosporine to Oral MTX Useful Steps in a Tight Control Strategy for RA?
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Purpose: Methotrexate (MTX) is widely used as the DMARD of first choice in the treatment of rheumatoid arthritis (RA) patients. In an earlier strategy trial (CAMERA) in early RA patients, a tight control MTX strategy proved to be more effective when compared to conventional MTX treatment. However, a substantial number of patients do not respond favorably enough to the maximally (tolerable) dose MTX and need more intensified treatment. Within the CAMERA strategy these intensified treatment steps were defined as subcutaneous (sc) MTX instead of oral MTX treatment; in case this was not effective enough, was contraindicated or caused adverse effects, cyclosporine was added to oral MTX treatment with a simultaneous reduction of the dose MTX to a maximum of 15mg/wk. The aim of this study was to investigate the effectiveness of these two treatment strategy steps.

Method: The change in disease activity (DAS28) over one month after taking the scMTX step was compared to the average 3 monthly change before taking the step. For the cyclosporine strategy step the change in DAS28 over 3 months after taking this step (since cyclosporine has a slow onset of action) was compared to the average 3 monthly change before taking this step. Analyses were performed separately for patients who needed the step because of insufficient effect and for those who needed it because of adverse effects. Additionally, analyses of individual responses and time on treatment were performed.

Results: Of the 151 patients within the tight control strategy arm of the CAMERA study, 57 needed the scMTX strategy step (21 because of adverse events, 36 because of insufficient effect) and 40 the cyclosporine strategy step (20 and 20, respectively). These patients had a mean age of 54 years, 69% was female, and 54% was RF^+. For the scMTX strategy step the DAS28 decreased over the 4 months evaluation period ($p=0.47$ for adverse events, $p<0.01$ for insufficient effect). The decrease in DAS28 between baseline and 4 months was 0.4 and 0.6 points for adverse events and insufficient effect, respectively. For the cyclosporine strategy step no (significant) trend in DAS28 over time was observed. For patients taking the scMTX strategy step because of adverse events, the mean improvement in DAS28 exceeded the mean 3 month improvement in DAS28 before this step by 0.08 units ($p=0.83$); for patients taking the step for insufficient effect this was 0.29 DAS28 units ($p=0.08$). For patients taking the cyclosporine strategy step because of adverse events the DAS28 increased with 0.26 units ($p=0.44$) and for those needing the step because of insufficient effect, the decrease was 0.15 units ($p=0.68$).

Conclusion: Although not statistically significantly (probably due to low numbers), the scMTX strategy step seems to be effective in early RA patients needing this step because of insufficient effect of oral MTX. The cyclosporine strategy step appears not to be effective, possibly due to concomitant lowering of the MTX dose.

References: Verstappen et al. Ann Rheum Dis. 2007;66:1443-9

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The A3 Adenosine Receptor as a Biological Predictive Marker in Rheumatoid Arthritis: Lessons From Phase II Clinical Studies.

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Purpose: The Gi protein associated A_3 adenosine receptor (A_3AR) is highly expressed in the inflammatory tissues and peripheral blood mononuclear cells (PBMCs) of patients with Rheumatoid Arthritis (RA). The A_3AR selective agonist CF101 has been shown to possess robust anti-inflammatory effect via de-regulation of the NF-κB signaling pathway and induction of inflammatory cell apoptosis. The purpose of this study was to evaluate the correlation between A_3AR expression at baseline and the response of RA patients to CF101 treatment. CF101 was given as a monotherapy (Phase IIa) or in combination with methotrexate (MTX, Phase IIb).

Method: The trials were multi-center, randomized, double-blind, parallel group dose-ranging (Phase IIa, n=74) or placebo controlled (Phase IIb, n=223) enrolling patients with active RA who failed MTX treatment. In the Phase IIa study, CF101 was given as a monotherapy, at doses of 0.1mg, 1.0mg or 4.0mg, after one month of washout from MTX. In the Phase IIb, CF101 at doses of 0.1mg, 1.0mg or placebo were added to stable doses of MTX. In both trials, CF101 was given orally, twice daily for 12 weeks. The primary efficacy endpoint was ACR20 response and secondary end point were ACR 50/70. To evaluate A_3AR protein expression levels in the PBMCs at baseline, blood samples were withdrawn from 18 patients (Phase IIa) and from 60 patients (Phase IIb). A_3AR expression levels were tested by western blot analysis and compared to that of healthy subjects (control).

Results: The Phase IIa study reached, whereas the Phase IIb study missed the primary efficacy end points. A_3AR expression levels at baseline were up-regulated in the Phase IIa and similar to control in the Phase IIb (2.46±0.0.398 and 1.29±0.125 fold vs. control, respectively).

Conclusion: A_3AR over-expression at baseline in the Phase IIa study was found to be directly correlated to the success of the response, whereas in the phase IIb study low A_3AR expression levels were associated with lack of response. It thus seems that A_3AR can be utilized as a biological marker to predict patient response to CF101.

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Decline of Mean Initial Prednisone Dose From 10.3 Mg/Day in 1980-1985 to 3.6 Mg/Day in 2000-2004, with Similar Efficacy Over 12 Subsequent Months. Theodore Pincus[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: To analyze the initial prednisone dose in 308 patients with rheumatoid arthritis (RA) treated between 1980 and 2004, in 5-year periods, and to assess efficacy in patients whose initial prednisone dose was <5 or □ 5 mg/day according to change in scores for functional status, pain and RAPID3 on a multidimensional health assessment questionnaire (MDHAQ) over 12 subsequent months.

Method: A database was maintained from 1980-2006 on all patients seen in a weekly academic rheumatology setting, which includes medications, laboratory tests, and scores at each visit for physical function (FN) and pain (PN) on a MDHAQ. Patient global estimate of status (PTGL) was added in 1996. Most patients took methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs) in addition to low-dose prednisone therapy. All RA patients seen from 1980-2004 were analyzed for the dose at the first visit with recorded prednisone therapy. The proportion of patients whose initial dose was <5, 5 and >5 mg/day was computed in 5-year periods: 1980-84, 1985-98, 1990-94, 1995-99, 2000-04. Mean changes in MDHAQ scores for FN, PN and RAPID3-estimate (RAPID3-EST: FN and PN without PTGL) over 12 months was compared in patients treated with <5 versus □5 mg/day, as few patients received >5 mg/day.

Results: Mean initial prednisone dose was 10.3 mg/day in 1980-84 vs 6.5 mg/day in 1985-89, 5.1 mg/day in 1990-94, 4.1 mg/day in 1995-99, and 3.6 mg/day in 2000-04. The proportion of patients whose initial dose was <5 mg/day was 0, 4%, 23%, 67% and 86% in the 5-year periods, while the proportion initially treated with >5 mg/day was 49%, 16%, 7%, 7% and 3%, and the proportion receiving 5 mg/day was 51%, 80%, 70%, 26% and 10%, in the respective 5-year periods. Overall, scores for FN, PN, and RAPID3-EST fell by 34%, 37% and 37% over 12 months in the group whose initial dose was <5 mg/day, and by 40%, 37% and 38% in patients whose initial dose was □5 mg/day. Substantially better results were seen after 1990, possibly associated with early concomitant methotrexate in most patients.

Year first seen	N	Mean (median) initial dose: mg/d	Percentage of patients taking initial dose: mg/d			Percent clinical change over 12 months*					
						Initial dose <5 mg/d			Initial dose ≥5 mg/d		
			<5	=5	>5	FN	PN	RAPID3-EST	FN	PN	RAPID3-EST
1980-84	37	10.3 (5)	0	51%	49%	--	--	--	+33%	+25%	+28%
1985-89	74	6.5 (5)	4%	80%	16%	–5%	–8%	–24%	+45%	+42%	+43%
1990-94	77	5.1 (5)	23%	70%	7%	+26%	+43%	+38%	+44%	+44%	+42%
1995-99	61	4.1 (3)	67%	26%	7%	+33%	+30%	+37%	+27%	+19%	+25%
2000-04	59	3.6 (3)	86%	10%	3%	+37%	+41%	+39%	+25%	+25%	+30%
TOTAL	308	5.6 (5)	37%	50%	13%	+34%	+37%	+37%	+40%	+37%	+38%

* "+" indicates improvement and "–" worsening in function and pain scores

Conclusion: The mean initial prednisone dose fell by more than 50% over a 25-year period, without significant differences in efficacy between patients receiving <5 versus □ 5 mg/day. Many patients with RA can be treated with doses of prednisone of <5 mg/day.

Disclosure: T. Pincus, None; **C. J. Swearingen**, None.

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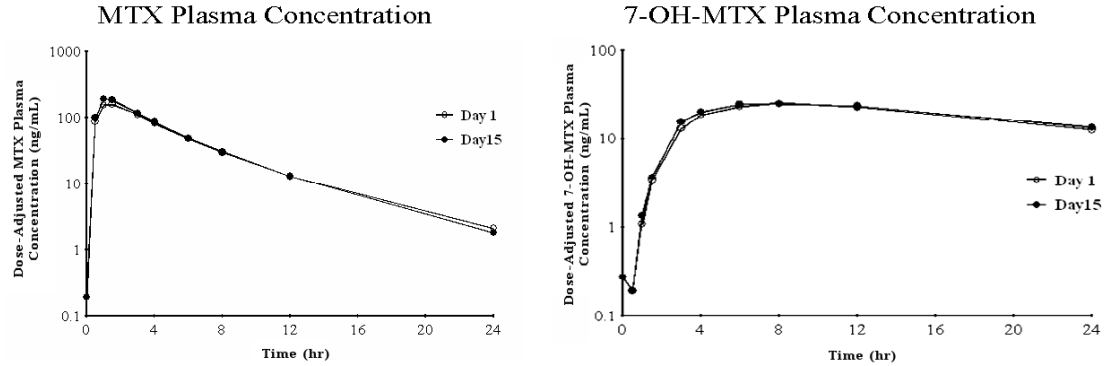
Co-Administration of the Oral S1P-Lyase Inhibitor LX2931 with Methotrexate Was Well Tolerated Over 14 Days in Patients with Stable Rheumatoid Arthritis. Roy Fleischmann[1], Kenny S. Frazier[2], Joel Freiman[2], Barbara Brooks[2], Tamas Oravecz[2], David Augeri[3], Michael Kelly[2] and Philip Brown[2], [1]Metroplex Clinical Research Center, Dallas, TX, [2]Lexicon Pharmaceuticals, Inc., The Woodlands, TX, [3]Princeton, NJ

Purpose: Sphingosine-1-phosphate (S1P) is a lipid metabolite affecting lymphocyte trafficking; the major route of S1P degradation is via S1P lyase (S1PL). Mice with reduced S1PL activity have significantly reduced circulating lymphocytes as a consequence of increased S1P content in lymphoid tissues. LX2931 (LX3305), an oral small molecule inhibitor of S1PL, is being developed as a potential therapeutic for autoimmune and inflammatory disorders. LX2931 exhibited significant activity in reducing the inflammatory response in preclinical arthritis models in the mouse and rat. In addition, co-administration of LX2931 with methotrexate (MTX) in the rat model revealed improved pharmacology over monotherapy alone.

Method: LX2931 (120 mg po QD) was evaluated in a randomized, double-blind, placebo controlled, study in 15 subjects (12 active, 3 placebo) diagnosed with stable rheumatoid arthritis (RA) to evaluate the PK, PD, safety and tolerability of co-administration with MTX. The study was conducted at a single center with all subjects receiving MTX at a stable dose between 7.5-25 mg per week.

Results: Co-administration of MTX with LX2931 was well tolerated over 14 days of dosing in patients with stable RA. The most commonly occurring adverse events included headache (26.7%), abdominal pain (20.0%), and nausea (20.0%). Among the abdominal pain events, one was mild and occurred while on study drug, two were mild to moderate and occurred after the last study dose. There were no clinically significant trends observed in laboratory values, vital signs, or electrocardiograms. No clinically significant changes in either MTX or LX2931 kinetics were observed (Figure). Slight increases in MTX $AUC_{(0\text{-last})}$, and C_{max} were observed at Day 15 with no changes in 7-OH-MTX or LX2931 PK.



Conclusion: Co-administration of LX2931 with MTX in patients with stable RA over 14 days was well tolerated with no clinically significant PK, PD, or safety interaction. These observations combined with preclinical and Phase 1 studies in healthy volunteers indicate that inhibition of S1PL by LX2931 may represent a new mechanism for immune modulation and justify further clinical development of LX2931 as a potential small molecule therapy for RA and other autoimmune and inflammatory disorders.

Disclosure: R. Fleischmann, Lexicon, 2, Lexicon, 5 ; **K. S. Frazier**, Lexicon Pharmaceuticals, Inc., 3 ; **J. Freiman**, Lexicon Pharmaceuticals, Inc., 3 ; **B. Brooks**, Lexicon Pharma, 3 ; **T. Oravecz**, Lexicon Pharmaceuticals, Inc., 3, Lexicon Pharmaceuticals, Inc., 1 ; **D. Augeri**, Lexicon Pharmaceuticals, Inc., 3 ; **M. Kelly**, Lexicon Pharmaceuticals, Inc., 3 ; **P. Brown**, Lexicon Pharmaceuticals, Inc., 3 .

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A Randomised, Single-Blind, Placebo-Controlled Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of a Single Intravenous Infusion of GSK315234 in Healthy Volunteers. Mark B. Baker[1], Marina Bendit[2], Andrea M. Campanile[2], Maria Feeney[3], Peter Hodsman[4] and John F. Toso[2], [1]GlaxoSmithKline, London, United Kingdom, [2]GlaxoSmithKline, King of Prussia, PA, [3]GlaxoSmithKline, Stevenage, United Kingdom, [4]Nucleus Network, Melbourne, Australia

Purpose: GSK315234 is a humanised IgG1 monoclonal antibody (mAb) against human Oncostatin M (OSM) and is being developed for the treatment of rheumatoid arthritis (RA). GSK315234 blocks the interaction of OSM with its cell surface signaling receptor, gp130. Oncostatin M is a member of the interleukin (IL)-6 family of secreted cytokines and is present in the inflamed synovium and blood of patients with RA. Preclinical data indicated that OSM drives pro-inflammatory responses and induces the production of acute phase reactants. OSM also drives cartilage degradation. This study will provide baseline safety, tolerability, pharmacodynamic and pharmacokinetic information in a healthy volunteer population which will enable the identification of well tolerated effective doses to be used in subsequent clinical studies.

Method: This was a single-blind, placebo-controlled, dose-escalation study in healthy volunteers (males and females of non childbearing potential). Single ascending intravenous doses of GSK315234 (0.003–30 mg/kg) were administered. Assessments included safety/tolerability, pharmacokinetics and pharmacodynamics.

Results: Seventy two subjects were dosed (48 with active and 24 with placebo) and 66 completed the study. There were no remarkable vital signs, electrocardiogram (ECG), hematology and chemistry changes or infusion reactions. There were clinically observed effects on platelets that matched the predictions of models of the preclinical data. A dose response relationship was observed indicating a maximal effect of a 23% reduction in platelets at the highest exposure of GSK315234. A pharmacodynamic analysis showed that the total OSM levels had a non-linear relationship to drug concentrations and could be modeled using an indirect response model (IC_{50} for the relationship to be 5 mg/mL and $t_{1/2}$ ~30min). The pharmacokinetics of GSK315234 was as expected and similar to other monoclonal antibodies of the same class (clearance 3.5mL/day/kg).

Conclusion: GSK315234 showed to be safe and well tolerated in healthy volunteers. Observation of platelet pharmacology clearly defines a broad therapeutic interval allowing a choice of doses that can be determined to cause no haematological adverse effects. It also provides proof that the binding of OSM and the elevation of total OSM has downstream consequences on OSM mediated pharmacology. The low clearance of GSK315234 would allow infrequent dosing and regimes similar to other mAbs in the clinic. This data, in combination with preclinical data, confirms OSM blockade by GSK315234 as a rheumatoid arthritis therapy worthy of further investigation.

Disclosure: M. B. Baker, GlaxoSmithKline, 3 ; **M. Bendit**, GlaxoSmithKline, 3 ; **A. M. Campanile**, GlaxoSmithKline, 3 ; **M. Feeney**, GlaxoSmithKline, 3 ; **P. Hodsman**, None; **J. F. Toso**, GlaxoSmithKline, 3 .

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Convincing Pharmacological Effects On Inflammation and Pain by Targeting the 5-HT_2 Receptors. C. Wenglén[1], G. Ekström[1], H. Arozenius[1], M. Siller[1], N. Palmqvist[1], A-C. Ryde[1], A. Sjödin[1], C. Klint[1], C. Flood[1], E. Seifert[2], A. Boman[2], P. Lek[2] and T. Lundstedt[2], [1]AnaMar Medical AB, Lund, Sweden, [2]AcurePharma AB, Uppsala, Sweden

Purpose: At inflammatory sites thrombocytes, the major source of peripheral serotonin (5-HT), accumulate and become activated. Thus, in the arthritic joints 5-HT is released into the synovial fluid where it boosts the inflammatory response by binding to 5-HT receptors on synovial cells. We have developed several compounds targeting the 5-HT_2 receptors. The compounds are structurally diverse, have different binding characteristics and pharmacological profiles. They have previously been shown to reduce IL-6 and TNF-α production *in vitro* and to diminish arthritis activity in two different animal models. The objective of the present study was to (1) further give evidence to that the effects of our compounds are mediated by antagonizing the 5-HT_2 receptors, (2) show effects of our compounds during ongoing inflammation in glucose-6-phosphate isomerase (GPI)-induced arthritis in the mouse, a third animal model of RA, (3) evaluate our compounds in an inflammatory pain model. Recently, one of our compounds entered the first tolerability and kinetic evaluation in a phase I clinical trial.

Method: The 5-HT_2 receptor expression pattern on our target cells was evaluated by RT-PCR. *In vitro* our compounds were added to rat synoviocytes together with commercial 5-HT_2 agonists to investigate their effects on IL-6 release. In GPI-induced arthritis, DBA/1 mice were immunized with rabbit GPI. The mice were orally treated with our compound AMAP102 (10 and 30 mg/kg) once daily and scored for arthritis. To investigate the effect of the compounds on inflammatory pain, AMAP102 and AMAP312 (1, 10 and 30 mg/kg) were orally administered to rats before injection of formalin into one of the paws. Nociceptive responses to the formalin injection that occurs in two phases were measured. The first phase is caused by the direct stimulation of nerve ends by formalin and the second represents the pain response to the inflammatory reaction.

Results: *In vitro* target validation experiments showed that the 5-HT_2 receptors are expressed on our target cells and that our compounds reverse the effects induced by selective 5-HT_2 agonists and thus likely act through the 5-HT_2 receptors. AMAP102, was shown to reduce

severity in the GPI-induced arthritis model, even when treatment was initiated after the first manifestations of disease. Finally, compounds from two different chemical classes, significantly reduced the inflammatory pain response at 1-30 mg/kg, without significantly influencing the first part of the nociceptive response.

Conclusion: The present study shows that impressive anti-arthritic effects are established by antagonizing the 5-HT_2 receptors with our proprietary compounds. In addition, the sensitivity to inflammatory pain is diminished. In conclusion, the study supports the clinical development of our compounds targeting the 5-HT_2 receptors.

Disclosure: C. Wenglén, Anamar Medical, 3 ; **G. Ekström**, Anamar Medical, 3 ; **H. Arozenius**, Anamar Medical, 3 ; **M. Siller**, Anamar Medical, 3 ; **N. Palmqvist**, Anamar Medical, 3 ; **A. C. Ryde**, Anamar Medical, 3 ; **A. Sjödin**, Anamar Medical, 3 ; **C. Klint**, Anamar Medical, 3 ; **C. Flood**, Anamar Medical, 3 ; **E. Seifert**, AcurePharmaAB, 4 ; **A. Boman**, AcurePharmaAB, 4 ; **P. Lek**, AcurePharma AB, 4 ; **T. Lundstedt**, AcurePharma AB, 4 .

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Drug Survival Time and Safety On Tocilizumab: Does Tocilizumab Differ From Anti-TNF Agents in Routine Practice? Kazuki Yoshida[1], Yasuharu Tokuda[2], Tsuyoshi Iida[1], Kaori Hosaka[1], Masako Utsunomiya[1], Tatsuo Kobayashi[1], Makiko Yamamoto[1], Kazuo Matsui[1] and Mitsumasa Kishimoto[1], [1]Kameda Medical Center, Kamogawa, Chiba, Japan, [2]University of Tsukuba, Tsukuba, Japan

Purpose: To compare the difference between Tocilizumab (TCZ) and anti-TNF agents (TNFs) on safety and drug survival time

Method: We studied a cohort of RA patients participating in the **KA**meda **RA T**NF inhibitor and Tocilizumab **E**ffectiveness and safety (KARATE) registry from Jan/2003 to Jun/2009. We examined the rate of serious adverse events (SAE: defined as use of IV antibiotics or hospitalization) between TCZ and TNFs in patients with at least 3 months follow-up. Baseline characteristics associated with SAE were analyzed by logistic regression model. Kaplan-Meier drug survival estimates at 6 and 9 months of the cohort were analyzed and hazard ratios of discontinuation were determined using Cox proportional hazard model.

Results: Baseline characteristics: We enrolled and analyzed 182 consecutive patients who received TCZ (n=26) and TNFs (n=156, IFX 88, ETN 64, ADA 4) in KARATE. For baseline characteristics, previous TNFs use (TCZ group 65% vs. TNFs group 10%, $p<0.001$) was significantly different between the two groups. There were no significant differences between the two groups for age (59 vs. 58 yrs for the TCZ and the TNFs groups, respectively), RF/anti-CCP positivity (81 vs. 87%), disease duration (8.6 vs. 7.9 yrs), mean baseline DAS28 (3) (3.6 vs. 3.5), mean steroid (PSL equivalent) dose (7.0 vs. 7.3 mg/day), MTX use (96 vs. 88%), diabetes (12 vs. 15%), COPD or ILD (0 vs. 12%, p=0.08), and chronic kidney disease (12 vs 3%, p=0.09).

SAE: No serious adverse events were observed in TCZ users, while 23 patients (15%) in TNFs users developed SAE (p=0.049, vs. TCZ) including 16 infections (7 bacterial pneumonia, 2 UTI, 1 cryptococcal pneumonia, MAC infection, septic arthritis, cellulitis, Listeria bacteremia, sepsis, and PCP), 1 AMI, 4 ILD exacerbation, 1 lung cancer, and 2 GI complications. Among baseline factors, age > 65 yrs (odds ratio, 2.8; 95% CI, 1.0 -7.6) was significantly associated with SAE.

Drug Survival: There was no significant difference in drug survival time between TCZ and TNFs (log rank test, p=0.77). At six and nine months, 90 and 81% of patients remained on TCZ and 83% and 78 on TNFs. The reason for discontinuation in all patients who discontinued TCZ (n=4) was for lack of efficacy. In TNFs users (n=86), the reasons for discontinuation included: lack of efficacy (35%), side effect (29%), MD preference (14%), patient preference (12%), good response (8%), and others 2%. There was a trend for higher risk of discontinuation of both TCZ and TNFs with age >65 yrs (hazard ratio [95% CI] 1.59 [0.97-2.60], p=0.06).

Conclusion: This study on patients treated in routine clinical practice indicates that drug survival time was comparable between TCZ and TNFs. TCZ may be safer than TNFs, although these results require further long term studies.

Disclosure: K. Yoshida, None; **Y. Tokuda**, None; **T. Iida**, None; **K. Hosaka**, None; **M. Utsunomiya**, None; **T. Kobayashi**, None; **M. Yamamoto**, None; **K. Matsui**, None; **M. Kishimoto**, None.

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Improvement of Cardiovascular Risk Markers with Atorvastatin Treatment in Rheumatoid Arthritis. Lotta Ljung[1], Marjatta Leirisalo-Repo[2], Hannele Yki-Järvinen[2], Riitta Koivuniemi[2], Antti Kuuliala[2], Kjell Karp[1], Solbritt Rantapää-Dahlqvist[1] and Robert Bergholm[2], [1]Norrland University Hospital, Umeå, Sweden, [2]Helsinki University Central Hospital, Helsinki, Finland

Purpose: To evaluate the effect of treatment with statin on endothelial function, arterial intima-media thickness, arterial distensibility, disease activity and lipid levels in moderately active, established rheumatoid arthritis (RA).

Method: 51 patients with RA were recruited for the study and received atorvastatin 40 mg daily (n=36, 26 women, 10 men) or placebo (n=15, 10 women, 5 men) for 24 weeks. DMARDs and oral corticosteroid treatments were kept stable during study period. Ultrasound performed measurements of common carotid artery intima-media thickness (IMT) and distensibility, brachial artery flow-mediated dilatation (FMD) and glyceryl trinitrate-dependent brachial artery responses (GTN), as well as clinical activity variables and serum lipid levels were obtained immediately before and after the 24-week period.

Results: The recruited patients had a mean (±SD) age of 60 (± 11) years, a mean disease duration of 17 (±10) years and a mean (± SEM) disease activity score (DAS28) at start of study of 4.20 (± 0.16). The groups were comparable regarding FMD, GTN, distensibility and total cholesterol/high density cholesterol (HDL) ratio at start of study.

FMD improved significantly in the statin treated group (5.5 ± 0.6 vs. 7.3 ± 0.6 %, p=0.02). FMD/GTN increased (0.41 ± 0.05 vs. 0.61 ± 0.09, p=0.04). No change was seen in the placebo group in the FMD or GTN measurements. The distensibility remained unchanged in the treated patients, but decreased in the placebo group leading to a significant difference of delta values between the groups (p=0.01). No change in pulse rate, systolic or diastolic blood pressure was seen in either group. An insignificant tendency towards a decrease in IMT was seen in the statin group (p=0.08).

DAS28 improved significantly in both groups, (-0.78 ±0.14, p<0.001 in statin, vs. -0.59 ±0.27, p=0.05, in placebo), but significant improvement of ESR (-7.5 ±1.7 mm, p<0.001) and CRP (-5.5 ± 1.6 mg/l, p=0.001) were only seen in the treated patients.

The atherogenic index; total cholesterol/HDL ratio, improved in the statin treated group (1.0 ± 0.1, p<0.001), and remained unchanged in the placebo group.

Conclusion: Our data suggests that treatment with atorvastatin may improve several markers of cardiovascular risk or atherosclerosis, as endothelial dysfunction, dyslipidemia and inflammatory laboratory parameters in established, moderately active RA.

Disclosure: L. Ljung, None; **M. Leirisalo-Repo**, None; **H. Yki-Järvinen**, None; **R. Koivuniemi**, None; **A. Kuuliala**, None; **K. Karp**, None; **S. Rantapää-Dahlqvist**, None; **R. Bergholm**, None.

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Phase I Single and Multiple Ascending Dose Studies to Investigate the Safety, Tolerance and Pharmacokinetics of CH-4051 in Healthy Male Subjects. Aletha Veenendaal[1], John Boland[2] and Lawrence A. Hewitt[2], [1]Kendle International, Utrecht, Netherlands, [2]Chelsea Therapeutics, Charlotte, NC

Purpose: Methotrexate (MTX) is the gold standard treatment for rheumatoid arthritis. However its use is frequently limited by common side effects including hepatotoxicity, nephrotoxicity, and gastrointestinal distress (nausea and diarrhea). It is hypothesized that a significant proportion of the toxicity profile of MTX is attributed to its hydroxylated and polyglutamylated metabolites. Therefore, an antifolate that is metabolically stable, that does not convert to toxic metabolites, yet maintains the efficacy of MTX should prove to be a superior therapy.

CH-4051 is a metabolically stable antifolate and is the more potent “L” isomer of the racemic mixture CH-1504. In a recent double-blind, randomized phase II study in MTX naive RA patients, CH-1504 in the dose range of 0.25 to 1.0 mg QD showed comparable efficacy to MTX and a better safety profile.

It is our proposition that CH-4051 will demonstrate superior efficacy and safety to MTX. As such we conducted a phase I study of the safety, tolerance and pharmacokinetics (PK) of single and multiple doses of CH-4051 in a single-center, double-blind, randomized, clinical trial.

Method: This study was conducted in accordance with ICH/GCP guidelines by Kendle International Utrecht, The Netherlands following favorable opinions from an Independent Ethics Committee and national Competent Authority.

This study consisted of a Single Ascending Dose (SAD) trial followed by a 14 day Multiple Ascending Dose (MAD) trial. In both SAD and MAD portions of the study 4 groups of healthy male volunteers were studied. Six subjects per group in the SAD and 8 subjects per group in the MAD were randomized 5:1 and 6:2 respectively to CH-4051 or placebo p.o. Doses tested were 5, 10, 20 and 40.0 mg in the SAD and 5, 7.5, 10, and 20 mg in the MAD. Subjects remained under clinical supervision for the duration of the dosing and PK collection periods. Dose

escalation occurred following a review of the previous group's safety and tolerance data. Safety assessments included: AEs, hematology, serum biochemistry, urinalysis, vital signs, physical examination and ECG.

Results: There were no serious AEs in either study; no AE was definitively attributed to CH-4051and all possibly related AEs resolved with cessation of dosing. In the SAD study no AEs led to study discontinuation or major intervention. In the MAD study, 7 AEs in 5 subjects led to study discontinuation at higher doses. These AEs included blepharitis, upper abdominal pain and vomiting, increased ALT and AST, and an unconfirmed case of melena. With respect to PK parameters; T_{max} occurred ~1-2h post dose and $T_{1/2}$ was approximately 4 h. C_{max} increased in a greater than dose proportional manner from 5 to 10 mg and a less than dose proportional manner from 10 to 40 mg.

Conclusion: CH-4051 was safe and well tolerated in a single dose up to 40.0 mg and multiple doses up to 7.5 mg daily for 14 days. PK parameters indicate CH-4051 is suitable for daily dosing.

Disclosure: A. Veenendaal, Kendle International, 5 ; **J. Boland**, Chelsea Therapeutics, 3 ; **L. A. Hewitt**, Chelsea Therapeutics, 3 .

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DAS28 and RAPID3 Based On Patient Questionnaire Scores Are More Likely Than ESR to Indicate a Quantitative Abnormality at Initiation of Methotrexate Therapy, to Monitor Improvement in Status in 201 Patients with Rheumatoid Arthritis. Theodore Pincus[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: To identify the likelihood of an abnormal value for 6 quantitative measures in 201 patients with rheumatoid arthritis (RA) at initiation of methotrexate (MTX) treatment in usual care. The 6 measures were: erythrocyte sedimentation rate (ESR); multidimensional health assessment questionnaire (MDHAQ) scores for function (MDHAQ-FN), pain (PN) and patient global estimate (PTGL); RAPID3 (routine assessment of patient index data); and disease activity score (DAS28). We compared the 6 measures at initiation of MTX in 201 patients with RA who began MTX therapy between 1980 and 2004.

Method: All patients seen between 1980-2004 at a weekly academic rheumatology clinic completed a MDHAQ at each visit, which included scores for MDHAQ-FN (0-3, converted to 0-10 for RAPID3) and PN (0-10) since 1980, and after 1996, PTGL (0-10), and capacity to score RAPID3 (0-30). Most patients with RA also had an ESR measured on the date of initiation of MTX therapy, and many unselected consecutive patients at different periods had a swollen joint count and tender joint count to allow calculation of a DAS28. Abnormal values were ESR $\geq$ 28 mm/h, MDHAQ-FN (0-3) >0.5, PN and PTGL (0-10) >2, RAPID3 scores (0-30) >6, indicating moderate or high (>12) severity, and DAS28 scores >3.2, indicating moderate or high (>5.1) activity. RAPID3-EST, i.e., RAPID3 without PTGL (correlated with RAPID3 at rho $\geq$ 0.9), was calculated for patients seen prior to 1996. The proportion of patients with abnormal vs normal values for these measures at the visit when MTX was initiated was analyzed. ESR from the previous visit was available in 64 of the 201 patients, and was examined to determine if an abnormal ESR may have been more likely at that visit than on the date of MTX initiation.

Results: Among 201 RA patients on the date of MTX initiation, abnormal values were seen for ESR in 49% of patients, compared to 70% for MDHAQ-FN, 85% for PN, 82% for PTGL and RAPID3, 83% for RAPID3-EST, and 87% for DAS28. Median ESR was 27, suggesting that ~50% of patients would not meet inclusion criteria for clinical trials. Median DAS28 was 5.0, suggesting that almost 50% of patients had DAS28 high activity (>5.1). Median RAPID3 was 12.9 and RAPID3-EST 13.3, suggesting that slightly more than 50% of patients met the criterion for RAPID3 high activity (>12). No meaningful differences were seen according to ESR at the previous visit.

Measures and indices in 201 RA patients at initiation of MTX: median values, and % of patients with normal vs abnormal values

Measure (range)	Median	Definition of abnormal	% Normal	% Abnormal
ESR (0-150 mm/h)	27	≥ 28	50.8%	49.3%
MDHAQ-FN (0-3)	1.0	> 0.5	29.9%	70.1%
PN (0-10)	5.1	> 2	15.0%	85.0%
PTGL (0-10)	5.0	> 2	17.9%	82.1%
RAPID3 (0-30)	12.9	> 2	18.2%	81.8%
RAPID3-EST (0-30)	13.3	> 2	16.9%	83.1%
DAS28 (0-10)	5.0	> 3.2	13.5%	86.5%

Conclusion: ESR was considerably less likely than any other Core Data Set measure or DAS28 or RAPID3 to be abnormal in patients with RA at the time of initiation of MTX. Textbooks continue to suggest ESR "is increased in nearly all patients with active RA" (Lipsky PE. In: Fauci et al, *Harrison's Rheumatology.* New York: McGraw-Hill; 2006. p 85), although ESR has been reported to be normal in 40% of RA patients at presentation (Wolfe F, Michaud K, *J Rheumatol* 1994;21:1226-37 and Sokka T et al, *J Rheumatol* 2009 epub). Patient MDHAQ/RAPID3 scores are easily collected in standard clinical care, and appear more useful than ESR in many patients to monitor status quantitatively and to document possible improvement in clinical status over time in patients with RA.

Disclosure: T. Pincus, None; **C. J. Swearingen**, None.

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Cholesterol 27-Hydroxylase but Not Apolipoprotein E Contributes to A2A Adenosine Receptor Enhanced Reverse Cholesterol Transport. Taiese C. Bingham[1], Saj Parahath[2], Allison Reiss[3], Edwin S. L. Chan[4], Edward Fisher[1] and Bruce N. Cronstein[5], [1]NYU School of Medicine, New York, NY, [2]Winthrop-University Hospital, Mineola, NY, [3]Winthrop University Hospital, Mineola, NY, [4]New York University School of Medicine, New York, NY, [5]New York Univ Med Ctr, New York, NY

Purpose: Unlike other DMARDs methotrexate diminishes the risk of Atherosclerotic Cardiovascular Disease (ASCVD) in patients with Rheumatoid Arthritis and adenosine, acting at adenosine A2A receptors, has been shown to mediate the anti-inflammatory effects of methotrexate. Adenosine inhibits the first step in formation of atherosclerotic plaque, foam cell formation in macrophages and this effect appears to be mediated by enhanced expression of cholesterol 27-hydroxylase, an enzyme involved in reverse cholesterol transport. We therefore asked whether the effect of adenosine A2A receptors on foam cell formation in vitro are mediated by apoE or 27-hydroxylase (27OH'ase), proteins involved in reverse cholesterol transport.

Method: THP-1 cells, a human monocytoid cell line, were infected with lentiviral vectors expressing siRNA for either apoE or 27OH'ase or scrambled RNA and infected cell lines were selected by incubation with puromycin. Foam cell formation was induced in THP-1 cells by incubation with interferon-γ (500U/ml) and % foam cells enumerated in 5 high power fields. 3H-Cholesterol efflux was measured after loading with label.

Results: Specific lentiviral siRNA infection markedly reduces apoE ($p < 0.0001$, apoE siRNA vs. control, n=3) or 27OH'ase mRNA ($p < 0.0001$, 27-hydroxylase siRNA vs. control, n=3) and protein ($p < 0.0107$, 27-hydroxylase siRNA vs. control n= 3) in THP-1 cells. Despite diminished apoE expression CGS-21680 (1μM), an adenosine A2A receptor agonist, inhibits IFNγ-induced foam cell formation ($p < 0.0002$, IFNγ CGS vs. IFNγ alone, n= 4) but has no effect on foam cell formation in 27OH'ase KD cells. CGS21680 increases cholesterol efflux in wild type and apoE1 KD cells (from 9.5% to 17.5+2.5% and from 10.0+2% to 17.5 +2%, respectively) but not 27OH'ase KD cells.

Conclusion: Adenosine A2A receptor-mediated increases in reverse cholesterol transport leading to diminished foam cell formation explains the anti-atherosclerotic effects of methotrexate.

Disclosure: T. C. Bingham, Patents on use of adenosine A2A receptor agonists to promote wound healing and use of A2A receptor antagonists to inhibit fibrosis. Patent on use of adenosine A1 receptor antagonists to treat osteoporosis and other diseases of bone. Patent on the use o, 4, Board Member, Vilcek

Foundation , 6, King Pharmaceuticals NIH Vilcek Foundation , 2, CanFite Biopharmaceuticals received for membership in Scientific Advisory Board, 1, Cypress Bioscience, Inc. King Pharmaceutical (licensee of patents above) CanFite Biopharmaceuticals Bristol-Myers Squibb Cellzome Tap Pharmaceuticals Prometheus Laboratories Regeneron (Westat, DSMB) Sepracor Amgen Endocyte Protalex Allos, Inc. Combinator, 5 ; **S. Parahath**, None; **A. Reiss**, None; **E. S. L. Chan**, King Pharmaceuticals, Excaliard Pharmaceuticals, 2 ; **E. Fisher**, None; **B. N. Cronstein**, CanfFite, 3, Cypress Bioscience, Inc. King Pharmaceutical (licensee of patents above) CanFite Biopharmaceuticals Bristol-Myers Squibb Cellzome Tap Pharmaceuticals Prometheus Laboratories Regeneron (Westat, DSMB) Sepracor Amgen Endocyte Protalex Allos, Inc. Combinator, 5, SLE Foundation, Inc., NY Arthritis Foundation, Board member Vilcek Foundation, 6, King Pharmaceuticals, 7, NIH, 2 .

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Clinical Control Induced by Epitope Specific Therapy in Rheumatoid Arthritis Is Associated with T-Cell Immune Deviation From Pro-Inflammatory (Th1/Th17) to Regulatory Phenotype (Th2/Treg). Th. van den Broek, N. Schechter, C. Cover, N. Seaver and Salvatore Albani, Arizona Arthritis Ctr, Tucson, AZ

Purpose: Immune therapy in a Phase II, placebo controlled trial in rheumatoid arthritis patients with a pro-inflammatory epitope from the heat shock protein dnaJ (dnaJP1, s5 mg qd op for six months) led to clinical improvement and to a tolerogenic immune deviation. Differences in immune function could be found at trial entry between responders and non responders in the dnaJP1 treatment group. Immune phenotype comprising of the co-expression of anergic/tolerogenic co-stimulatory molecules PD-1, CTLA-4, B7H-1 and FoxP3 was found as a pre-requisite for responsiveness. Clinical efficacy correlated with a reduction in TNFα by T cells to dnaJP1 in vitro. To further dissect the mechanisms of immune deviation, we analyzed the T cell lineage commitment (TH1/TH17 versus TH2/tolerogenic) and suppressive function of isolated T cell populations.

Method: Clinical responders (ACR20 response) treated with dnaJP1 (n=3) or Placebo treated clinical non-responders (n=5) were used. PBMC from time points T0 and Tend were cultured with dnaJP1 or anti-CD3CD28. T cells were enriched by MACS, then FACS sorted by CD4CD127+ (Teff) and CD4CD25+CD127- (Treg). Both populations were used for TaqMan real-time PCR analysis and CFSE suppression assay data. An aliquot of Teff was used for FACS analysis.

Results: DnaJP1 treated clinical responders downregulated TH17 associated markers, IL23R, IL12R and intracellular IL17A, in Teff cells at Tend, as measured by FACS. No differences were seen between T0 and Tend with placebo treated clinical non-responders. With dnaJP1 treated clinical responders, gene expression by TaqMan confirmed the downregulation of TH17 markers, RORC ($p<0.05$) and IL17A. Besides diminished Th17 phenotype, a deviation in cell lineage from a Th1 to a Th2/tolerized cell type was seen in Teff as evidenced by downregulation of Tbet and TNFα, and an upregulation of GATA-3 and IL-10 production. Treg cells from Tend showed superior suppression of Teff over Tregs isolated at T0 from dnaJP1 treated clinical responders (11.88% vs 39.32% Teff suppression, n=2).

Conclusion: Immune therapy with dnaJP1 led to clinical improvement and immune tolerance induction. These data suggest that clinical control in response epitope-specific therapy is mediated by an immune deviation in T cell lineage commitment of Teff from a proinflammatory (TH1/TH17) to a tolerogenic (TH2/tolerized) phenotype, as well as increased suppressive capability of Treg.

Disclosure: T. van den Broek, None; **N. Schechter**, None; **C. Cover**, None; **N. Seaver**, None; **S. Albani**, None.

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Clinical Control in Patients with Rheumatoid Arthritis Is Associated with Restoration of Diverse Subpopulations of Regulatory T Cells, Including a Novel Subtype Relying On the PD1-B7-H1 Pathway. Theo van den Broek, Nicole Schechter, Cathleen Cover, Norma Seaver, Farah Bughio, Nick Shen and Salvatore Albani, Arizona Arthritis Ctr, Tucson, AZ

Purpose: We focused on different subtypes of regulatory T cells discriminated by membrane markers, including the co-expression of PD-1, an otherwise well established marker of anergy. In preliminary studies we found PD-1 to be increased in T cell from patients who respond to the various therapies described here. PD-1 ligand B7H1 was also elevated in APC from the same responsive patients. We employed two systems.

Method: PBMC from 5 rheumatoid arthritis patients treated with epitope specific tolerization to a pro-inflammatory peptide (dnaJP1) in a Phase II trial.,were compared at trial entry (T0) and at the end (Tend). All the patients reached an ACR20 response at the end of the 6 month trial. A second system employed 6 patients on ETN and MTX,(n=3) or MTX alone (n=3). Clinical control was determined as a DAS-score of <3.2 (n=4)

The following T cells were sorted by FACS, CD4CD127+ (Teff), CD4CD25+CD127- (nTreg), CD4CD25+CD127-PD1+ (PD1+ Treg), CD4CD25+CD127-PD1- (PD1- Treg) and CD4CD25-CD127-PD1+ (CD4+PD1+). Gene expression was studied by TaqMan real-time PCR. CFSE suppression assay was used to determine the capability of Treg to suppress Teff proliferation.

Results: In both systems the expression of IL-10 was only upregulated in PD1+ Treg and CD4+PD1+. Clear differences were seen between the different Treg populations, especially in the ETN group and the dnaJP1 treated group. In these groups, PD1+ Treg have a higher expression of TGFBeta, and the opposite is observed for the PD1- Treg.

Suppression did differ between the different Treg groups. PD1-Treg and CD4+PD1+ suppressed the most (86-92% Teff suppression), followed by nTreg (78-82%) and PD1+ Treg (76-79%). With dnaJP1 therapy nTreg suppressed the most (63.74%), followed by PD1+ Treg (57.09%), CD4+PD1+ (26.45%) and PD1-Treg (1.62%).

% of suppression	Etanercept and Methotrexate	dnaJP1 T0	dnaJP1 Tend
CD4CD25+CD127- (nTreg)	78-82%	11.41%	63.74%
CD4CD25+CD127-PD1+ (PD1+ Treg)	76-79%	61.22%	57.09%
CD4CD25+CD127-PD1- (PD1- Treg)	86-92%	1.37%	1.62%
CD4CD25-CD127-PD1+ (CD4+PD1+)	86-92%	1.85%	26.45%

Conclusion: We examined diverse regulatory T cell populations and identified a novel type of Treg cell expressing PD1+ that is not anergic but shows suppressive capability with distinct functional differences between non-PD1 expressing cells. The induced expression of B7-H1 on APCs seen with clinical response might be the trigger for the generation of this specific Treg population. These data suggest the existance of novel circuit of active immune tolerization which seems relevant to clinical improvement.

Disclosure: T. van den Broek, None; **N. Schechter**, None; **C. Cover**, None; **N. Seaver**, None; **F. Bughio**, None; **N. Shen**, None; **S. Albani**, None.

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Glucocorticoids Decrease the Expression of Synovial Citrullinated Proteins in Rheumatoid Arthritis. Dimitrios Makrygiannakis, Shankar Revu, Petra Neregård, Marianne Engström, Lars Klareskog and Anca Irinel Catrina, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

Purpose: Citrullination has previously been reported to be an inflammation associated process. Peptidylarginine deiminase (PAD) 2 and 4 are the PAD enzymes expressed in the rheumatoid arthritis (RA) synovium, while a mouse monoclonal antibody (F95) has been found to be associated with an intracellular pattern which is specific for RA synovium and which correlates with anti-citrullinated-protein antibody levels. The aim of the current study was to compare the expression of PAD2, PAD4 and citrullinated proteins between RA and healthy synovium and to study the effect of anti rheumatic drugs on synovial expression of CP and PAD enzymes. (MTX), infliximab (IFX) and etanercept (ETA) on PAD2, PAD4 and F95 expression in RA synovium.

Method: Synovial biopsies were obtained from 15 RA patients treated with intra-articular glucocorticoids (IAG), 13 RA patients treated with methotrexate (MTX), 9 RA patients treated with infliximab (IFX) and 13 RA patients treated with etanercept (ETA). Synovial tissue was also obtained from 8 healthy individuals. The presence of PAD2 and PAD4 was immunohistochemically detected with 2 rabbit polyclonal antibodies for each enzyme and the presence of citrullinated proteins with the F95 antibody. Biopsies were evaluated by double blind semi-quantitative analysis on a 4-grade scale (0-3). Additionally synovial tissue from an RA patient obtained during open joint surgery was cultured in vitro to further study the direct effect of the drugs on synovial citrullination. Statistical analysis was performed using the Wilcoxon test.

Results: F95 staining was present in 40/50 RA patients (both extracellular and intracellular) while none of the 8 healthy individuals exhibited an intracellular pattern and only one exhibited an extracellular pattern in low amounts. PAD2 expression was higher in RA in comparison to healthy synovial tissue, while PAD4 expression did not differ.

Treatment with MTX and TNF antagonists did not alter the expression of PAD enzymes and CP, with the exception of a reduction in PAD4 expression (statistical significance with one of the 2 antibodies used) in the IFX treated group. In contrast, IAG treatment resulted in down-regulation of both the expression of intracellular citrullinated proteins (F95) and of the PAD4 enzyme. This finding was confirmed in the cultured biopsy demonstrating no changes in the expression of PAD2 and a decrease of F95 and PAD4 expression following glucocorticoid treatment.

Conclusion: The RA specific pattern of intracellular citrullination is absent in healthy synovium and specific targeted by glucocorticoids.

Disclosure: D. Makrygiannakis, None; **S. Revu**, None; **P. Neregård**, None; **M. Engström**, None; **L. Klareskog**, None; **A. I. Catrina**, None.

ACR Poster Session A

Scleroderma and Fibrosing Diseases
Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Open Label Use of Mycophenolate Mofetil in Diffuse Systemic Sclerosis. Max Shenin, Elizabeth Grace, Steffan W. Schulz, Manisha D. Naik, Wen Xiong and Chris T. Derk, Thomas Jefferson University, Philadelphia, PA

Purpose: Mycophenolate mofetil is an inosine monophosphate dehydrogenase inhibitor, that inhibits the proliferative responses of T and B lymphocytes as well as antibody production by B-lymphocytes. Recent studies have also suggested that this agent may also have an anti-fibrotic effect. Based on these actions mycophenolate mofetil appears to be a novel agent for the treatment of systemic sclerosis, especially during early disease where an inflammatory infiltrate precedes the development of fibrosis. We set out to examine the efficacy of this agent in systemic sclerosis.

Method: We recruited 15 patients with early onset diffuse systemic sclerosis to take part in an open label study using mycophenolate mofetil to treat their disease over a 12 months period. The primary outcome measure was the modified Rodnan skin score (mRSS) while secondary outcomes included the Medsger severity score, pulmonary function studies, 2D- echocardiograms and the SF-36 questionnaire.

Result: The mRSS was significantly improved in those patients who tolerated the medication for more than 3 months ($p<0.0001$), and there was statistically significant improvement in the Medsger severity scores of the general ($p=0.05$), peripheral vascular ($p=0.05$) and skin scores ($p=0.0003$). The SF-36 scores were improved ($p=0.05$) and the pulmonary function studies showed a trend towards improvement though not of statistical significance. The mean pulmonary artery pressure by 2D echocardiography did not change.

Conclusion: In this prospective open label study of mycophenolate mofetil for the treatment of early diffuse systemic sclerosis we observed significant improvements in skin scores, peripheral vascular involvement and patient perceived health status. Pulmonary function studies did not worsen as expected but rather showed a trend towards improvement. Controlled trials are needed to further investigate this.

Disclosure: M. Shenin, None; **E. Grace**, None; **S. W. Schulz**, None; **M. D. Naik**, None; **W. Xiong**, None; **C. T. Derk**, Aspreva Pharmaceuticals, 2 .

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Four-Year Survival in the TRUST Cohort of Bosentan-Treated Patients with Pulmonary Arterial Hypertension Related to Connective Tissue Disease. Christopher P. Denton[1], J. Pope[2], Hans-Hartmut Peter[3], Armando Gabrielli[4], Martin Doelberg[5] and Loic P. Guillevin[6], [1]Royal Free Hospital, London, United Kingdom, [2]St Joseph Health Care, London, ON, [3]Med. Universitätsklinik, Freiburg, Germany, [4]Azienda Ospedaliera Umberto I, Ancona, Italy, [5]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, [6]Hopital Cochin, Paris, France

Purpose: Pulmonary arterial hypertension (PAH) is a major complication of connective tissue disease (CTD). In the prospective TRUST cohort of 53 patients with PAH-CTD, bosentan therapy was well tolerated and associated with a Kaplan-Meier survival estimate of 92% (95% CI: 85–100) at 1 year, 82% (95% CI: 72–93) at 2 years, and 70% (95% CI: 57–83) at 3 years (1,2). Here we report 4-year survival data from TRUST, which is the last data collection in this cohort.

Methods: Bosentan was administered to patients with PAH-CTD in WHO functional class (FC) III according to product labeling for at least 2 years. Patients were followed for 4 years from treatment start (baseline). Survival and change from baseline in WHO FC (imputed as class IV in case of death) were collected. Probability of survival at different time points was estimated by Kaplan-Meier method.

Results: Of 53 PAH-CTD patients enrolled (mean age 62.7 years, 83% female, 96% Caucasian), 29 patients had limited cutaneous scleroderma (lSSc), 13 diffuse cutaneous scleroderma (dSSc), 6 overlap CTD, and 5 systemic lupus erythematosus. Eight patients had signs of right heart failure at baseline. Mean time from PAH diagnosis was 45.2 weeks at baseline. Twenty-five patients received bosentan monotherapy for more than 2 years from baseline and 15 received bosentan treatment (monotherapy or combination) for at least 4 years. At 4 years, data were available for 36 of the 53 patients. No 4-year data were available for 9 patients who were lost to follow-up (6 of them due to local administrative reasons) and for 8 patients who had their last hospital visit between Year 3 and Year 4. Nineteen patients died by year 4, with an overall survival probability (Kaplan Meier estimate) of 58.3% (95% CI: 43.3–73.2). The percentage of patients with improvement or stabilization of WHO FC from baseline was 40% (95% CI: 23.9–57.9).

Conclusion: A limitation of the present results is that 4-year data were not available for 17 of the 53 patients. Our findings are in accordance with the results reported at the 1-, 2- and 3-year time points of the TRUST cohort (1,2) and are consistent with previously reported data in the PAH-CTD subpopulations of two placebo-controlled trials (3). The observation that all patients were in FC III and some already presented with right heart failure at baseline highlights the PAH severity in this cohort despite potential selection bias. Hence, the observed 4-year survival estimate of 58% in FC III, right heart catheter proven PAH compares favorably with historical data reported after a follow-up of only one year (4).

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Disclosure: C. P. Denton, Genzyme Corporation, 2, Actelion Pharmaceuticals Ltd, 2, Aspreva Pharmaceuticals, 2, Encysive Pharmaceuticals, 2, Digna Pharmaceuticals, 2, Actelion Pharmaceuticals Ltd, 5, Encysive Pharmaceuticals, 5 ; **J. Pope**, Roche Pharmaceuticals, 2, Actelion Pharmaceuticals Ltd, 2, Actelion Pharmaceuticals Ltd, 5, Amgen Wyeth, 2, Abbott Laboratories, 2, Bristol-Myers Squibb, 2, Novartis Pharmaceutical Corporation, 2, Roche Pharmaceuticals, 5, Amgen Wyeth, 5, Abbott Laboratories, 5, UCB, 5, Bristol-Myers Squibb, 5, Schering, 5 ; **H. H. Peter**, None; **A. Gabrielli**, None; **M. Doelberg**, Actelion Pharmaceuticals Ltd, 1, Actelion Pharmaceuticals Ltd, 3 ; **L. P. Guillevin**, Actelion Pharmaceuticals Ltd, 5, Actelion Pharmaceuticals Ltd, 9 .

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Progression of Esophageal Dysmotility in Scleroderma. Asia Mubashir[1], Fahd Saeed[2], Mozafareddin Karimeddini[1] and Naomi F. Rothfield[3], [1]University of Connecticut Health Center, Farmington, CT, [2]University of Connecticut Health Center, Farmington, [3]University of Connecticut, Farmington, CT

Purpose: Scleroderma is a multisystem disorder that affects the esophagus in approximately 90 % of the patients. There are no reported studies on the progression of esophageal involvement. The objective of our study was to longitudinally evaluate esophageal transit time in patients with scleroderma.

Method: We did a retrospective chart review of all patients with scleroderma seen by rheumatology faculty at the University of Connecticut Health Center, between 1995 and 2008 .Patients were included if they were greater than 18 years of age and had a total of two or more esophageal transit time (ETT) studies at least one year apart. ETT studies were routinely done yearly on all scleroderma patients. Patients had ETT studies done in upright and supine position and were evaluated for dysmotility in proximal and distal portions for each of the positions. Normal esophageal emptying demonstrates 90% clearance of tracer by 10 seconds and greater than 95% clearance by 30 seconds.

Results: There were 102 patients : Eighty patients (78.4%) had limited scleroderma (LS) and 22 (21.5%) had diffuse scleroderma (DS). 382 esophageal transit time studies were analyzed over 13 years: 293 (76.7%) in LS and 89 (23.3%) in DS. 21 (95.4%) DS patients had worsening dysmotility (mean years 5.6%), 1 patient showed no change. LS, 47 (58.8 %) patients showed progressive worsening (mean years 6), 15 (18.8 %) patients showed no change and 18 (22.5 %) patients had improvement (8.8 mean years).

Conclusion:

Type	Worse	Stable	Improved
Limited	47	15	18
Diffuse	21	1	0

p value (Yates chi square) 0.02

Our study showed a significant difference between limited and diffuse scleroderma. 58.8 % of LS patients worsened whereas 95 % of DS patients worsened. In addition, no DS patient improved and 22.5% of LS improved. (Yates chi square p= 0.02)

Disclosure: A. Mubashir, None; **F. Saeed**, None; **M. Karimeddini**, None; **N. F. Rothfield**, None.

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A Clinically Defined Subset of dcSSc Is Associated with Elevated Serum IL-6 Level. Voon Ong, Svetlana Nihtyanova, Carol M. Black and Christopher P. Denton, Royal Free Hospital, London, United Kingdom

Purpose: IL-6 is a pleiotropic cytokine and it has been implicated in SSc pathogenesis. We analysed the relationship between serum IL-6 levels and the inflammatory response and modified Rodnan skin score (mRSS) in SSc. Based upon the known stimulatory effect of IL-6 on thrombopoiesis, we also hypothesised that a subgroup of diffuse cutaneous systemic sclerosis (dcSSc) patients with elevated platelet counts might have higher levels of IL-6.

Method: This was a cross-sectional study of SSc patients and healthy controls. These include three subgroups of SSc cases: dcSSc with high platelets (n=20, mean platelet count: 458 x 10^9/L, IQR: 418-508), dcSSc with normal platelets (n=19, mean platelet count: 276 x 10^9, IQR: 242-313), limited cutaneous SSc(lcSSc) (n=22, mean platelet count: 264 x 10^9, IQR: 227-297) and 15 controls. Serum IL-6 and soluble IL-6 receptor (sIL-6r) levels (in pg/ml) were determined by ELISA. Associations between serum IL-6 and CRP, platelet count, peak and concurrent skin score were determined by Pearson's correlation coefficient. IL-6 levels were subdivided into three categories: High (>10 pg/ml), Low (<10 pg/ml and > 3.12 pg/ml) and undetectable (below quantitation limit, < 3.12 pg/ml). Categorical data were analysed by Chi-square test.

Results: A majority of the cases were female: 77% and 96% in dcSSc and lcSSc respectively compared to 53% in controls. The age of the subjects was similar in all cohorts (mean±SD, years): 55.1±10.3 dcSSc, 59.1±11.4 lcSSc and 53.7±11.4 controls. Duration of disease (mean±SEM,months) for lcSSc and dcSSc was 152.6±23.9 and 52.4±7.0 respectively. Disease duration (mean±SEM,months) was longer in dcSSc with elevated platelets (57.0±11.9) than those with normal platelets (47.3±6.9).

IL-6 levels were significantly elevated in 55% of the dcSSc cohort with thrombocytosis compared to only 21% of the dcSSc cohort with normal platelets ($p<0.001$). In contrast, a majority of the lcSSc (75%) and control (87%) cohorts had undetectable IL-6 levels. Moreover, IL-6 levels were positively correlated with platelet count in SSc ($r=0.5$, $p<0.001$). However, there were no significant differences in sIL-6R levels across all cohorts ($p=0.16$) and no correlation was observed between sIL-6R levels and platelet count ($r= -0.15$, $p=0.23$). There was strong association between serum IL-6 and CRP in the total cohort ($r =0.74$, $p<0.001$) and this correlation remained significant in the dcSSc with elevated platelets cohort ($r =0.5$, $p<0.001$). In addition, serum IL-6 levels positively correlate with concurrent mRSS ($r=0.48$, $p=0.02$) but not with peak mRSS ($r=0.19$, $p=0.40$). There was moderate correlation between platelet count and concurrent mRSS ($r=0.33$, $p=0.05$).

Conclusion: These results suggest that IL-6 may be a potential biomarker for skin disease in SSc and that thrombocytosis in dcSSc patients may selectively identify those with high IL-6, and higher mRSS. Together these data support further exploration of the pathogenic role of IL-6 in SSc and suggest that a targeted therapeutic strategy against IL-6 may be worthwhile.

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Demographics and Previous Complications/Interventions in Patients with Digital Ulcers and Different Subsets of Scleroderma: Preliminary Findings From the DUO Registry. Christopher P. Denton[1], Loïc Guillevin[2], Thomas Krieg[3], Barbara Schwierin[4], Daniel Rosenberg[4], Mariabeth Silkey[4] and Marco Matucci-Cerinic[5], [1]Royal Free Hospital, London, United Kingdom, [2]Université Paris Descartes, Paris, France, [3]Universität zu Köln, Köln, Germany, [4]Actelion Pharmaceuticals, Allschwil, Switzerland, [5]University of Florence, Firenze, Italy

Purpose: Digital ulcers (DU) are a frequent, persistent and debilitating manifestation of systemic sclerosis (SSc). The DUO Registry is a European, multi-center, prospective, observational cohort study of patients with DU associated with SSc. Here, we describe the history of complications/interventions, and the concomitant medications prescribed for DU, in patients with DU and limited SSc, diffuse SSc or overlap SSc/Mixed connective tissue disease (CTD) at enrolment into the DUO Registry.

Methods: This is a registry in which patients with ongoing DU disease undergo clinical assessments and receive standard medical care, as determined by the patient's physician. All consenting consecutive patients with ongoing DU disease, irrespective of treatment regimen, are enrolled. Since April 2008, data collected has included demographics, relevant SSc and DU medical history, complications of and interventions for DU disease, including relevant medications.

Results: To 19 May 2009, 684 patients have been enrolled, with 47% limited SSc, 41% diffuse SSc, 9% Overlap SSc/Mixed CTD and 3% Other (eg. Lupus erythematosus, SSc type not specified). The patients with limited SSc have a higher age (mean=56.2yrs, SD=13.4) than the patients with diffuse SSc (mean=50.8 yrs, SD=14.0). The following table describes previous complications/interventions and DU-specific concomitant medication reported at enrolment.

	Limited SSc (n/N*, %)	**Diffuse SSc (n/N*, %)**	**Overlap SSc/ Mixed CTD (n/N*, %)**
History of DU complications and DU interventions			
Hospitalization	171/288, 59.4%	132/253, 52.2%	23/52, 44.2%
Soft tissue infection requiring antibiotics	121/272, 44.5%	94/232, 40.5%	19/54, 35.2%
Gangrene	97/279, 34.8%	66/249, 26.5%	17/56, 30.4%
Surgical amputation	39/231, 16.9%	21/194, 10.8%	5/50, 10.0%
DU-specific concomitant medications at enrolment			
Immunosuppressants	8/313, 2.6%	11/273, 4.0%	6/60, 10.0%
Analgesic/anti-inflammatories	67/313, 21.4%	63/273, 23.1%	18/60, 30.0%
Systemic antibiotics	44/313, 14.1%	36/273, 13.2%	8/60, 13.3%
Topical DU treatments	78/313, 24.9%	69/273, 25.3%	11/60, 18.3%
Prostacyclines	109/313, 34.8%	85/273, 31.1%	25/60, 41.7%
Other medications	131/313, 41.9%	105/273, 38.5%	23/60, 38.3%

*The denominator varies according to the number of available observations

Conclusion: DU are a major morbidity across the scleroderma spectrum. Use of DU-specific concomitant medications, complications of infection, gangrene and amputation occur frequently in all major disease subsets. Greater physician awareness and a more consistent approach to management are likely to improve outcomes.

Disclosure: C. P. Denton, Genzyme Corporation, 2, Actelion Pharmaceuticals, 2, Aspreva Pharmaceuticals, 2, Encysive Corporation, 2, DigNa Pharmaceuticals, 2, Actelion Pharmaceuticals, 5, Encysive Pharmaceuticals, 5 ; **L. Guillevin**, Actelion Pharmaceuticals, 5 ; **T. Krieg**, Actelion Pharmaceuticals, 5 ; **B. Schwierin**, Actelion Pharmaceuticals Ltd, 3 ; **D. Rosenberg**, Actelion Pharmaceuticals Ltd, 3 ; **M. Silkey**, Actelion Pharmaceuticals Ltd, 3 ; **M. Matucci-Cerinic**, Actelion Pharmaceuticals Ltd, 5 .

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Development of the Scleroderma Disease Activity Index (SDAI). M. Hudson[1], Marilyse Julien[1], Murray Baron[2], Canadian Scleroderma Research Group and Russell Steele[1], [1]McGill University, Montreal, QC, [2]Jewish General Hospital, Montreal, QC

Purpose: Measuring disease activity in systemic sclerosis (SSc) is necessary to provide a conceptual structure to study this poorly-defined disease and as an outcome measure for interventional studies. The purpose of this study was to develop a disease activity index for SSc.

Method: Data from a large, pan-Canadian cohort of SSc patients was reviewed. From 1800 variables available in the database, 61 were retained based on an extensive literature search and review by 2 scleroderma experts working by consensus for face and content validity. The selected variables included 54 independent variables (disease duration, disease subset, physician ID and 51 variables selected as possible indicators of disease activity in SSc) and 7 response variables. Of 745 patients entered into the registry, 191 had complete data on the abovementioned variables and were selected for this analysis. Advanced statistical methods were used to identify the best set of variables for inclusion in a new Scleroderma Disease Activity Index (SDAI).

Results: Baseline characteristics of the patients included for the analysis were as follow: 87% female, mean age 54.5 (± 12.2) years, mean disease duration 10.7 (± 8.9) years; 39% diffuse disease. The mean physician global assessment of disease activity in the last week measured using a numerical rating scale ranging from 0-10 was 2.3 (±1.9). Lasso regression analysis using the physician global assessment of disease activity as response variable performed best and allowed the identification of 11 independent variables predictive of disease activity in SSc. Of these, 4 were patient-reported [severity of Raynaud's phenomenon (RP) in the last week measured using a numerical rating scale ranging from 0-10 (coefficient 0.21), average number of episodes of RP per week in the past month (coefficient 0.24), worsening of scleroderma in the past month (coefficient 0.24), and severity of shortness of breath in the past week measured on a numerical rating scale ranging from 0-10 (coefficient 0.33)], 4 were assessed by physicians [pulse rate per minute (coefficient 0.16), presence of basilar crackles (0.05), modified Rodnan skin score ranging from 0-51 (coefficient 0.75), and swollen joint count ranging from 0-28 (coefficient 0.16)], and 3 were lab-based [weight loss in the past year in lbs (0.13), hematocrit (coefficient 0.03) and forced vital capacity measured as percent predicted (coefficient -0.06)]. These variables accounted for 32.5% of the variance in the physician global assessment of disease activity.

Conclusion: Using data from a large multi-centered cohort of SSc patients, we developed a new and simple measure of disease activity in SSc, the Scleroderma Disease Activity Index (SDAI), with face and content validity. Further testing is underway to verify construct validity and assess sensitivity to change.

Disclosure: M. Hudson, None; **M. Julien**, None; **M. Baron**, None; **R. Steele**, None.

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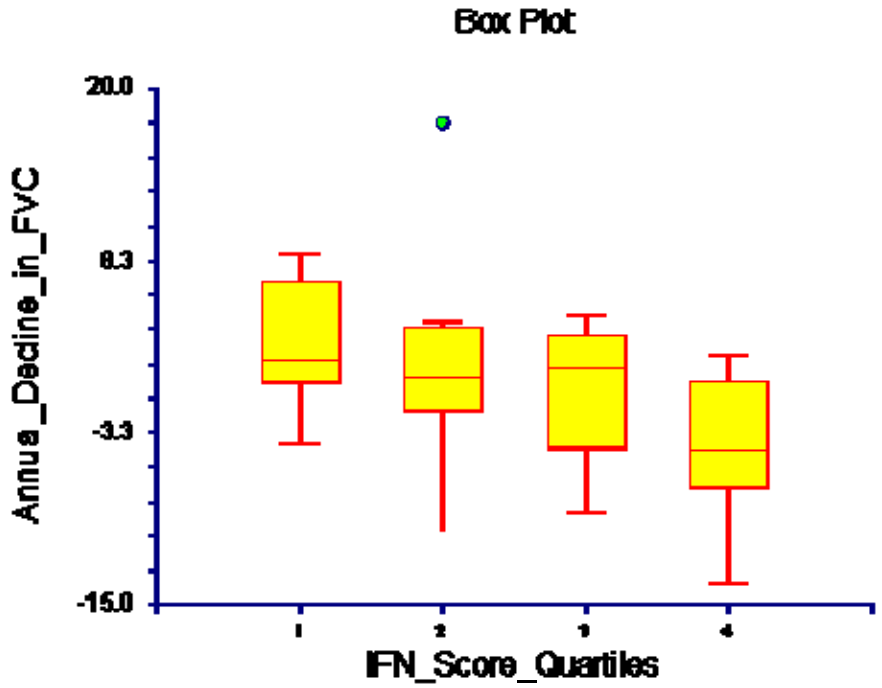
The Whole Blood Interferon Score Predicts Progression of Interstitial Lung Disease in Systemic Sclerosis. Shervin Assassi[1], Filemon K. Tan[1], Terry A. McNearney[2], Rosa Estrada-Y-Martin[1], Hilda T. Draeger[3], Jason Anderson[1], Frank C. Arnett[4] and M. Mayes[5], [1]Univ of Texas Houston, Houston, TX, [2]Univ of Texas Med Branch, Galveston, TX, [3]Univ of Texas San Antonio, San Antonio, TX, [4]University of Texas Medical School at Houston, Houston, TX, [5]U.Texas Houston, Houston, TX

Purpose: An upregulation of interferon inducible genes (IFNIG) in the peripheral blood of systemic sclerosis (SSc) patients has been previously reported. *In vitro* studies suggest IFN α and γ might have anti-fibrotic effects. We investigated whether the IFNIG score could predict the rate of decline in forced vital capacity (FVC) among SSc patients.

Method: The peripheral blood gene expression profile of early SSc patients (disease duration <5 years) was examined utilizing whole genome BeadChips. None of the study participants were treated with immunosuppressive agents at the time of blood draw. We calculated a previously described composite score for IFNIG's in all samples. Baseline and follow up FVC values were obtained and annual rate of decline in percent predicted FVC was calculated. We examined the correlation of baseline clinical parameters and IFNIG score with an annual rate of decline in FVC.

Results: A total of 36 patients had two pulmonary function tests that met the ATS/ERS standards for spirometry. The proportion of patients with diffuse disease was 63.89% (23/36). Anti-topoisomerase, anti-centromere and anti-RNA polymerase III antibodies were present in 6, 3, and 10 patients, respectively. Only 2 patients were current smokers. There was a time difference of 1.55 ± 0.6 years between the two FVC measurements. The disease type (p=0.698), disease duration (p=0.448) and presence of anti-topoisomerase antibodies (p=0.976) did not correlate with the annual decline in FVC. There was a trend for association of baseline FVC with the decline in FVC (p=0.054, r= 0.11) whereas the IFNIG score showed a significant negative correlation with the outcome (p=0.011, r= -0.42). Figure 1 demonstrates the reverse relationship between the quartiles of IFNIG score and the annual rate of decline in FVC indicating that higher IFNIG scores may be a marker of protection against progression of interstitial lung disease in SSc. In the bivariate model of baseline FVC and IFNIG score as independent factors, the IFNIG score retained its significantly negative correlation with the decline in FVC (p=0.027).

Conclusion: The interferon score is reversely related to the rate of decline in FVC and may be a useful biomarker to predict the progression of interstitial lung disease in systemic sclerosis patients.



Disclosure: S. Assassi, None; **F. K. Tan**, None; **T. A. McNearney**, None; **R. Estrada-Y-Martin**, None; **H. T. Draeger**, None; **J. Anderson**, None; **F. C. Arnett**, None; **M. Mayes**, None.

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Anti-Topoisomerase I Antibody Develops Simultaneously with Clinical Onset of Systemic Sclerosis through De Novo T Cell-Dependent Process. Masataka Kuwana[1] and Junichi Kaburaki[2], [1]Keio University School of Medicine, Tokyo, Japan, [2]Shin-akasaka Clinic, Tokyo, Japan

Purpose: Anti-topoisomerase I (topo I) antibody is highly specific to patients with systemic sclerosis (SSc), but underlying mechanisms that elicits this autoantibody response still remain unclear. In this study, we have investigated when and how anti-topo I antibody response emerges using blood samples obtained before and after SSc becomes clinically evident.

Method: Eight patients were selected from 98 patients with diffuse cutaneous SSc and anti-topo I antibody in our database, based on availability of serial serum samples including those obtained before onset of first non-Raynaud's phenomenon manifestation of SSc. Autoantibody assays were performed by indirect immunofluorescence and immunoprecipitation (IP) assay using radio-labeled cellular extracts. Levels, isotype distribution (IgG/IgM), and epitope reactivities of anti-topo I antibodies were evaluated by enzyme-linked immunosorbent assay using recombinant topo I fragments as antigen sources. In some instances, topo I-reactive T cells in circulation were quantified by limiting dilution of sorted peripheral blood CD4+ T cells followed by evaluation of a topo I-specific T cell response.

Results: A total of 12 sera obtained at a mean of 33.8 months (range 3-70) before SSc onset were available from 8 patients. All sera showed a positive anti-nuclear antibody at a titer ranging from 1:40 to 1:2560, but none of them was positive for anti-topo I despite use of highly sensitive IP assay. In contrast, anti-topo I was detected in all patients at SSc diagnosis, which was made a mean of 8.6 months (range 1-18) after the onset of first non-Raynaud's symptom. Anti-topo I isotype distribution was further evaluated serially in 2 cases in whom diagnosis of SSc was made within 3 months of the onset. In case #324, IgM anti-topo I alone was weakly positive one month after she noticed puffy fingers, although sera obtained at 3 and 50 months earlier were negative for anti-topo I. Three months later, skin thickness and interstitial lung disease became apparent with a prominent increase in IgG anti-topo I (isotype-switch). In case #336, IgM and IgG anti-topo I were positive three months after onset of puffy fingers despite the absence at 14, 38, and 48 months earlier. IgM anti-topo I became undetectable in one year, but IgG anti-topo I level increased and remained high with prominent expansion of topo I-reactive CD4+ T cells in circulation. Serial analysis of reactivities to epitopes on topo I revealed acquisition of IgG reactivity to previously unrecognized epitopes within one year after the onset (epitope-spreading).

Conclusion: Unlike lupus autoantibodies, development of anti-topo I antibody and clinical onset of SSc are concurrent events in patients with diffuse cutaneous SSc, although positive antinuclear antibody test precedes many years before onset of the disease. In addition, emergence of the anti-topo I antibody response follows a stepwise process of de novo T cell-dependent humoral immune response: production of IgM antibody followed by isotype-switch and epitope-spreading.

Disclosure: M. Kuwana, None; **J. Kaburaki**, None.

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Validation of the Qualitative and Semiquantitative Assessment of the Scleroderma Spectrum Patterns by Nailfold Videocapillaroscopy: Preliminary Results. V. Smith[1], Carmen Pizzorni[2], Filip De Keyser[3], Saskia Decuman[3], Jens T. Van Praet[3], Ellen Deschepper[3], Alberto Sulli[2] and Maurizio Cutolo[4], [1]Ghent University Hospital, Ghent, Belgium, [2]University of Genova., Genova, Italy, [3]UGent, Ghent, Belgium, [4]Research Laboratory and Academic Unit of Clinical Rheumatology, Genova, Italy

Purpose: Validation of the qualitative[1] and semiquantitative[2] scoring of nailfold videocapillaroscopy (NVC) scleroderma spectrum patterns in systemic sclerosis (SSc).

Method: Two raters from different centres, blindly assessed the NVC images of 71 consecutive SSc patients qualitatively as NVC scleroderma spectrum patterns ((“early”, “active”, “late” or “scleroderma-like” pattern), or “within normal limits”) and semiquantitatively by calculating the mean score for capillary loss, giant capillaries, microhaemorrhages and capillary ramifications. Inter/intrarater agreement was assessed by calculation of proportion of agreement and by kappa coefficients. Rater agreement of ordered categorical data was assessed by intraclass correlation coefficients.

Results: The inter/intrarater proportion of agreement to qualitatively distinguish the NVC scleroderma spectrum patterns from the “within normal limits” pattern was 90% and 96%, whereas the agreement to distinguish between the scleroderma and the “scleroderma-like” NVC patterns 62% and 81%. The agreement of the semiquantitative scoring, as assessed by intraclass correlation coefficient, was 0.96 and 0.95

for capillary loss; 0.84 and 0.95 for giant capillaries; 0.90 and 0.95 for microhaemorrhages, and 0.64 and 0.95 for capillary ramifications. Mean score classes 2 and 3 of capillary loss were associated with trophic digital skin lesions (pitting scars and skin ulcers) ($p = 0.039$).

Conclusion: This study demonstrates significant reliability of qualitative assessment of NVC scleroderma spectrum patterns and of their semiquantitative scoring between raters of different centres. The clinical associations observed between capillary loss and the clinical finding of pitting scars and skin ulcers in SSc patients underscores the construct validity of the NVC.

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2. Sulli A, Secchi ME, Pizzorni C, Cutolo M. Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. *Ann Rheum Dis*. 2008;**67**:885-7.

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Estimated Systolic Pulmonary Artery Pressure Versus Tricuspid Regurgitant Jet Velocity as Screening Tools for Pulmonary Hypertension in Systemic Sclerosis: The PHAROS Experience. Karmela K. Chan[1], Leslie R. Harrold[1], Firas Alkassab[1], Virginia D. Steen[2] and The PHAROS investigators, [1]Univ of Massachusetts Med Schl, Worcester, MA, [2]Georgetown University Medical Center, Washington, DC

Purpose: Pulmonary hypertension (PH) is the leading cause of death in patients with longstanding systemic sclerosis (SSc), with an estimated prevalence of 8-15%. Measurement of the pulmonary arterial pressure via right heart catheterization (RHC) remains the gold standard for establishing this diagnosis. However, given the invasive nature of RHC, other screening modalities have been used, namely echocardiography. The sensitivity of the echocardiographic estimation of systolic pulmonary artery pressure (SPAP) is reported to be 0.79 - 1.00, while the specificity is 0.6 - 0.98. SPAP is dependent upon two variables (based on the Bernoulli equation): estimated right atrial pressure and tricuspid regurgitant velocity (TRV). Since RA pressure estimation is quite subjective, it has been proposed that TRV might be more accurate than SPAP in screening for PH. Therefore, we sought to evaluate the performance of these 2 parameters in predicting PH in an observational cohort of SSc patients.

Methods: PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) is a multicenter web-based observational registry of SSc patients who are either at risk for, or have an established diagnosis of, PH; with a current total number of 286 enrolled subjects. Patients were included in this analysis if they have had an echocardiogram (reporting both SPAP and TRV) and a RHC within 180 days of each other. Sensitivity and specificity for SPAP and TRV were calculated for different cutoffs, and the area under the ROC curve was calculated using logistic regression analysis.

Results: There were 50 patients who met the inclusion criteria. Of these, 44 (88%) were female. Thirty (60%) had limited cutaneous SSc. Thirty two (64%) patients had PH based on RHC. The table displays the results of the analysis for different cutoffs of SPAP and TRV

Variable	Sensitivity (%)	Specificity (%)	False Positive Rate (%)	False Negative Rate (%)	Correctly Classified (%)
SPAP>35 mmHg	100	28	72	0	74
SPAP>40 mmHg	94	39	50	10	76
TRV> 2.5 m/s	100	33	67	0	74
TRV> 3.0 m/s	81	55	44	19	72

Not surprisingly, increasing the cutoff for either parameter improved the specificity but resulted in decreased sensitivity. When both parameters were considered as continuous variables, the area under the ROC curve for predicting PH was 0.86 (95% CI 0.76-0.96) for SPAP and 0.84 (95% CI 0.73-0.95) for TRV demonstrating the overlap in the predictive capability.

Conclusion: This study suggests that SPAP and TRV provide excellent sensitivity to screen for PH in SSc patients and perform equally well. The low specificity, however, indicates that RHC should remain the gold standard for establishing the diagnosis. Echocardiography is operator- and technique- dependent, so neither parameter can be viewed as an optimal screening tool on its own. Several screening algorithms have been suggested but which of these will provide the best accuracy remains to be determined. This study suggests that incorporating either SPAP or TRV in such algorithm is likely to provide similar predictive capability.

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Functional and Morphological Evaluation of the Digital Microcirculation with Laser Doppler Imaging and Nailfold Capillaroscopy in Systemic Sclerosis. Marcelo J.U. Correa, Luis Eduardo C. Andrade and Cristiane Kayser, Universidade Federal de São Paulo, São Paulo, Brazil

Purpose: Laser Doppler imaging (LDI) is a recently developed method for assessing superficial skin blood flow in systemic sclerosis patients (SSc) and Raynaud´s phenomenon. Nailfold capillaroscopy (NFC) is widely used for early diagnosis and for evaluation of structural microcirculation alterations in SSc. This study aimed to investigate the dynamic behavior of fingertip skin microvascular blood flow before and after cold stimulus (CS) using LDI in SSc patients and in healthy controls and to compare functional abnormalities on LDI with morphological microangiopathy evaluated by NFC in SSc.

Methods: 44 SSc patients (26 with limited and 18 with diffuse cutaneous form) with Raynaud´s phenomenon (3 M, 41 F; 47.4±10.5 years old) and 31 healthy controls (1 M, 30 F; 47.5±8.0 years old) were included. Disease duration was 5.9±5.5 years. Vasoactive drugs were discontinued 3 days before the procedure. After acclimatization for 1 hour at 24ºC, all subjects underwent NFC followed by LDI measurement. NFC was performed in a stereomicroscope (Olympus - SZ40) under 10-20 x magnification. The following parameters were analyzed in the ten digits of the hands: (1) number of capillary loops/mm, (2) number of enlarged and giant capillary loops, and (3) vascular deletion score. NFC parameters were calculated as the average obtained in all analyzed fingers. Skin blood flow of the dorsum of 4 fingertips (excluding the thumb) of the left hand was measured using LDI (Moor LDI-VR, Moor Instruments) at baseline and at 1, 4, 10, and 25 minutes after CS (submersion of both hands in water at 15^{o}C for 1 minute). The mean perfusion of the 4 fingertips was considered for analysis. Fingertip blood flow (FBF) was expressed in arbitrary perfusion units (PU) with respect to a calibration standard for the LDI scanner.

Results: LDI showed significantly lower baseline FBF in SSc patients as compared to controls (296.9±208.8 vs 496.6±141.5 PU; $p<0.001$) and also in all time points after CS ($p<0.001$). There was a significant decrease in FBF after CS as compared to baseline in SSc patients and in controls, followed by recovery of the blood flow 25 minutes after CS in healthy controls (FBF 25 min after CS 442.4±174.7 PU; $p=0.996$ vs baseline), but not in SSc (FBF 25 min after CS 209.9±185.1 PU; $p<0.001$ vs baseline). There was no correlation between baseline FBF and the severity of NFC parameters in SSc patients (number of capillary loops, $p=0.556$, $r=0.091$; number of enlarged and giant capillary loops, $p=0.87$, $r=-0.025$; vascular deletion score $p=0.219$, $r=-0.189$).

Conclusion: LDI showed lower digital blood flow before and after CS in SSc when compared to healthy controls and allowed objective measurement of blood perfusion in SSc. There was no correlation between functional and morphological microvascular abnormalities measured by LDI and NFC in SSc. LDI and NFC are complementary tools for evaluation of different aspects of the microangiopathy in SSc patients.

Disclosure: M. J. U. Correa, None; **L. E. C. Andrade**, None; **C. Kayser**, None.

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Long-Term Beneficial Effects of Statins On Vascular Manifestations in Patients with Systemic Sclerosis. Masataka Kuwana[1], Yuka Okazaki[1] and Junichi Kaburaki[2], [1]Keio University School of Medicine, Tokyo, Japan, [2]Shin-akasaka Clinic, Tokyo, Japan

Purpose: Microvasculopathy in systemic sclerosis (SSc) mainly affects small arteries, leading to Raynaud's phenomenon and painful digital ulcers. Statins have cholesterol-independent pleiotropic effects, which can improve endothelial functions and/or promote vascular repair through mobilization of endothelial progenitor cells (EPCs). Recent clinical trials suggested potential benefits of statins on vascular manifestations of SSc over a relatively short period (≤ 4 months). In this study, we conducted a 24-month, open-label study to evaluate the long-term effects of statins on vascular symptoms in SSc patients and to examine whether statins promote vasculogenesis as part of their clinical efficacy.

Method: Ten SSc patients were enrolled. All patients took atorvastatin at 10 mg/day for 24 months. A daily Raynaud's phenomenon attack diary and questionnaires for the assessment of global measures of health and psychological scales were assessed in addition to circulating angiogenic factors and endothelial activation/injury markers at 0 (pre-treatment), 1, 3, 12, and 24 months of treatment. EPCs positive for CD34, CD133, and VEGFR2 were serially quantified by cell sorting and 3-color flow cytometry, in accordance with recommendations proposed by the EULAR Scleroderma Trials and Research group expert panel, except the use of a viability marker.

Results: Eight patients (4 diffuse and 4 limited cutaneous SSc) completed the 24-month atorvastatin treatment. Two patients dropped out: one required cyclophosphamide for interstitial lung disease; and the other required bosentan for pulmonary arterial hypertension. None of the patients experienced any adverse events during the atorvastatin treatment. Raynaud's phenomenon improved during atorvastatin treatment, with significant reductions in the Raynaud's condition score ($P = 0.01$) and the patients' assessment by visual analog scale ($P = 0.0003$). The SSc-associated up-regulation of angiogenic factors (VEGF and bFGF) and vascular endothelial activation/injury markers (soluble VCAM-1 and E-selectin) were all reduced ($P < 0.01$ for all comparisons). Improvement in these parameters was best at 12 and 24 months of treatment. In 3 patients who had digital ulcers at the time of entry, the mean number of new digital ulcers prior to enrollment was 4.7/year, but this decreased to 3.3 at the 12-month assessment and 2.7/year at the 24-month assessment. Atorvastatin treatment resulted in a 1.2- to 6.1-fold increase (3.1 ± 1.8) in the EPC number at one month from the baseline ($P < 0.01$). However, the number peaked at one month and decreased thereafter, despite the continuous use of atorvastatin.

Conclusion: This pilot study suggests that statins may be beneficial in treating vascular manifestations of SSc, and these effects persisted for at least for 24 months. Notably, the longer the patients took atorvastatin, the greater the effects we observed. These pleiotropic effects are mediated primarily through improvement of endothelial functions, since statin treatment did not correct the defect in EPC recruitment.

Disclosure: M. Kuwana, None; **Y. Okazaki**, None; **J. Kaburaki**, None.

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Clinical Usefulness of Anti-RNA Polymerase III Antibody Measurement by Enzyme-Linked Immunosorbent Assay. Masataka Kuwana[1], Takashi Satoh[1], Shinichi Sato[2], Kazuhiko Takehara[3] and Anti-RNAP III Antibody Investigator Group, [1]Keio University School of Medicine, Tokyo, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Kanazawa University Graduate School of Medical Science, Kanazawa City, Japan

Purpose: Autoantibodies reactive with RNA polymerase (RNAP) III were highly specific for systemic sclerosis (SSc) and strongly associated with diffuse cutaneous involvement and renal crisis. In clinical settings, detection of the anti-RNAP III antibody is extremely important, because it helps identify patients with a high risk for developing renal crisis, but routine measurement of the anti-RNAP III antibody has not been feasible in clinical laboratories. Recently, an enzyme-linked immunosorbent assay (ELISA) kit for detecting the anti-RNAP III antibody has become available. This study was undertaken to evaluate the clinical usefulness of measuring anti-RNAP III antibody with a commercially available ELISA in Japanese patients with SSc.

Method: This multicentre study involved 354 patients with SSc, 245 with non-SSc connective tissue diseases (CTDs), and 102 healthy controls. ELISAs were used to detect anti-RNAP III antibody, anti-topoisomerase I (topo I) antibody, and anticentromere antibody (ACA). The presence of anti-RNAP III antibody in selected serum samples was confirmed by immunoprecipitation assay. Severity of individual organ involvements in SSc patients was evaluated using the Medsger's scale that has been modified to conform to Japanese patients, who have less extensive skin and tendon involvement.

Results: By ELISA, anti-RNAP III antibody was detected in 38 (10.7%) patients with SSc, 3 (1.2%) with non-SSc CTD, and no healthy controls. The clinical specificity for SSc was excellent (98.8%), although a small number of false-positives occurred. The sensitivity of the anti-topo I and ACA ELISAs for SSc was 59.9%, which increased to 68.2% without a reduction in specificity when the anti-RNAP III measurement was added. Anti-RNAP III, anti-topo I, and ACA were generally mutually exclusive, but 8 (21%) of the 38 anti-RNAP III-

positive sera had concomitant ACA. Clinical features associated with positivity for the anti-RNAP III antibody were diffuse cutaneous SSc, a high total skin score, and renal crisis, consistent with previous studies that used an immunoprecipitation assay. Furthermore, on clinical severity scales, SSc patients with anti-RNAP III antibody scored worse for general health and higher for skin and joint/tendon involvement than anti-RNAP III antibody-negative patients ($P < 0.05$ for all comparisons).

Conclusion: The measurement of anti-RNAP III antibody by ELISA is useful in routine clinical practice, since it helps diagnose SSc and identify a disease subset with severe skin involvement and a high prevalence of renal crisis.

Disclosure: M. Kuwana, MBL and INOVA Diagnostics, 7 ; **T. Satoh**, None; **S. Sato**, None; **K. Takehara**, None.

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Close Temporal Relationship Between Onset of Cancer and Scleroderma in Patients with RNA Polymerase I/III Antibodies. Ami A. Shah, Antony Rosen, Laura K. Hummers, Fredrick M. Wigley and Livia Casciola-Rosen, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: A close, at times concurrent, temporal relationship between the development of scleroderma and malignancy has been observed suggesting the immune response to tumor neoantigens may induce the scleroderma disease process in a subset of patients. In this study, we evaluated whether the temporal relationship between scleroderma and malignancy onset differed by autoantibody status among patients with scleroderma and cancer. We further investigated whether the nucleolar antigen RNA polymerase I/III was abnormally expressed in cancerous tissue of scleroderma patients.

Method: Participants were scleroderma patients followed at a tertiary Scleroderma Center who had a new or past diagnosis of malignancy, an available serum sample, and an existing cancer pathology specimen available for histologic confirmation of cancer diagnosis. Scleroderma onset was determined by the date of the first non-Raynaud's symptom. Sera were tested for autoantibodies against topoisomerase I by ELISA and against RNA polymerase I/III by both immunoprecipitation and ELISA. Paraffin sections from cancerous tissue of 3 scleroderma patients who had anti-RNA polymerase I/III antibodies were studied, and normal tissue sections were utilized as controls. Tissue sections were incubated with a monoclonal antibody against RNA polymerase, and staining was visualized with diaminobenzidine. Clinical and demographic characteristics were compared across autoantibody categories using the Kruskal Wallis test and the Fisher's exact test where appropriate.

Results: Twenty four subjects were enrolled. Seven tested positive for anti-RNA polymerase I/III (Group 1), 5 for anti-topoisomerase I (Group 2), and 12 for neither antibody (Group 3). Age, gender, race, smoking status, disease severity indices, and the frequency of ILD or PAH did not differ statistically between groups. The median duration of scleroderma at cancer diagnosis differed significantly between groups: -1 year in Group 1, +13.4 years in Group 2, and +5.1 years in Group 3 ($p=0.011$). The median duration of Raynaud's at cancer diagnosis followed a similar trend with a duration of 0 years in Group 1, +13.2 years in Group 2, and +6.6 years in Group 3 ($p=0.054$). We then examined pathology tissue from the tumors of 3 patients who produced antibodies to RNA polymerase I/III and found robust nuclear RNA polymerase staining. In striking contrast to the prominent staining noted in cancerous tissues, normal tissue paraffin sections showed minimal staining.

Conclusion: There is a close temporal relationship between onset of cancer and scleroderma in patients with antibodies to RNA polymerase I/III suggesting a common etiopathogenesis. Enhanced antigen expression in cancerous tissue from scleroderma patients suggests that malignancy may drive the expression of scleroderma in a subset of scleroderma patients.

Disclosure: A. A. Shah, None; **A. Rosen**, None; **L. K. Hummers**, None; **F. M. Wigley**, None; **L. Casciola-Rosen**, None.

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An Open Label Trial of the Endothelin Receptor Antagonist Bosentan in Scleroderma Renal Crisis (BIRD-1). Henry Penn[1], Aine Burns[1], Carol M. Black[2] and Christopher P. Denton[3], [1]Royal Free Hospital, London, United Kingdom, [2]Royal Free Hospital, London, [3]UCL Medical School, London, United Kingdom

Purpose: Scleroderma renal crisis (SRC) is a life-threatening complication affecting approximately 5% of cases of systemic sclerosis. Endothelin-1 is a potent vasoconstrictor peptide which has proliferative effects on endothelium and is found at high levels in plasma and in

renal biopsy material in SRC. The non-selective endothelin receptor antagonist (ETRA) bosentan is an established therapy for SSc associated pulmonary arterial hypertension and ischaemic digital ulceration. We have undertaken an open label pilot study of bosentan in SRC (BIRD-1).

Method: Cases within 6 weeks of confirmed of SRC received six months bosentan at a dose of 62.5mg for 1 month then 125mg twice daily for 5 months. 10 cases were screened, and six enrolled. Outcome measures included 1 year mortality, renal function, and blood pressure control. These were compared with a recent historic cohort of 49 SRC cases managed at our centre from 2000-2004.

Results: The mean (SD) age of the BIRD-1 cohort was 52 (11.5) years. 5 were female and only one was classified as lcSSc. The median duration of SSc at time of SRC was 6 months (range 2-72). Demographic and baseline clinical variables were not significantly different for the comparator cohort. All cases were treated with ACE inhibitors at full therapeutic doses. Clinical outcomes are summarised in Table 1. One case withdrew from the study after developing encephalopathy attributable to SRC. One case died at 2 months of multi-organ failure after discontinuing bosentan and dialysis. Bosentan was well tolerated with no significant drug related serious adverse events occurring. Three of five patients developed rebound phenomena on withdrawing bosentan – two with severe Raynaud's phenomenon, and three developed hypertension requiring one or two additional anti-hypertensive agents. Levels of ET-1 were elevated in all cases at SRC (median healthy controls 0.50pg/ml; SRC 1.48 pg/ml; $p<0.0005$), and increased further with bosentan therapy (1.46 pg/ml vs 3.05; t test $p<0.05$). N-terminal pro brain natriuretic peptide levels were also elevated, and high levels prior at presentation were associated with requiring dialysis (log values dialysed 3.61, non-dialysed 2.36, $p=0.028$).

Conclusion: Bosentan appears safe and well tolerated in conjunction with ACEi therapy for SRC. Overall, mortality and dialysis rates were not significantly different to our recent historic comparator cohort. A larger controlled study would be needed to fully assess therapeutic potential.

Table 1		2000-5 cohort (n=49)	BIRD-1 cohort (n=6)
Median (range) BP at presentation		195/114 (130-250/80-180)	194/118 (150-253/90-140)
Median (range) serum creatinine at presentation (microMol/L)		191 (82-1123)	185 (94-251)
Dialysis rates in survivors	at 1 mth	34/49 (69%)	3/6 (50%)
	at 12 mths	21/43 (48%)	2/5 (40%)
eGFR median (range) ml/min for cases not on dialysis	at 3 mths	31 (21-83)	66 (43-85)
	at 6 mths	36.5 (19-66)	68 (59-107)
	at 12 mths	41 (23-70)	72 (62-107)
Mortality at 1 year		6/49 (12%)	1/6 (16%)

Disclosure: H. Penn, Actelion Pharmaceuticals , 2 ; **A. Burns**, None; **C. M. Black**, None; **C. P. Denton**, Pfizer Inc, 5, Actelion Pharmaceuticals UK, 5, Actelion Pharmaceuticals UK, 2 .

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Gender and Ethnicity Differences in Patients with Diffuse Systemic Sclerosis Participating in 3 Large Randomized Clinical Trials.

M. Nashid, H. Agrawal, PP Khanna, P. Maranian, D. E. Furst, P. J. Clements and D. Khanna, UCLA, Los Angeles, CA

Purpose: Although non-Caucasian (Non-Cau) are more likely to develop dsSSc compared to Caucasians (Cau), it is not clear whether they have the same disease course after developing dcSSc. In addition, impact of gender on the disease course of dcSSc is unclear. Our objective

was to assess the course of modified Rodnan skin score (MRSS), HAQ-DI, and FVC% predicted between male versus female and Cau versus Non-Cau with dcSSc participating in 3 RCTs.

Method: Data from 3 RCTs (D- Penicillamine, recombinant human relaxin, and type I collagen) were pooled and analyzed. Baseline characteristics were compared in male vs. female and Cau vs. Non- Cau. A linear mixed effects model with patient as random effect was used to model the predictors of MRSS, HAQ- DI, and FVC. The primary independent variables were time-in-study and its interaction with gender (male and female) and ethnicity (Cau and Non- Cau). Other covariates included disease duration and age for MRSS model. For HAQ-DI model, we also accounted for the swollen (SJC) and tender joint count (TJC), digital ulcer, and baseline MRSS. For FVC%, we adjusted for baseline MRSS and BMI as covariates.

Results: On average males were heavier and taller, had a higher serum creatinine, serum hematocrit, but lower HAQI- DI scores compared to females ($p< 0.05$, Table). For ethnicity analysis, Cau were older, had a higher MRSS and FVC% but lower TJC than Non- Cau ($p< 0.05$; Table). In the linear mixed models, the course of MRSS, HAQ-DI, and FVC was not significantly different between males vs. females and Cau vs. Non- Cau. Time in the study was an independent predictor of improvement in MRSS and HAQ-DI.

Conclusion: Our post hoc analysis of RCTs suggests that gender and ethnicity have no influence on the disease course once patients develop dcSSc. These findings should be replicated in larger observational cohorts.

	Male		**Female**		**Cau**		**Non-Cau†**
	n	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**
Age (yrs)	92	47.57(12.79)	403	47.45(11.63)	36149.41(11.6)		134	42.24(10.89)*
Female (%)		N/A		N/A	29080.3%		113	84.3%
Cau (%)	71	77.17%	290	71.96%		N/A		N/A
Non- Cau	21	22.83%	113	28.04%		N/A		N/A
Dz Duration (Mths)	92	26.53(26.91)	403	27.1(24.23)	36127.34(24.82)		134	26.06(24.54)
Weight (Ibs)	89	177.3(36.34)	399	147.51(32.33)*	355152.79(34.07)		133	153.4(37.57)
Height (in.)	84	67.72(4.56)	358	62.69(3.14)*	32163.6(4.07)		121	63.79(3.71)
MRSS, 0-51	92	24.91(8.47)	403	25.38(7.78)	36125.75(8)		134	24.07(7.54)*
Tender Joint Count	59	1.19(2.02)	271	1.37(2.12)	2361.09(1.85)		94	1.96(2.54)*
Physician Global, 0-100	62	44.85(22.35)	293	47.19(21.5)	26546.57(22.08)		90	47.4(20.39)
Patient Global, 0-100	62	44.2(27.68)	298	45.39(26.81)	26944.59(26.96)		91	46.96(26.9)
Diffusing Capacity (%)	91	69.97(21.31)	397	70.56(20.38)	35871.3(20.27)		130	68.11(21.16)
Forced Vital Capacity (%)	92	86.03(16.91)	401	84.32(16.88)	35986.71(16.18)		134	79.1(17.53)*
Cutaneous Ulcer (number)	36	0.78(1.53)	152	0.82(1.92)	1310.82(1.72)		57	0.79(2.14)
HAQ-DI, 0-3	91	0.99(0.65)	401	1.24(0.7)*	3581.21(0.68)		134	1.13(0.74)
S. Creatinine	92	0.92(0.33)	397	0.73(0.25)*	3560.77(0.27)		133	0.75(0.3)
S. Hematocrit	92	40.96(3.89)	397	38.32(3.58)*	35638.87(3.79)		133	38.7(3.77)
SF- 36 PCS	59	35.56(11.57)	295	33.59(10.56)	26433.81(10.75)		90	34.23(10.78)
SF- 36 MCS	59	51.01(8.95)	295	49.16(10.09)	26449.64(9.72)		90	48.98(10.53)

***P< 0.05; † 79 patients were African American/ 55 patients were other races**

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A Disease Damage Index for Canadians with Systemic Sclerosis. Kevin Keen[1], Jenny Walker[2], Marie Hudson[3], Viktoria Bassarguina[1], Murray Baron[4] and Canadian Scleroderma Research Group, [1]University of Northern British Columbia, Prince George, BC, [2]Flinders University, Adelaide, Australia, [3]McGill University and Jewish General Hospital, Montreal, QC, [4]Jewish General Hospital, Montreal, QC

Purpose: Disease activity and damage indices facilitate collection of standardized information and provide an important means of objectively documenting a subject's disease state. A disease severity index is a composite measure of activity and damage. Disease severity indices for systemic sclerosis (SSc) have been developed in the United States and Sweden. An SSc disease activity index has been developed in Europe and another is under development in Canada. The purpose of this ongoing study is to develop a disease damage index for SSc.

Method: A cross-sectional analysis of 654 patients enrolled in the Canadian Scleroderma Research Group Registry was undertaken and after review, 42 variables encompassing 9 organ systems were retained for further study. Rheumatologists' global assessment of damage was chosen as the gold standard in the development of an aggregate damage score (the Canadian Scleroderma Damage Index, or CSDI). Statistical methods included multiple linear regression and multivariate techniques such as principal component analysis and factor analysis.

Results: Among the 654 subjects, the limited-diffuse ratio was 1.3:1. The female-male ratios were 8.6:1 for limited SSc (lSSc) and 4.3:1 for diffuse SSc (dSSc). Mean global damage was 2.50 (SD = 2.19) for 112 lSSc subjects with complete data and 4.12 (SD = 2.51) for 65 dSSc subjects with complete data. Both means are somewhat low with mean global damage for lSSc being significantly lower than that of dSSc ($P < 0.0001$). The 42 explanatory variables in the separate multiple linear regression models for lSSc and dSSc were able to account for 72% and 86%, respectively, of the variation in the rheumatologists' global assessment of damage. The most meaningful among the explanatory variables were the modified Rodnan skin score for the whole body, the number of digits with loss of pulp, whether there had been an SSc renal crisis, the New York Heart Association class, whether the electrocardiogram was abnormal, whether pericardial effusion was present, and whether oxygen was being used at home.

Conclusion: Preliminary damage scales have been developed for patients with lSSc and dSSc. These will be tested among a larger sample of rheumatologists and are presented for peer review.

Disclosure: K. Keen, None; **J. Walker**, None; **M. Hudson**, None; **V. Bassarguina**, None; **M. Baron**, None.

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Atherosclerosis in Patients with Systemic Sclerosis in Stockholm, Sweden. Annica Nordin, Lena Björnådal, Kerstin Jensen-Urstad and Elisabet Svenungsson, Karolinska Institutet, Stockholm, Sweden

Purpose: Previous studies demonstrate that several systemic autoimmune diseases are associated with an increased prevalence of atherosclerosis. Besides traditional risk factors, systemic inflammation seems to be an important factor for atherosclerosis in these patients. We compared atherosclerosis and its risk factors in patients with Systemic Sclerosis and controls.

Methods: 81 consecutive patients (62,4 ± 12,6 years) who fulfilled the American College of Rheumatology criteria for Systemic Sclerosis(SSc) and 80 population-based controls (62,2 ± 12,8 years) matched for sex, age and region of living participated. As a surrogate measure for atherosclerosis we studied the frequency of plaque and the mean IMT (intima media thickness), measured by B-mode ultrasound. Traditional risk factors for cardiovascular disease and biomarkers of systemic inflammation were measured.

Results: Plaques were found in 49,5% of the patients and in 41% of the controls. Mean IMT was 0,69 mm ± 0,11 in patients and 0,69 mm ± 0,14 in controls. Neither plaque occurrence nor IMT differed significantly. The patient with SSc were more likely to be current or former smoker than controls (54% vs. 35%, $p < 0,001$). The patients had more systemic inflammation than controls: Sedimentation Rate 17,6 ± 13,5 mm vs 11,8 ± 6,7mm ($p<0,05$), hsCRP 3,6 ± 4,5 mg/l vs 2,5± 2,8 mg/l ($p=0,05$), alpha-1-antitrypsin 1,6 ± 0,35 g/l vs 1,4 ± 0,2 g/l (<0,001)

and orosomucoid 0,83± 0,16 g/l vs 0,75 ± 0,17 g/l (p<0,01). The patients BMI was lower than controls 24,4 ± 3,3 kg/m² vs 26,1± 3,8 kg/m²(p<0,05).

Lipid levels, blood-pressure, blood glucose or waist hip-ratio did not differ between patients and controls.

In multivariable-adjusted logistic regression models (including age, systolic blood pressure BMI, cholesterol, triglycerides (TG), smoking and hsCRP), independent predictors of plaque among patients was age (p=0.007) and TG(p=0,04) and among controls age(p<0,0001) and smoking (p<0,02).

Conclusion: Atherosclerosis was not more prevalent in SSc patients than in population-based controls. Smoking and markers of inflammation were more common in patients.

Disclosure: A. Nordin, None; **L. Björnådal**, None; **K. Jensen-Urstad**, None; **E. Svenungsson**, None.

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Antibodies to Sulfated N-Acetyllactosamine (LacNAc) Are Prevalent in Patients with Systemic Sclerosis and Associated with Pulmonary Hypertension. Thomas Grader-Beck[1], Francesco Boin[1], Stephan von Gunten[2], David F. Smith[3], Antony Rosen[1] and Bruce S. Bochner[4], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Bern, Bern, Switzerland, [3]Emory University School of Medicine, Atlanta, GA, [4]Johns Hopkins Asthma and Allergy Center, Baltimore, MD

Purpose: Differential glycosylation of proteins and lipids plays an important role in the regulation of numerous physiological processes. The endothelium and extracellular matrix, two key tissue components affected in systemic sclerosis (SSc), contain various highly glycosylated structures (glycans). We hypothesized that the immune response in SSc may target distinct glycans, leading to the development of specific anti-glycan antibodies.

Method: A printed glycan array containing 320 glycans was used to screen pooled sera from 40 randomly selected SSc patients and 40 healthy controls for anti-glycan antibodies. Binding was quantified by fluorescence. Antibodies to sulfated LacNac were determined in 181 individual sera from SSc patients and 40 healthy controls by ELISA using an anti-human Fc gamma specific secondary antibody for detection, a high-titer positive SSc serum as standard and a cut-off of 3 SD above healthy controls. Statistical analysis of clinical associations was performed using student's t-test and logistic regression.

Results: Sulfated LacNac was identified as a dominant target of SSc sera initially by printed glycan array screening. Immunogenicity was predominantly conferred by sulfation at position 4 of galactose (4S-LacNAc), but not at position 3 or 6 (13.6 fold; 3.0 fold and 0.9 fold compared to controls; respectively). Subsequently, an anti-sulfated LacNAc specific ELISA was developed to screen individual sera. 27/181 (14.9%) patients were positive for anti-4S-LacNAc antibodies compared to only 1/40 (2.5%) of healthy controls. Anti-4S-LacNAc positive SSc patients had a higher prevalence of pulmonary hypertension as determined by an RVSP > 40 mmHg on echocardiogram (15/27; 55.7% versus anti-4S LacNac negative patients 49/154; 31.8% p=0.02). The odds ratio for pulmonary hypertension was 2.6 (1.1, 6.3) after adjusting for age, gender, race and disease type. Anti-4S-LacNAc positive patients accounted for 23.4% of all patients with pulmonary hypertension. There was no association between anti-4S-LacNAc positivity and disease type (limited versus diffuse SSc) or the presence of anti-topoisomerase I or anti-centromere antibodies.

Conclusion: This is the first study to report that sera from SSc patients contain high titer IgG antibodies targeting glycan structures. 4S-LacNac was identified as a frequent target of the antibody response in SSc and antibody positivity was associated with echocardiographic evidence of pulmonary hypertension. These results suggest that specific posttranslational carbohydrate modifications may act as important immunogens in SSc. Further studies will determine whether these antibodies target 4 sulfated LacNAc expressed on the endothelium or extracellular matrix and thus may play a role in disease pathogenesis.

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Factors Associated with Oesophageal Involvement in Systemic Sclerosis: a High-Resolution Manometry Study. Arnaud Hot, Sabine Roman, Jacques Ninet and François Mion, Hopital Edouard Herriot, Lyon, France

Purpose: Oesophageal involvement occurs in about 80% of patients with systemic sclerosis, with a marked diminution of peristaltic pressures in the distal two-thirds of the oesophagus and hypotension of the lower oesophageal sphincter (LES). Manometric techniques have improved in a step-wise fashion from a single pressure channel to the development of high-resolution manometry (HRM) with up to 36 pressure sensors. Our aims were to determine if oesophageal involvement in systemic sclerosis, early detected by high-resolution manometry (HRM), was associated with other organ involvement and with a particular autoantibody profile.

Method: Forty-nine consecutive patients (46 females, mean age 53 years, range 21-80) with systemic sclerosis were included. Oesophageal motility was characterized with HRM. Esophageal aperistaltis was defined as an absence of esophageal waves in the 2 distal thirds of the esophagus and hypoperistaltism as 30% or more of distal esophageal waves with a $\geq$ 2-cm defect in the 30-mmHg isobaric contour. The demographic data, duration of the disease, presence of other organ involvement and autoantibodies (Antinuclear antibodies (ANA), anti-Scl70 antibody (Scl70), anticentromere antibodies (ACA)) were recorded. Chi square test was used to compare the association between these criteria and oesophageal involvement.

Results: Forty patients (81.6%) had a decreased oeso-gastric junction (EGJ) pressure (<10 mmHg). Oesophageal body dysmotility was present in 35 patients (71.5%), with a very monomorphic presentation: aperistaltis in 25 cases, and hypoperistaltism in 10. Hypotensive EGJ and oesophageal dysmotility were associated in 29 patients (60.4%). The velocity of proximal contractions was higher in patients with esophageal body dysmotility compare to patients with normal peristalsis (median 10.8 cm/s vs 5.4, p=0.02) whereas amplitude and duration of proximal waves did not differ. Oesophageal body dysmotility was present in all 14 patients with a diffuse skin involvement (all with positive Scl70) and in 60% of the 35 others (all but 2 with negative Scl70) (p = 0.01). ACA were positive in 51 % of patients with oesophageal body dysmotility and in 93% of patients without oesophageal involvement (p=0.02). No significant association was observed between oesophageal body dysmotility and other organ involvement. Hypotensive EGJ alone was not significantly associated with any of the above-mentioned factors.

Conclusion: This first HRM series confirms the high prevalence of EGJ hypotension and esophageal body dysmotility in systemic sclerosis. The velocity of proximal oesophageal contractions is increased in patients with oesophageal body dysmotility. Oesophageal body dysmotility, strikingly monomorphic when present, is associated with diffuse skin involvement, positive Scl70 and negative ACA antibodies.

Disclosure: A. Hot, None; **S. Roman**, None; **J. Ninet**, None; **F. Mion**, None.

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Results of A Pilot Randomized Placebo Controlled Trial in Raynaud's Phenomenon (RP) with St. John's Wort (SJW). Deanne Malenfant[1], Kelly Summers[2], Nooshin Samadi[3], Ash Bonner[4] and Janet Pope[5], [1]Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, [2]University of Western Ontario, London, ON, [3]St. Joseph's Health Care, London, ON, [4]McMaster University, Hamilton, ON, [5]St Joseph Health Care, London, ON

Purpose: Most of the treatments for Raynaud's Phenonomen (RP) cause hypotension which can limit the tolerability of drugs in RP. St. John's Wort (SJW) is a plant extract which works on serotonin receptors as well as other properties. It is proven to be effective in mild to moderate depression. Thus we thought it could possibly affect serotonin receptors of blood vessels and help RP, and one RCT demonstrated that prescription selective serotonin receptor inhibitors (SSRIs) can improve RP.

Method: We performed a double blind RCT with a two week run in where patients had to have at least 14 attacks over two weeks and then they were randomized to SJW or identical placebo for 6 weeks, stratifying by primary and secondary RP (and within secondary by SSc or other CTD). Testing was done to ensure quality of SJW. Serum was collected at each visit and patients kept a diary recording all RP attacks (#/day, duration of each and severity). Tests of vascular mediators included: sE-Selectin, sVCAM-1, sICAM-1, MMP-9, tPAI-1, cytokines, and VEGF were done and between groups comparisons were made with ITT analyses. Data were analyzed blinded to allocation (group A and B).

Results: 27 patients were screened (some withdrew consent or failed due to insufficient number of attacks) and 18 were randomized (2 primary RP, 16 secondary RP of whom 8 had SSc) with 8 on active SJW and 10 on placebo. The between groups differences on # of RP attacks over 1 day (decrease in the mean # of attacks per day) were 0.75 in active and 1.01 in placebo, p=0.06 (favoring placebo). Duration and severity of attacks was not different between the two groups. There were within group differences between the baseline and completion of the study where frequency, severity and duration of attacks improved, some of which were statistically significant, but active SJW did not

alter RP more than placebo. The serum analyses demonstrated that there were no between groups differences on all parameters studied. There was one SAE (a patient with diffuse SSc and atrial fibrillation hospitalized for congestive heart failure on active treatment.)

Conclusion: This study demonstrates that there is not benefit both clinically and from a basic science perspective with SJW in RP.

Disclosure: D. Malenfant, None; **K. Summers**, None; **N. Samadi**, None; **A. Bonner**, None; **J. Pope**, Webber Naturals, 2 .

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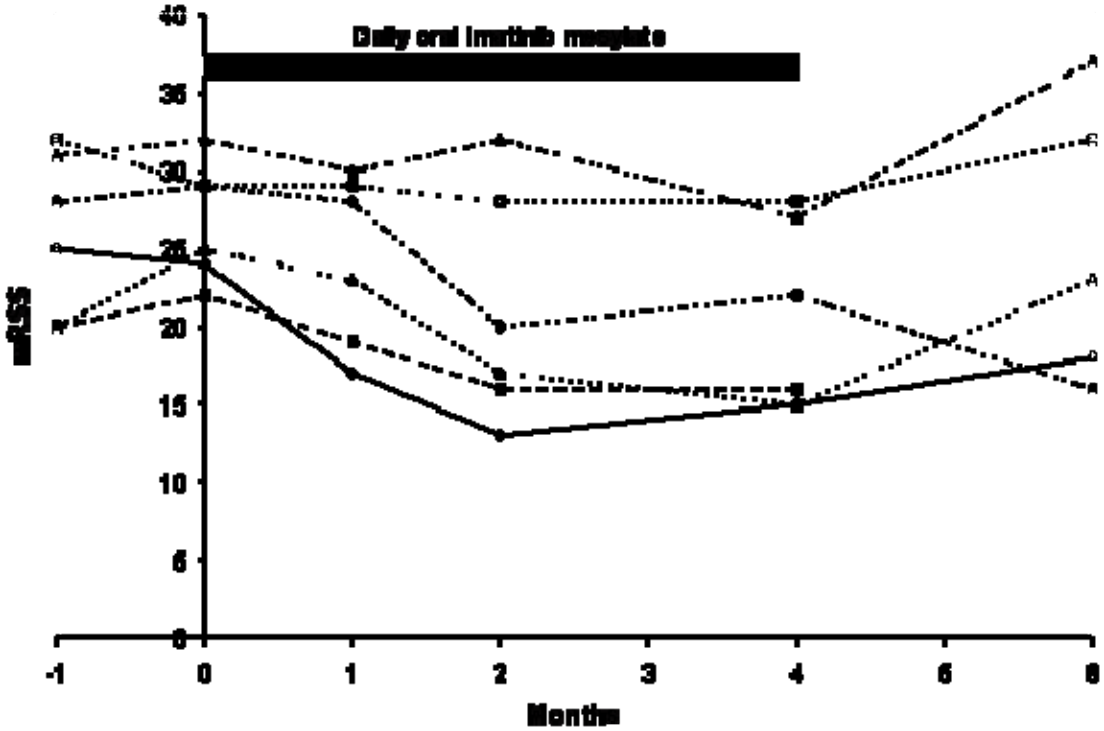
Efficacy and Safety of Oral Imatinib Mesylate in Patients with Nephrogenic Systemic Fibrosis. Jonathan Kay[1], Mary E. Sullivan[2] and Tejas V. Patel[3], [1]University of Massachusetts Medical School, Worcester, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Brigham & Women's Hospital, Boston, MA

Nephrogenic systemic fibrosis (NSF) is an extremely debilitating and painful condition that affects individuals with chronic kidney disease (CKD) following gadolinium exposure during imaging studies. NSF is characterized by rapidly progressive skin hardening, tethering and hyperpigmentation, predominantly on the extremities, often associated with joint contractures and visceral fibrosis. Although no therapy has been proven effective for this prevalent and devastating disorder with increased early mortality, 3 patients with NSF have experienced softening of skin and improvement in joint mobility with oral imatinib mesylate (IM) (J Kay & WA High. *Arthritis Rheum*. 2008;58:2543-8; S Chandran et al. *Am J Kidney Dis*. 2009;53:129-32). This tyrosine kinase inhibitor selectively inhibits signaling mediated by c-Abl, c-kit, and the PDGF receptor, as well as Smad-independent signaling by the TGF-β receptor.

Purpose: This pilot study was undertaken to assess the efficacy of IM in improving skin changes of NSF and the safety and tolerability of IM in patients with CKD and NSF.

Methods: Twelve patients with biopsy-proven NSF were enrolled in a 6-month, open-label clinical trial. One patient died before receiving study drug; 11 patients began treatment with oral IM 400 mg daily, with dose reduction to 200 mg daily allowed for gastrointestinal intolerance. Six patients completed 4 months of IM therapy, and were then observed for 2 months off of IM. The primary outcome measure was change in the modified Rodnan skin score (mRSS) at 4 months. Secondary outcome measures included assessment of safety. Skin biopsies were performed upon initiation and completion of 4 months of drug therapy.

Results: At baseline, subjects were 67% male with mean age 65.5 yrs (range 37-93 yrs); 11 had stage 5 CKD (10 were receiving hemodialysis and 1 had a functioning renal allograft) and 1 had stage 3 CKD. All 6 subjects who had completed 4 months of IM experienced improvement in mRSS from baseline, most markedly within the first 2 months of treatment, with reduction in mRSS of 24% ± 14% (mean ± SD, range 3-40%). Following discontinuation of IM, mRSS worsened in 4 individuals.



All adverse events were expected, of which nausea, vomiting, and diarrhea were the most common. One subject discontinued IM because of neutropenia, another because of skin rash, and 2 others because of anemia. Another subject died of complications following a hip fracture that were unrelated to IM therapy.

Conclusion: This is the first clinical trial to demonstrate reduction in skin tethering in patients with NSF. The improvement observed with IM treatment was evident relatively soon after initiation of therapy. The majority of patients tolerated treatment with IM. Expected adverse events were observed, of which gastrointestinal intolerance was the most common. Because skin changes recurred following discontinuation of IM, a longer duration of treatment may be necessary. Further study of this promising targeted therapy for fibrosis is warranted.

Disclosure: J. Kay, Novartis Pharmaceutical Corporation, 2 ; **M. E. Sullivan**, None; **T. V. Patel**, None.

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High Prevalence of Left Ventricular Diastolic Dysfunction (LVDD) in Minorities with Systemic Sclerosis (SScl) and Clinical Impact of LVDD Severity. Jina Chung, Soha Dolatabadi, Arsen Hovanesian and George A. Karpouzas, Harbor-UCLA Medical Center, Torrance, CA

Purpose: Cardiac involvement is common in patients (pts) with SScl. Pulmonary hypertension (PH) confers significant mortality. Prevalence and severity of LVDD due to SScl have been challenging to determine due to confounding factors, such as hypertension (HTN), diabetes mellitus (DM) or significant left heart diseases. Accurate assessment of LVDD will allow early diagnosis of myocardial involvement and elucidate its impact on the development of PH. We investigated the prevalence of LVDD and its clinical impact in SScl pts using transthoracic echocardiography (TTE) with pulsed wave spectral and tissue Doppler imaging after excluding the aforementioned parameters.

Methods: We evaluated 56 pts and 83 TTE's fulfilling ACR criteria for SScl, largely minorities, with follow-up in a single academic center. Twenty six pts and 39 TTE's were excluded due to severe lung disease (FVC<60%, TLC<60%), heart disease (LVEF<50%, ≥ moderate mitral or aortic regurgitation or stenosis), HTN or DM. TTE included 2D, M mode, Color, spectral and tissue Doppler techniques. LVDD

severity was classified as: impaired relaxation (I), pseudonormal pattern (II), reversible (III), and irreversible (IV) restrictive pattern. PH was defined as tricuspid regurgitation peak gradient ≥ 31 mmHg (JACC 2009; 54:s55-66). LV hypertrophy (LVH) was defined as septum or inferolateral wall thickness >12 mm. Data was analyzed with Fisher's exact test.

Results: Thirty pts with 44 TTE's were included for analysis (table 1). PH was present in 9.1%. Twenty four of 44 studies (54.5%) had normal diastolic function, 16/44 (36.4%) stage I LVDD, and 4/44 (9%) stage II. No pt had Stages III or IV LVDD. LVH was present in 5/44 (11.4%) likely due to SScl. LVH was significantly higher in stage II LVDD compared to normal (p=0.016). However, functional limitation defined as ≥NYHA class II did not correlate with more advanced LVDD.

Conclusion: LVDD was present in 45.5% of TTE's in our predominantly minority population with SScl and no other confounding factors, suggesting myocardial involvement of SScl. Most showed impaired relaxation. However, 9% had more advanced LVDD and stronger correlation with LVH and PH. The presence of stage II LVDD reflects increased left atrial pressure and may impact diagnosis of PH. Clinical implications of LVDD stages should be explored in larger scale studies.

Table 1: Patient Characteristics and Results.

Age (yr)	44.2±11.4		
Female (%)	81.8		
Hispanics (%)	73		
AA (%)	14		
Other (%)	12		
LVDD stage	**Normal**	**Stage I**	**Stage II**
n- studies (%)	24/44 (54.5)	16/44 (36.4)	4/44 (9.1)
n-LVH (%)	0/24 (0)	3/16 (18.8) OR=12.7 (CI=0.6-265), p=0.056	2/4 (50) OR=49 (CI=1.8-1334),p=0.02
PH (%)	6	18	25
≥ NYHA class II (%)	44	44	33
a-Scl-70 Ab (%)	14	15	25
a-centromere Ab (%)	25	15	50
a-nucleolar Ab (%)	23	15	50

Disclosure: J. Chung, None; **S. Dolatabadi**, None; **A. Hovanesian**, None; **G. A. Karpouzas**, Centocor, Inc., 8, Abbott Immunology Pharmaceuticals, 8, Actelion Pharmaceuticals US, 8, Actelion Pharmaceuticals, 2 .

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Topical Application of Vascana, a Novel Nitroglycerin Formulation, Provides 8 Hours of Local Absorption but Limited Systemic Exposure. Jeffrey K. Gregory and Frederick J. Dechow, MediQuest Therapeutics, Inc., Bothell, WA

Purpose: To assess the pharmacokinetic properties of Vascana (formerly MQX-503), a novel topical nitroglycerin (GTN) formulation under study for the treatment of Raynaud's, compared to 2% nitroglycerin ointment under 2 different application scenarios

Method: 2 separate studies comparing the pharmacokinetic properties of Vascana applied to the fingers to those of 2% GTN ointment applied to the chest were performed. The first study of 12 normal subjects measured systemic exposure to GTN when Vascana (mean 2.65 mg GTN) was applied to the dominant hand. Blood was drawn from the antecubital vein of the non-dominant arm for both drug

applications. Thus, GTN levels ($T_{1/2}$ = 1-3 min) were measured after distribution and substantial metabolism had taken place with both drugs. The second study of 6 normal subjects measured local absorption of GTN from the site of Vascana application. Vascana (mean 5.22 mg GTN) was applied to both hands. Blood was drawn from an antecubital vein for both drug applications. Thus, blood was drawn only centimeters from the site of one half of the Vascana application; GTN metabolism would be very limited at that distance. Plasma levels were measured up to 12 and 8 hours after drug application, respectively. In both studies, plasma levels of GTN and its glyceryl dintrate metabolites (1,2 glyceryl dintrate and 1,3 glyceryl dinitrate) were measured using LCMS with negative ion electrospray ionization with a lower level of detection of 40 pg/ml.

Results: In the first study, GTN was detectable at one very low level (41 pg/ml) in only one patient 1 hour after receiving Vascana. The mean GTN area-under-the-curve (AUC in pg·hr/ml) was 2.1 with Vascana and 1111.3 with ointment. The mean GTN T_{max} was 1.0 hr and 4.0 hr, respectively. The mean GTN C_{max} was 3.5 and 173.9, respectively. The mean AUCs for 1,2 glyceryl dinitrate were 675.7 and 15946.3, respectively. The mean AUCs for 1,3 glyceryl dintrate were 69.7 and 3421.2, respectively.

In the second study, the mean GTN AUC (pg·hr/ml) was 7228 with Vascana and 1383 with ointment. The mean GTN T_{max} was 5.25 hr and 4.21 hr, respectively. The mean GTN C_{max} was 2163 and 402, respectively. The mean GTN plasma concentrations at 8 hr were 1163.7 and 212.3. The mean AUCs for 1,2 glyceryl dinitrate were 8755 and 16429, respectively. The mean AUCs for 1,3 glyceryl dintrate were 2273 and 3148, respectively.

Headaches, an adverse event seen in up to 85% of patients treated with nitroglycerin ointment, were seen in 3 Vascana and 8 ointment treatments in the first study and 2 and 4 treatments, respectively, in the second study.

Conclusion: Application of Vascana to the fingers results in substantial local absorption of GTN for at least 8 hours but in minimal systemic exposure, especially when compared to nitroglycerin ointment. This is reflected in Vascana's historically favorable safety profile in which headaches and dizziness were seen at rates (17.5% and 7.4%, respectively) similar to vehicle (15.3% and 6.0%, respectively).

Disclosure: J. K. Gregory, MediQuest Therapeutics, Inc., 1, MediQuest Therapeutics, Inc., 3 ; **F. J. Dechow**, MediQuest Therapeutics, Inc., 1, MediQuest Therapeutics, Inc., 3 .

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Anorectal Sphincter Function in Systemic Sclerosis (SSc). Karin Franck-Larsson[1], Wilhelm Graf[2], Karin Edebol Eeg-Olofsson[2], Hans Axelson[2] and Anders Rönnblom[2], [1]Uppsala University, Uppsala, Sweden, [2]Uppsala University Hospital, Sweden

Purpose: In a previous population-based study, we have reported that 30% of the SSc patients suffer from fecal incontinence to varying extent (Franck-Larsson et al, Eur J Gastroenterol Hepatol 2009). The aim of the present study is to elucidate the underlying mechanisms.

Method: A cohort of 25 SSc patients with and without fecal incontinence underwent clinical anorectal examination and investigations with proctoscopy, anorectal three-dimensional ultrasound, anorectal manometry, pudendal nerve terminal motor latency, standard EMG and single fiber EMG, and answered questionnaires on symptoms and quality of life (SF-36).

Results: Forty-four % reported incontinence to solid and/or liquid feces. Rectocele was present in 30%, and peri-anal scleroderma skin changes in 30% of the patients.

Sonographic abnormalities, either as thin sphincters or sphincter defects, were present in 17%, all in patients with incontinence to solid and/or liquid feces. These morphologic changes were inversely associated to the resting pressure at 1-2 cm and to squeezing pressure at 2 cm (p=0,035 and 0,028 respectively, Mann-Whitney U), and were also associated to incontinence to solid feces and defecation problems (p=0,017 and 0,026 respectively, Pearson Chi Square).

Failure to increase anal pressure at attempted squeeze was seen in 28%. Increased fiber density was recorded bilaterally in 61% and unilaterally in another 22% of the patients. In patients with increased fiber density, maximum squeeze pressure was significantly lower at 2 and 3 cm (p=0,019 and 0,006 respectively Mann-Whitney U) in comparison with patients with normal fiber density; however, symptoms did not differ between the groups. Distal pudendal nerve latency was increased in 21%.

Conclusion: In patients who reported fecal incontinence, decreased squeeze pressure were recorded in the high pressure zone, and thin or defect sphincters. A majority of the SSc patients had increased fiber density, possibly indicating previous nerve injury with consequent

reinnervation. We concluded, that both structural and neurogenic mechanisms are likely to influence the development of fecal incontinence in SSc patients.

Disclosure: K. Franck-Larsson, None; **W. Graf**, None; **K. Edebol Eeg-Olofsson**, None; **H. Axelson**, None; **A. Rönnblom**, None.

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Transition FROM "EARLY Systemic Sclerosis" to Definite Systemic Sclerosis. Sheila Melchor[1], Atusa Movasat[1], Beatriz E. Joven[1] and PE. Carreira[2], [1]Hospital 12 de Octubre, Madrid, Spain, Madrid, Spain, [2]Hospital 12 de Octubre, Madrid, Spain

Purpose: To analyze: a) the time between the onset of Raynaud and the diagnosis of systemic sclerosis, according to the 1980 ACR Criteria(1), in a series of consecutive patients diagnosed of early systemic sclerosis, according to the criteria proposed in 2001 for early SSc criteria(2); and b) the clinical differences between patients fulfilling and not fulfilling the 1980 ACR criteria after a follow-up period.

Method: Demographic (birth date, sex) and clinical data (date of Raynaud onset, smoking habit, HBP, hyperlipemia, mRSS, presence of hand edema, ischaemic lesions, arthritis, gastrointestinal, pulmonary or cardiac symptoms, ANA, aScl70, anticentromere (ACA) and aRNP antibodies) of all patients sent for a capillaroscopy to the rheumatology department between 1994 and 2008 because of Raynaud phenomenon were included prospectively in a data base created in 1994. All patients showing typical SSc capillaroscopic findings and/or ANA (+), and no criteria for other autoimmune disease, were diagnosed as early SSc, followed at least yearly, and diagnosed of definite SSc when they presented the 1980 ACR criteria. Time between Raynaud onset and first capillaroscopy, and definite SSc diagnosis or last visit was analyzed. Clinical differences between patients with definite or early SSc diagnosis after the follow-up period were compared with Chi square and t tests.

Results: From 670 patients sent for capillaroscopy during the study period, 74 (10 m, 64 f; 52±16 y) were diagnosed as early SSc(2). At capillaroscopy, median time from Raynaud was 3.3 y (mean 8.2±9.7 y). Forty nine (66%) had pathologic capillaroscopy, 69 (93%) ANA, and 46 (62%) both. Five (7%) had aScl70, 47 (64%) ACA and 9 (12%) aRNP. Thirty two (43%) presented hand edema, 54 (73%) sclerodactily, 7 (10%) ischaemic lesions, 7 (10%) pulmonary fibrosis, and 34 (47%) esophageal involvement. After a median of 3 years (mean 4.3±4.1 y) of follow-up, and a median of 12 years (mean 11±10.3) from Raynaud onset, 31 patients (42%) achieve an SSc definite diagnosis, in all cases as limited cutaneous SSc. The other 43 patients (58%) remained as early SSc. Patients who maintained the diagnosis of early SSc after the follow-up had less ischaemic lesions (OR=0.09; 95%CI 0.01-0.9; p=0.02) and pulmonary fibrosis (OR=0.1; 95%CI 0.01-0.9; p=0.04), than patients who developed the 1980 SSc classification criteria(1), but not other differences between both groups were found.

Conclusion: A large percentage of patients (nearly 60%) with Raynaud phenomenon and clinical findings suggestive of SSc remain undiagnosed after long term follow-up, according to the 1980 ACR classification criteria for SSc(1). In our series, only including the presence of ANA or the capillaroscopic changes characteristic of SSc as minor criteria, as suggested by LeRoy and Medsger in 2001(2), would allow the classification of all our pre-scleroderma patients as definite SSc. This would be important to be able to include these patients in clinical trials.

Bibliography

(1) Preliminary criteria for the classification of systemic sclerosis. Arthritis Rheum 1980; 23:581-90.
(2) LeRoy EC and Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001; 28:1573-6.

Disclosure: S. Melchor, None; **A. Movasat**, None; **B. E. Joven**, None; **P. Carreira**, None.

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Prognostic Role of ECG in Pulmonary Hypertension Associated with Systemic Sclerosis (SSc). Cathryn Byrne-Dugan, Elena Schiopu, Ann J. Impens, James R. Seibold and Kristine Phillips, University of Michigan, Ann Arbor, MI

Purpose: To examine whether ECG parameters in patients with systemic sclerosis (SSc) and pulmonary arterial hypertension are associated with survival.

Methods: Consecutive patients in a tertiary care referral center with PAH and a confirmed diagnosis of scleroderma between 2000 and 2009 were assessed. Clinical examination, medications, ECG, echocardiogram, BNP, six minute hallwalk, pulmonary function tests and imaging, and right heart catheterization results were recorded. The following measurements were recorded from each ECG: P-wave amplitude in lead II; mean frontal QRS axis; QRS duration; R-wave and S-wave deflections in leads I and V1-V6; and T-wave configurations in the precordial leads. These ECG variables were correlated with hemodynamic variables on right heart catheterization.

Results: Of the 40 patients included in this study, 35 (88%) were women. In these patients with a diagnosis of SSc and pulmonary hypertension, mortality was high, with most of the 31 deaths occurring within 1-2 years of PAH diagnosis. Patients with improved survival were more likely to have normal ECGs. More than half of the patients in the study had abnormalities of the right ventricle, either structural or physiologic. Twenty-three patients had evidence of right axis deviation (QRS >90 degrees) and sixteen of these patients exhibited right ventricular strain in the precordial leads. Evidence of right ventricular strain by ECG (ST deviation and T wave inversion in V1-V3) was associated with decreased survival ($p<0.05$). Although only one had a complete right bundle branch block, five other patients had incomplete right bundle branch block. Right ventricular hypertrophy was seen with increased frequency, as was an increased p wave amplitude (>0.25 mV in lead II).

Conclusion: ECG results reflecting abnormalities in the right ventricle are associated with a poor prognosis and may be useful for therapeutic decisions in patients with SSc.

Disclosure: C. Byrne-Dugan, None; **E. Schiopu**, Actelion Pharmaceuticals, Inc., 8 ; **A. J. Impens**, None; **J. R. Seibold**, None; **K. Phillips**, None.

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Profile of Pre-Scleroderma Evolution. Beatriz Rodriguez-Lozano, Esmeralda Delgado-Frias, Vanesa Hernandez-Hernandez, Maria Angeles Gantes-Mora, Elisa Trujillo-Martín and Sagrario Bustabad-Reyes, Hospital Universitario de Canarias, La Laguna; Tenerife, Spain

Purpose: To describe the pattern of evolution and identify possible predictive risk factors in the pre-scleroderma phase.

Method: Retrospective study of patients diagnosed with pre-scleroderma based on the presence of Raynaud´s phenomenon and positive autoantibodies (nucleolar pattern ANA or anti-Scl-70 or anticentromere antibodies) and/or capillaroscopic findings of scleroderma pattern, during a period of 10 years. These patients were referred to our Rheumatolgy Department for capillaroscopy during the years 1999-2001. Clinical evaluation was performed (degree of cutaneous involvement using a modified Rodnan skin score, ANA and specificities, capillaroscopy performed by the same observer, ECG, chest radiography, respiratory function tests (spirometry/DLCO), echocardiogram, esophageal manometry and renal function) at the baseline and end of the study. At baseline, none of the patients met the criteria for the classification of SSc (ACR 1980).

Results: Of 290 patients undergoing capilloroscopy in the period 1999-2001, 17 patients (7%), all women, median age 52 years (19-62), were diagnosed with pre-scleroderma (7%) and 1 patient with diffuse SSc after the first clinical/immunological/ capillaroscopic evaluation. Reasons for performing capillaroscopy in the selected population were: Raynaud´s (65%), early "puffy" scleroderma (12%) and Raynaud´s with positive Scl-70/ anticentromere antibodies (18%). Baseline capillaroscopic patterns (Maricq) were: Slow escleroderma (5.28%), active scleroderma (3.17%), non-specific pattern of connective tissue disorders (6.34%) and normal (4. 23%). Clinical data included finger edema (12. 62%), dysphagia (11. 62%), pathologic esophageal manometry (47%)(inferior esophageal sphincter hypotonia:7; esophageal aperistalsis: 1), chest radiography with interstitial pattern (4.24 %) with DLCO/VA alteration in 2 patients. At baseline, no patients presented sclerodactyly-type skin involvement associated with lung involvement. Follow-up during 8-10 years was performed in 15 patients (one was lost to follow up and one died after 3 years). Evolution to defined SSc was found in 5 patients (30%) : 4 diffuse (1 being the patient who died) and 1 with SSc sub-type CREST. All these patients at baseline had presented: Raynaud, positive Scl-70 or anticentromere antibodies, cutaneous involvement of the sclerodactyly or visceral (esophageal) type and slow capillaroscopic pattern of scleroderma.

Conclusion: Of all patients referred for capillaroscopy in a 3-year period, 7% were diagnosed with pre-scleroderma.

In this exploratory study, evolution to defined SSc was observed in 30% of these patients after a 10-year follow up period.

Given the infrequency of this disease, multicenter studies are required to be able to draw conclusions with statistical power. However, all those patients who evolved to SSc presented the following at baseline: Raynaud´s, positive anti-Scl-70 or anticentromere, early edematous scleroderma or visceral (esophageal) involvement and slow capillaroscopic pattern of scleroderma.

Disclosure: B. Rodriguez-Lozano, None; **E. Delgado-Frias**, None; **V. Hernandez-Hernandez**, None; **M. A. Gantes-Mora**, None; **E. Trujillo-Martín**, None; **S. Bustabad-Reyes**, None.

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Nearly Half of the Patients with Severe Primary Pulmonary Arterial Hypertension Associated to Systemic Sclerosis Do Not Fulfill the 1980 ACR Classification Criteria for the Disease. Beatriz E. Joven, M. José Ruiz-Cano, Raquel Almodovar, Pilar Escribano, Miguel A. Gómez-Sánchez and PE. Carreira, Hospital 12 de Octubre, Madrid, Spain

Purpose: To investigate the fulfillment of ACR 1980 Preliminary Classification Criteria for Systemic Sclerosis[(1)] (SSc) in a group of patients with severe primary pulmonary hypertension associated to systemic sclerosis followed in the same University Hospital

Method: All patients with SSc, fulfilling either the 1980 ACR SSc preliminary classification criteria[(1)] or the proposed 2001 classification criteria for early SSC[(2)] were prospectively included in a database created in 1989, containing demographic and clinical information. In the database, severe primary pulmonary arterial hypertension (PAH) was defined as a mean pulmonary arterial pressure (PAP), obtained in right heart catheterization higher than 50 mm Hg, in the absence of pulmonary fibrosis, thromboembolic disease or other known causes of pulmonary hypertension. Severe PAH patients were selected and the presence of the 1980 ACR criteria for SSc classification was analyzed. Odds ratio with 95%CI was used to measure the strength of association between qualitative variables and t test for independent samples to analyze the differences between quantitative variables.

Results: Out of 298 patients included in the SSc database, 24 (8%, 1m, 23f) presented severe PAH. Only 13 (54%) fulfilled the 1980 ACR criteria for SSc classification. Four had diffuse and 20 limited cutaneous disease. ANA were positive in 22 (92%) and ACA in 17/22 (77%). One of ACA positive patients had also aScl70 antibodies. Capillaroscopy was characteristic of SSc in 11 patients in which the technique was performed. All patients not fulfilling the 1989 ACR SSc classification criteria presented Raynaud, sclerodactily and ANA positivity. Besides 7/9 had ACA and 5/5 pathologic capillaroscopy. The only difference between patients fulfilling or not the ACR criteria was the presence of ischaemic ulcers, only present in patients fulfilling them (p=0.002). Thirteen patients died, including 4 not fulfilling ACR SSc classification criteria, 11 because of PAH, after 3.3±4.6 years of PAH diagnosis.

Conclusion: Nearly half of the patients with PAH associated to SSc do not fulfill the 1980 ACR preliminary classification criteria for the disease. All patients with PAH-SSc not fulfilling the classification criteria show clinical symptoms of SSc (Raynaud, sclerodactily, capillaroscopic changes) and present ANA (mainly ACA) in their sera. To be able to include these patients in clinical trials following international guidelines, it would be necessary to revise the actual classification criteria. According to our series, only including the presence of ANA or the capillaroscopic changes characteristic of SSc as minor criteria, as suggested by LeRoy and Medsger in 2001[(2)], would allow the classification of all our PAH patients as SSc.

Biography

(1)Subcommittee for scleroderma criteria of the ARA diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of SSc. Arthritis Rheum 1980; 23:581-90
(2) LeRoy EC and Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001; 28:1573-6.

Disclosure: B. E. Joven, None; **M. J. Ruiz-Cano**, None; **R. Almodovar**, None; **P. Escribano**, None; **M. A. Gómez-Sánchez**, None; **P. Carreira**, None.

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Elevated sVEGFR-1 Is a Candidate Biomarker for Pulmonary Dysfunction in Patients with Systemic Sclerosis. Ziad A. Taimeh, Jessica Gordon, Emma J. MacDermott, Lilliana Barillas, Jamie Mersten, Roland Duculan, Robert Spiera, Mary K. Crow and Kyriakos A. Kirou, Hospital for Special Surgery, New York, NY

Purpose: Circulating mediators of angiogenesis include vascular endothelial growth factor (VEGF) and its soluble receptor (sVEGFR-1), which binds VEGF and inhibits its biologic activities in vivo. These factors may reflect and contribute to dysregulated angiogenesis in patients with Systemic Sclerosis (SSc). In the present study, we measured levels of VEGF and sVEGFR-1 in a cohort of patients in the scleroderma registry at our institution and related these findings to clinical and laboratory parameters.

Method: Sera from 80 patients with SSc, 20 patients with systemic lupus erythematosus (SLE) and 20 healthy donors (HD) were obtained along with data from histories, physical exams, and medical records. Sera were assayed for VEGF and sVEGFR-1 using ELISA kits per the manufacturer's protocol, and values were expressed in pg/ml. Bivariate statistical analysis was performed to compare levels between SSc and control groups, and between subgroups of SSc patients with respect to differences in disease duration (early vs late disease) and key disease manifestations [presence or absence of digital tip ulcers (DTU), interstitial lung disease (ILD) and pulmonary hypertension (PAH)].

Results: Median circulating levels of VEGF were higher in patients with SSc (493) than in those with SLE (348; p=0.0016) or healthy donors (HD) (360; p=0.019). Median levels of sVEGFR-1 were also significantly higher in the SSc group (115) relative to HD (99; p=0.01), but were similar to SLE (110). VEGF levels positively correlated with sVEGFR-1 levels (r=0.39; p=0.0004). Patients with early disease (<5 years) had significantly higher levels of VEGF (548) compared to patients with late disease (376), and VEGF/sVEGFR-1 was higher in early disease (5.23 vs 3.63; p=0.033). Patients with a history of DTU tended to have lower levels of VEGF (497) compared to those with no ulcers (621; p=0.2), and no differences in sVEGFR-1 levels. In contrast, patients with Interstitial Lung Disease (ILD), defined by lung fibrosis (by X-Ray or CT Scan) or pulmonary function tests [forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCo) less than 80% of predicted, showed higher values of sVEGFR-1 (121) than patients without ILD (109; p=0.04), with no difference in VEGF levels. In addition, serum levels of sVEGFR-1 negatively correlated with FVC (r=-0.39; p=0.013) and DLCo (r=-0.33; p=0.03).

Conclusion: Levels of serum VEGF and sVEGFR-1 were elevated in patients with SSc. Higher levels of VEGF occurred in early SSc. In contrast, levels of sVEGFR-1 were high in both early and late disease. Increased sVEGFR-1 in SSc patients with important pulmonary disease raises the question of whether this is a hypoxia-induced phenomenon or whether sVEGFR-1 directly contributes to the pathogenic process. sVEGFR-1 may be a candidate biomarker useful for predicting or detecting pulmonary dysfunction.

Disclosure: Z. A. Taimeh, None; **J. Gordon**, None; **E. J. MacDermott**, None; **L. Barillas**, None; **J. Mersten**, Rudolph Rupert Scleroderma Research Program, 2 ; **R. Duculan**, None; **R. Spiera**, None; **M. K. Crow**, Biogen Idec, 5, Bristol-Myers Squibb, 5, Idera, 5, MedImmune, 5, Roche Pharmaceuticals, 5, Merck Serono, 5, Novo Nordisk, 5 ; **K. A. Kirou**, None.

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Gynecologic and Obstetric History IN Systemic Sclerosis (SSC) PATIENTS IN Spain: A Case Control Study. N. Dorado, M. Pérez, MA Roldán, SI Piedrabuena, BE Joven and PE. Carreira, Hospital 12 de Octubre, Madrid, Spain

Purpose: To analyze: 1.gynecologic and obstetric (gyn-obs) history in systemic sclerosis (SSc) patients, compared with healthy controls; 2.the influence of SSc in patients gyn-obs history; and 3.if this influence is different in SSc subgroups.

Method: A semistructured questionnaire on gyn-obs history was sent to all SSc women followed between 1995-2008 in the rheumatology department of a University Hospital, and to an age-matched control group, comprised by women seen in rheumatology because of mechanical problems, without any evidence of autoimmune disease. SSc patients information: age at onset, SSc subgroup (diffuse or limited), clinical data (lung, renal or cardiac involvement, pulmonary hipertension (PH), antibodies (ANA, anticentromere (ACA), a-Scl70)), had been previously included in a prospective database containing demographic and clinical information. The following groups were analyzed: whole SSc and control group; patients and control older than 45; control group with SSc subgroups (diffuse, limited, ACA (+), aScl70 (+), with interstitial lung disease); control group with SSc patients with disease onset before 35; SSc diffuse and limited; SSc ACA (+) and (-); SSc aScl70 (+) and (-). Chi square and t test were used to analyze differences between groups. Univariate logistic regression was used to analyze the influence of SSc presence in gyn-obs history.

Results: Questionnaire was answered by 98/150 SSc patients and 94/150 controls, with a mean age of 55±15 and 52±12 years, respectively. In the SSc group, 63(64%) had limited and 35(36%) diffuse disease, 25(27%) had lung involvement, 26(28%) had aScl70 and 41(43%) had ACA. The only difference in the gynecologic history was less frequent use of postmenopausal hormonal substitutive therapy (HST) in SSc group (OR=0.3; 95%CI 0.1-0.7; p= 0.005). In obstetric history, SSc patients have been ever pregnant (OR=0.44; 95%CI 0.2-0.9; p= 0.02), and have had the intention to become pregnant less frequently (OR= 0.5; 95%CI 0.2- 0.9; p= 0.04) than controls. There were no differences between ever pregnant women in number of pregnancies or percentage of alive new-born. Similar results were obtained when women older than 45 years were analyzed. These differences were higher when only diffuse SSc or aScl70 (+) patients were analyzed, but were not present when only limited or ACA (+) patients were analyzed. Patients with SSc onset before 35 years were less frequently pregnant (OR=0,2; 95%CI=0.1-0.6; p=0.004), and have had ever the intention to become pregnant (OR=0.3; 95%CI=0.1-0.6; p=0.004), than age

adjusted controls. When analyzing subgroups of SSc patients, diffuse and aScl70 (+) patients showed similar results. Menopause happened at earlier age (p=0.001) and was not natural more often in the diffuse and aScl70 subgroups (OR=0.1; 95%CI= 0,03-0,5; p=0,003)

Conclusion: SSc patients, especially those with diffuse disease or aScl70 antibodies, are less often ever pregnant and have less intention to become pregnant than healthy controls. These is confirmed for patients with disease onset before 35 years. SSc patients are less frequently treated with HST after menopause. Menopause occurs earlier and is more often not natural in SSc patients with diffuse disease and aScl70 antibodies.

Disclosure: N. Dorado, None; **M. Pérez**, None; **M. Roldán**, None; **S. Piedrabuena**, None; **B. Joven**, None; **P. Carreira**, None.

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CANCER Incidence In Systemic Sclerosis In Spain: A Case Control Study. Beatriz E. Joven, Regina Fare, Francisco J. Colina, Belen Ramos and PE. Carreira, Hospital 12 de Octubre, Madrid, Spain

Purpose: To analyze: 1) the incidence of cancer in a large series of SSc patients, followed a University Hospital during the last 28 years; 2) to compare with a control group, and 3) to compare disease presentation in SSc patients with and without cancer.

Method: Demographic and clinical data from all SSc patients regularly followed in the rheumatology department of our Hospital were prospectively included in a data base created in 1989. A sex and age-matched control group of patients seen in the rheumatology department because of mechanical problems during the same period, was randomly selected. Patients with cancer were obtained from the cancer registry in our hospital. Type of cancer, extension, know risk factors for cancer development (family history, smoking habit, other toxics), cancer treatment and outcome were obtained from the patients charts. For SSc patients, temporal relationship with SSc was also obtained. Chi square, t test, bivariate logistic regression was used to analyze differences in cancer incidence between both groups and differences between SSc patients with and without cancer.

Results: From 270 SSc patients (86% females), 28 (24 f, 5 m) had any type of cancer: 8 breast, 1 lung, 2 colon, 11 skin (1 melanoma, 7 basal cell carcinoma, 1 lip ductal terminal carcinoma, 2 epidermoid). Five patients (3 basal cell carcinoma, 1 colon, 1 breast) presented a second cancer (basal cell carcinoma in all cases). From 317 control patients (86% females), 20 (14 f, 6 m) had any type of cancer: 3 breast, 4 skin, 3 prostate, 10 others. Cancer incidence was higher in SSc patients, without statistical significance (p=0.09), but skin cancer was more frequent in SSc patients (OR=3.3; 95%CI 1.05-10.6; p=0.04), especially in female group (OR=6; 95%CI 1.3-27.8; p=0.02). Although breast cancer was also more frequent in SSc patients, this difference was not significant (p=0.1). No other differences were found between SSc and control group in cancer incidence. Within the SSc group, 8 patients were smokers and 5 had family history of cancer. Mean age at cancer diagnosis was 59±13. Neoplasia was localized in 24 and metastatic in 4. Cancer treatments included surgery (26 cases), quimiotherapy (10) and radiotherapy (4). Cancer was considered cured in 22, and 6 patients died from the neoplasia. Six patients had a cancer recidiva. Cancer was previous to SSc development in 9 (7±5 y), coincidental with SSs (less than 12 months) in 2, and posterior in 17 (20±15 y). Skin cancer presented after SSc diagnosis in 73% of cases. Eleven patients had diffuse and 17 limited disease. ANA was positive in 86%, ACA in 40% and Scl70 in 13%. Patients with cancer tended to be older at first SSc symptom (p=0.04), but there were not any other clinical differences between SSc patients with and without cancer.

Conclusion: The incidence of skin cancer in Spain is higher in SSc patients after SSc diagnosis than in control population, especially in females. This finding suggests that SSc patients should receive special advice about sun exposure. Although other types of cancer, as breast cancer, might be more frequent in SSc patients, our study is unable to confirm these data. Cancer does not seem to have a worse outcome in SSc than in control population, and does not seem to be associated to special features in SSc patients.

Disclosure: B. E. Joven, None; **R. Fare**, None; **F. J. Colina**, None; **B. Ramos**, None; **P. Carreira**, None.

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Autoantibody Profiles in Systemic Sclerosis More Predictive of Clinical Outcomes Than Disease Subset Classification. Laisvyde Statkute[1], Mary Carns[1], Spencer Huang[1], Monique E. Hinchcliff[1] and John Varga[2], [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL

Purpose: Systemic sclerosis (SSc) clinical subtypes, diffuse (dcSSc) and limited (lcSSc), have been associated with specific autoantibodies (autoAb): anticentromere (ACA) for lcSSc and topoisomerase 1 (topo-1) for dcSSc. Patients with lcSSc/topo-1 and patients with dcSSc/ACA could be referred as "atypical". Additionally, patients lacking ACA or topo-1 likely express 1 of less common SSc-specific autoAb (double negative, DN). We compared different subsets of patients (by clinical subtype and autoAb) to determine if specific autoAb or clinical subtype is more predictive of particular SSc manifestations.

Methods: 254 consecutive patients with SSc seen at the Northwestern Scleroderma Program between 2005 and 2008 were evaluated retrospectively. Subjects were assigned into 1 of 6 groups based on clinical classification and autoAb (determined by ELISA). T and Chi square tests were utilized, $p<0.005$ was used for level of significance.

Results: 167 patients (66%) had lcSSc and 87 (34%) had dcSSc. 27% of lcSSc patients were ACA+ and 23% were Topo-1+. 5% of dcSSc patients were ACA+ and 35% were Topo-1+. 50% of lcSSc, 60% of dcSSc and 53% of total were DN.

Patients with lcSSc who had topo-1 were more likely to have pulmonary fibrosis (PF) and less likely to have pulmonary hypertention (PH) compared to other lcSSc patients with either ACA or DN. No patients with topo-1 or ACA developed scleroderma renal crisis (SRC). Within 1st group of comparison (dcSSc/topo-1 vs lcSSc/topo-1) presence PF was comparable (97 vs 83%, p=0.073). In group 2 (dcSSc/ACA vs lcSSc/ACA), PF was present in 50 vs 24%, isolated PH in 25 vs 28%, not statistically significant. For group 3 (dcSSc/topo-1 vs dcSSc/ACA), rate of PF (97 vs 50%) and isolated PH (0 vs 25%) differed significantly. Group 4 (dcSSc/DN vs dcSSc/ACA) showed no differences in PF, PH or isolated PH. dcSSc/DN had 4 SRC cases (8%); 23% had severe cardiac involvement and 9 patients (17%) died. Within group 5 (lcSSc/topo-1 vs lcSSc/ACA), PF (83% vs 24%, $p<0.001$) including severe (16 vs 4%) was more prevalent in patients with topo-1. Group 6 (lcSSc/topo-1 vs lcSSc/DN) showed similar significant differences in rates of PF (83 vs 54%) and isolated PH (0 vs 13%). lcSSc/DN demonstrated another 3 SRC cases (4%) and frequent (15%) severe cardiac involvement.

Conclusion: While ACA is rare in patients with dcSSc, topo-1 is frequent in patients with lcSSc.Topo-1 positive lcSSc patients are at higher risk for PF than other lcSSc patients. However, no patients with topo-1 developed SRC. These results indicate that while ACA is useful in delineating clinical subsets of SSc, topo-1 is less predictive. Furthermore, autoantibodies are more predictive of severity and disease outcomes than clinical subsets. In particular, disease manifestations and severity in lcSSc patients who are topo-1 positive are comparable to those in dcSSc patients.

Disclosure: L. Statkute, None; **M. Carns**, None; **S. Huang**, None; **M. E. Hinchcliff**, None; **J. Varga**, None.

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Pharmacokinetics of Oral Treprostinil in Patients with Systemic Sclerosis (SSc) and Digital Ulcer Disease. Elena Schiopu[1], Kristan Rollins[2], Michael Wade[2] and James R. Seibold[1], [1]University of Michigan, Ann Arbor, MI, [2]United Therapeutics Corp, Research Triangle Park, NC

Purpose: Fibrotic arteriosclerosis with endothelial dysfunction is the hallmark of SSc (scleroderma) and is the underlying cause of clinical complications including Raynaud's phenomenon, digital ulcers, pulmonary hypertension and renal crisis. Prostacyclins are proven effective therapies for pulmonary hypertension, but delivery systems can be either cumbersome (IV, SQ) or targeted (inhalation). Treprostinil diethanolamine (TDE), an oral prostacyclin ($PGI_{2)}$ analogue, is in development as an oral sustained release (SR) tablet. The availability of a formulation permitting convenient systemic delivery might have applicability to non-pulmonary SSc vascular complications. The objective of this study was to evaluate the disposition of TDE SR in patients with systemic sclerosis with peripheral vascular complications.

Methods: Patients with SSc (as defined by the ACR criteria) and evidence of peripheral vaso-occlusive disease (defined as presence or history of an active digital ulcer within the past 6 months) participated in this study. Subjects with PAH were excluded. A single 1 mg TDE SR oral dose was administered in the morning following a standardized 500 kcal breakfast. Fourteen blood samples were obtained over 24 hrs and plasma concentrations of treprostinil quantified by liquid chromatography/mass spectrometry. Pharmacokinetic (PK) parameters were calculated using non-compartmental analysis.

Results: Eight subjects were recruited (7 females / 1 male). The mean age was 48.5 years and the mean disease duration was 12.8 years. Five subjects had limited SSc and three had diffuse SSc. We compared the PK data to those obtained from a pool of healthy volunteers. Results are shown as geometric mean (CV%).

Parameter	SSc N=8	Healthy Volunteers N=128
$AUC_{0\text{-}24hr}$ (hr*pg/mL)	3908 (62%)	2974 (49%)
Cmax (pg/mL)	671 (42%)	601 (48%)
Tmax (hr)	4.2 (42%)	4.1 (48%)
Total Clearance (L/hr)	247 (59%)	325 (48%)
$T_{1/2}$(hr)	3.96 (87%)	3.38 (63%)

SSc exhibited similar mean maximum plasma concentrations and modestly higher AUC values (by mean factors of 1.1 and 1.3). Headache and nausea were the most commonly reported adverse events in three and two SSc subjects, respectively.

Conclusion: TDE SR is absorbed and had no unexpected adverse effects following administration of a single 1 mg dose in SSc patients with peripheral vascular disease. Although the study population was expected to display a variable degree of absorption due to SSc-related gastro-intestinal complications, the pharmacokinetic profile was comparable to that observed in healthy volunteers. Multiple dose PK studies are in progress and will support dosing guidelines in controlled trials in SSc patients.

Disclosure: E. Schiopu, Actelion Pharmaceuticals US, 8, United Therapeutics, 2 ; **K. Rollins**, United Therapeutics, 3, United Therapeutics, 1 ; **M. Wade**, United Therapeutics, 3, United Therapeutics, 1 ; **J. R. Seibold**, United Therapeutics, 5, United Therapeutics, 2 .

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C-Reactive Protein (CRP) Is Associated with High Disease Activity in SSc. Results From the Canadian Scleroderma Research Group (CSRG). J. Pope[1], Sarah Harding[2], Sarit Khimdas[3], Ash Bonner[4] and Murray Baron[5], [1]St Joseph Health Care, London, ON, [2]University of Western Ontario, London, ON, [3]Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, [4]McMaster University, Hamilton, ON, [5]Jewish General Hospital, Montreal, QC

Purpose: It has been reported that elevated ESR in SSc increases morbidity and mortality. Little is known about the predictive value of the CRP in SSc.

Method: The CSRG is a large multi-site dataset comprised of annually assessed SSc patient physical exam and laboratory parameters. Statistical comparisons were made for CRP in early vs late SSc, diffuse vs limited, association with skin score and disease activity (MD and patient assessment of disease activity). CRP was drawn annually and normal is up to 8.0mg/L.

Results: 938 patients were analyzed of whom 47% (413) had diffuse SSc and 41 were early diffuse patients (<3 years from first non-Raynaud's symptom). Patient baseline characteristics are reported below:

	Total	All Limited	All Diffuse	Early diffuse <3yrs	Late diffuse >3years
N	938	455	413	41	366
% Female	86	88	83	78	83
Mean Age	55.4 (12.3)	57.6 (12.0)	53.1 (12.2)	52.2 (12.32)	53.1 (12.21)
Mean CRP (mg/L)	9.76 (19.3)	9.39 (18.05)	10.18 (20.54)	17.17 (29.82)	9.27 (19.05)
% with Elevated CRP(>8mg/L)	26.8	25.5	28.6	37.8	26.7
Mean ESR (mm/h)	22.69 (21.5)	20.92 (20.29)	24.74 (22.8)	27.94 (28.63)	24.10 (21.58)
% with Elevated ESR(>20mm/h)	39.5	36.0	43.8	36.1	44.3
Mean (SD) mRSS	10.29 (9.5)	5.52 (4.37)	16.39 (10.5)	21.8 (10.41)	15.74 (10.28)

% mRSS >10	36.1	12.7	65.3	87.8	62.6
Correlation (r): CRP vs mRSS	.197**	.144**	.315**	.040	.326**
Correlation (r): CRP vs MD Global Assessment	.282**	.222**	.389**	.486**	.363**
Correlation (r): CRP vs Patient Global Assessment	.199**	.118*	.279**	.016	.285**
Mean difference in CRP between Tendon Friction Rubs yes – no	2.43	3.49	7.21*	19.19	5.16
Correlation (r): CRP vs ESR	.348**	.324**	.372**	.550**	.341**

Baseline characteristics reported as mean (SD) and Spearman's rho. P-values for comparison with CRP based on 2-tailed T-test *p<0.05, **p<0.01

Though some of the data may not be consistent in all subsets, CRP was significantly associated overall with modified Rodnan Skin Score (mRSS), MD and patient global assessments and ESR. The mean difference in CRP between tendon friction rubs (yes and no) was significant for diffuse SSc.

Conclusion: It appears that CRP is elevated in many SSc patients especially early diffuse SSc. It is associated with other active signs of disease such as tendon friction rubs and MD and patient global assessments. Interventions that lower CRP may be worth pursuing in active SSc.

Disclosure: J. Pope, None; **S. Harding**, None; **S. Khimdas**, None; **A. Bonner**, None; **M. Baron**, None.

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Modified-Release Sildenafil Reduces Raynaud's Attack Frequency in Systemic Sclerosis. Ariane L. Herrick[1], Frank van den Hoogen[2], Armando Gabrielli[3], Nihad Tamimi[4], Carol Reid[4], Damian O'Connell[4], Maria-Dolores Vazquez-Abad[4] and Christopher P. Denton[5], [1]University of Manchester, Salford Royal Hospital, Salford, United Kingdom, [2]Rheumatology, Nijmegen, Netherlands, [3]Università politecnica delle Marche, Ancona, Italy, [4]Pfizer Ltd, Sandwich, United Kingdom, [5]UCL Medical School, London, United Kingdom

Purpose: To examine the effect of sildenafil in patients with Raynaud's phenomenon (RP) secondary to limited cutaneous systemic sclerosis (SSc).

Methods: This double-blind, placebo-controlled study randomized 57 patients with RP/SSc to receive modified-release (MR) sildenafil 100 mg once daily for 3 days followed by MR sildenafil 200 mg once daily for 25 days or placebo. The primary endpoint was the change in the number of Raynaud's attacks per week, expressed as a percentage change from baseline, assessed using analysis of covariance (ANCOVA) with treatment as a factor and baseline as a covariate. Secondary endpoints included Raynaud's condition score (RCS) and pain score (assessed using ANCOVA), serum biomarkers (soluble vascular and intercellular adhesion molecules and pro-collagen type I N-terminal peptide) and endothelial dysfunction assessed by a peripheral arterial tone (PAT) device (summaries only). Efficacy was assessed in the per-protocol (PP) population (patients who received all treatments, completed diaries, and did not violate protocol). Digital ulcers and dyspepsia were exploratory endpoints.

Results: The PP population included 45 patients (sildenafil, n=20; placebo, n=25). The mean percentage change from baseline to day 28 in number of attacks per week was greater with sildenafil than placebo (–44.0% vs –18.1%, *P*=0.034); the mean number of attacks per week improved from 25.0 at baseline to 19.3 after placebo treatment, and from 30.5 to 18.7 after sildenafil treatment. Decreases from baseline in

RCS, duration of attacks, and Raynaud's pain score were not statistically significantly different between groups. Mean values and changes from baseline in PAT responses and serum biomarkers were similar between groups. The number of patients with digital ulcers improved with sildenafil from 5 (25%) at baseline to 4 (20%) at day 14 and to 3 (15%) at day 28; with placebo, the number of patients with digital ulcers was 3 (12%) at baseline, 4 (16%) at day 14, and 5 (20%) at day 28. The number of patients with dyspepsia was 5 (25%) at baseline and 9 (45%) at day 28 for sildenafil compared with 5 (20%) at baseline and 5 (20%) at day 28 for placebo. The most frequent treatment-emergent adverse events were headache and dyspepsia; the majority of adverse events were mild or moderate.

Conclusion: Sildenafil reduced attack frequency in patients with RP secondary to limited cutaneous SSc and was well tolerated. Sildenafil may be a treatment option in this patient population.

Disclosure: A. L. Herrick, Actelion Pharmaceuticals US, 5, ACTELION, MEDIQUEST, UNITED THERAPEUTICS, 9 ; **F. van den Hoogen**, None; **A. Gabrielli**, Roche Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Roche, Wyeth, 2 ; **N. Tamimi**, Pfizer Ltd, 3 ; **C. Reid**, Pfizer LTD, 3 ; **D. O'Connell**, Pfizer Ltd, 3 ; **M. D. Vazquez-Abad**, Pfizer Ltd, 3 ; **C. P. Denton**, Pfizer, Encysive, Actelion, GSK, Novartis, 5 .

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Differences in Overall Disability as Measured by the Health Assessment Questionnaire (HAQ) Between Patients with and without Digital Ulcers in Systemic Sclerosis (SSc): A Post Hoc Analysis of Pooled Data From Two Digital Ulcer Randomized Controlled Trial. J. Pope[1] and Caleb Zelenietz[2], [1]St Joseph Health Care, London, ON, [2]University of Western Ontario, London, ON

Purpose: We studied patients with SSc enrolled in two RCTs using bosentan which has been shown to prevent DU. Patients completed the Health Assessment Questionnaire (HAQ) at each study visit

Methods: Data from the studies were pooled to determine the within patient differences of the HAQ between groups with and without DU; where 309 were enrolled in the two trials of whom 133 were on placebo and 176 received bosentan. Patients were pooled irrespective of drug allocation. The patients were grouped by DU status at baseline and study end into: no DU at baseline and no DU at trial end, no DU at baseline and DU at trial end, DU at baseline and no DU at trial end, DU at baseline and DU at trial end. The components of the HAQ scores that are compared are overall disability, hand function, dressing, hygiene, and grip. The main outcome was difference in HAQ score between baseline and trial end in the 4 categories in a post hoc analysis (HAQ at baseline – HAQ at end of study) was calculated for each group. A negative change in HAQ is an improvement; whereas a positive is worsening.

Results: The groups that had a different DU status at baseline than at end had greater change scores for the majority of the HAQ components compared to groups whose DU status remained constant throughout the trial. Those who had a baseline DU and none at end improved their HAQ scores. (See table)

Changes in the Health Assessment Questionnaire in SSc with and without digital ulcers.

Group	Time Course	Overall Disability Index (SHAQ)	Hand Function Score	Dressing and Grooming Score	Hygiene Score	Grip Score
DU at baseline and end (N= 175)	Start	0.95 (0.65)	1.13 (0.76)	1.25 (0.88)	1.03 (1.00)	1.10 (0.88)
	End	0.92 (0.71)	1.04 (0.80)	1.23 (0.92)	0.90 (1.00)	0.98 (0.87)
	Change	-0.01 (0.37)	-0.06 (0.53)	0.02 (0.86)	-0.09 (0.72)	-0.10 (0.70)
No DU at baseline, no DU at end (N= 32)	Start	0.65 (0.69)	0.69 (0.68)	0.77 (0.69)	0.60 (1.00)	0.69 (0.83)
	End	0.69 (0.73)	0.70 (0.74)	0.81 (0.69)	0.66 (1.04)	0.63 (0.79)
	Change	0.02 (0.34)	0.01 (0.41)	0.03 (0.54)	0.03 (0.47)	-0.03 (0.70)
DU at baseline, no DU at end (N= 84)	Start	0.89 (0.67)	0.99 (0.73)	1.31 (0.86)	0.86 (0.98)	0.81 (0.78)
	End	0.74 (0.72)	0.77 (0.75)	0.90 (0.79)	0.69 (0.97)	0.73 (0.81)
	Change	-0.14 (0.43)	-0.22 (0.56)	-0.42 (0.80)	-0.16 (0.69)	-0.08 (0.66)

No DU at baseline, DU at end (N= 10)	Start	0.54 (0.57)	0.43 (0.45)	0.80 (0.63)	0.30 (0.48)	0.20 (0.42)
	End	0.65 (0.60)	0.70 (0.64)	0.80 (0.79)	0.90 (1.10)	0.40 (0.97)
	Change	0.11 (0.21)	0.27 (0.52)	0.00 (0.67)	0.60 (0.97)	0.20 (1.0)

* Digital Ulcers, Improvement on change is -; worsening change is +

Conclusion: Patients with a DU at baseline and no DU at trial end had improvements in all components of the HAQ. The cohort of patients with no DU at baseline and a DU at trial end had worsening of all but the grooming score; but numbers were small (N=10). The overall change in HAQ did not meet the minimal important difference (MID) of 0.22, but the Hand Function part of the HAQ seemed to be above the MID when DU were present and then healed. As expected, those patients with no change in DU status from baseline to trial end had no changes in HAQ.

Disclosure: J. Pope, Actelion Pharmaceuticals , 5 ; **C. Zelenietz**, None.

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Circulating Inhibitors of Angiogenesis in Scleroderma. Laura K. Hummers[1], Michael Simons[2], Fredrick M. Wigley[1] and Mary Jo Mulligan-Kehoe[3], [1]Johns Hopkins University, Baltimore, MD, [2]Yale University School of Medicine, New Haven, CT, [3]Dartmouth-Hitchcock Medical School, Lebanon, NH

Purpose: Multiple studies have suggested that an imbalance of pro-and anti-angiogenic factors may be a contributing factor leading to more significant vascular disease in scleroderma. In this study we examine a panel of circulating inhibitors of angiogenesis in a cross-section of patients with scleroderma.

Methods: Plasma samples for subjects and controls were obtained and ELISAs performed for soluble VEGF receptors 1 and 2, soluble endoglin, FGF receptor 1, PDGF, IL-4, angiostatin, decorin, endostatin, PEDF, thrombospondin-1, platelet factor-4. Clinical characteristics of scleroderma patients were obtained from a comprehensive clinical database and correlations between measured factors and clinical features were assessed by univariate and multivariate analysis.

Results: Scleroderma subjects (N=94) were mostly female (88%), Caucasian (82%), limited subtype (67%) and had a mean disease duration of 10.8 years. Levels of sVEGFR1, angiostatin, and TSP1 were all markedly higher in scleroderma subjects compared with controls even when corrected for multiple comparisons (Table). Interestingly, we also found levels of endostatin, sVEGFR2 and PEDF to be lower in scleroderma. When assessing for correlations between these factors and clinical features of the scleroderma, we found that sVEGFR1 was higher in patients with diffuse disease and sVEGFR2 showed an inverse relationship with measures of pulmonary vascular disease. Endoglin levels correlated with severity of Raynaud's phenomenon, the presence of centromere antibodies and inversely correlated with DLCO, but not other measures of pulmonary disease. Endostatin showed an inverse relationship with age, but a positive association with disease duration. PEDF levels were lower in those with more severe Raynaud's phenomenon. TSP-1 was higher in those with limited vs. diffuse disease and lower in those with ILD and PAH and a positive association with FVC.

Conclusion: Patients with scleroderma have marked and varied levels of circulating inhibitors of angiogenesis suggesting that the imbalance of these and other pro-angiogenic factors may be important in the development of scleroderma vascular disease.

Factor	Normal N=30	Scleroderma N=94	P value	Mult Comp
sVEGFR1, pg/ml	0	13.3	<0.00001	0.00012
sVEGFR2, pg/ml	393.9	326.2	0.002	0.024
sEndoglin, ng/ml	0.814	0.815	0.97	NA
FGFR, pg/ml	2224.6	2151.4	0.386	NA
PDGFR, pg/ml	5984	5906	0.70	NA
IL4, pg/ml	1.33	2.89	0.037	0.444
Angiostatin, ng/ml	40.6	53.4	<0.00001	0.00012
Decorin, ng/ml	286.3	292.5	0.76	NA
Endostatin, pg/ml	1976	1359	<0.00001	0.00012
PEDF, pg/ml	0.210	0.130	<0.00001	0.00012
TSP1, pg/ml	0.005	0.023	<0.00001	0.00012
PF4, ng/ml	10.3	11.3	0.03	0.36

Disclosure: L. K. Hummers, None; **M. Simons**, None; **F. M. Wigley**, None; **M. J. Mulligan-Kehoe**, None.

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Patients with Diffuse Cutaneous Systemic Sclerosis (dc SSc) Treated with Oral Type I Collagen (CI) Who Experienced, d 25% Improvement in Modified Rodman Skin Score (mRSS) Upregulated IL-10 Production to Specific Cyanogen Bromide (CB) Fragments of CI. Arnold E. Postlethwaite[1], Weng Kee Wong[2], Philip J. Clements[2], Andrew H. Kang[1], Jesse Ingels[1], D. E. Furst[2] and Investigators of the SSc Phase II Oral CI Clinical Trial, [1]UTHSC, Memphis, TN, [2]UCLA, Los Angeles, CA

Purpose: A recent placebo controlled trial of oral CI showed that Late Phase (3-10 yrs duration) dcSSc patients who completed the study and took oral CI for up to 12 months (mo.) had significant improvement in the mRSS at 15 months compared to those treated (Rx) with placebo (Arthritis Rheu 58: 1810-1822, 2008). IL-10 is a potent anti-fibrotic Th2 cytokine that is expressed by T regulatory type 1 (Tr 1) cells and is induced in some laboratory models of oral immune tolerance. The present study was designed to determine whether oral CI induced IL-10 production by PBMC stimulated by purified CB fragments of bovine CI.

Methods: PBMC at baseline and after 12 mo. daily oral CI or placebo treatments were cultured with purified CB fragments of bovine α1(I) and α2(I) and mRSS was determined at these and other times including at month 15 of the trial (3 months off study medication). Patients were grouped into four categories based on whether they were Rx with CI or Placebo and whether or not they had ≥ 25% improvement at month 15 from baseline in their mRSS. Paired t test were used to analyze data.

Results: Of the 168 enrolled in the original clinical trial, 113 completed assigned 12 mo. of treatment and had IL-10 and mRSS data at both baseline and at 15 mo. As a group, all 59 placebo patients did not have significant changes in 12 month IL-10 levels in supernatants from PBMC cultured with a1(I) or a2(I) CB peptides. In contrast, as a group, the 54 patients Rx with oral CI for 12 months had significant increases at 12 months from baseline in IL-10 in supernatants from PBMC cultured with a1(I) CB 2 (Δ=+134 pg/ml, p=0.0365); a1(I) CB3 (Δ=+ 93 pg/ml, p=0.0402); a1(I) CB7 (Δ=+127 pg/ml, p=0.0198), and a2(I) CB2 (Δ=+76 pg/ml, p=0.0402). Further subset analysis revealed that ≥ 25% CI Rx mRSS "responders" had significant 12 month increases in IL-10 in supernatants from PBMC cultured with α1(I) CB4 (p=0.0414), α1(I) CB5 (p=0.0414), α1(I) CB7 (p=0.0414) and α2(I) CB2 (p=0.0414). Patients who had < 25% increase in mRSS had significant elevations of IL-10 in supernatants from PBMC cultured with a1(I) CB2 (p=0.0351) and α1(I) CB3 (p=0.0090). The placebo

treated group did not have increase in IL-10 in supernatants from cultures of their PBMC with α1(I) CB peptides. Increased IL-10 was observed with α1(I) CB2 in placebo Rx mRSS non-responders.

Conclusion: Patients with dcSSc Rx with oral CI who had ≥ 25% in mRSS had an associated upregulation of the anti-fibrogenic cytokine IL-10 to specific epitopes in regions of α1(I) and α2(I) and provides a theoretical explanation of how oral CI may improve mRSS in some patients with dcSSc.

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ACR Poster Session A

Sjögren's Syndrome

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Lymphomas in a North American Sjögren's Syndrome Population. Jane Kang, Lytia Fisher and Frederick B. Vivino, University of Pennsylvania, Philadelphia, PA

Purpose: To describe lymphomas in a North American population with 1° or 2° Sjögren's syndrome (SS).

Method: Using a database of 527 patients with 1° or 2° SS diagnosed according to the American European Consensus Group (AECG) criteria and followed from 1/2/2003 to 2/30/2009, those with a concurrent diagnosis of lymphoma were selected and retrospectively studied. Information on demographics, sicca symptoms, extraglandular manifestations, and lymphoma presentation, year of diagnosis, cell type, and prognosis were obtained through review of electronic and paper charts.

Results: Nineteen patients had both lymphoma (prevalence 3.6%) and 1° or 2° SS. The mean age was 57.3 ± 15.2 years (18 – 79 years) at the first visit. Most patients were female (78.9%), Caucasian (94.7%), and had 1° SS (89.5%). The patient with 2° SS had CREST. The majority were ANA (94.7%) and SSA (68.4%) positive, with less being SSB (31.6%) positive. Six were SSA and SSB negative (31.6%). All had extraglandular involvement.

The mean age at lymphoma diagnosis was 56.1 ± 18.2 years (20 – 82 years). All but one patient developed sicca symptoms prior to their lymphoma diagnosis; this patient had Hodgkin's lymphoma diagnosed 33 years prior to the onset of sicca symptoms, and received chemotherapy and radiation. Eighteen of 19 patients had a single course with no evidence of recurrence during follow up. One patient had a right parotid gland MALT lymphoma, followed by recurrence on the contralateral side 6 years later. Most lymphomas presented as persistent salivary gland swelling (52.6%) or adenopathy (31.6%). MALT lymphoma was most common (57.9%), all of which were extranodal except one. No fatalities were noted during the study period. Detailed results are summarized in Table 1.

Table 1. Results

	MALT	Diffuse large B cell	Undifferentiated NHL	Small B cell	Hodgkin's	All lymphomas
Total	11 (57.9)	4 (21.0)	2 (10.5)	1 (5.3)	1 (5.3)	19
Age at lymphoma diagnosis	52.5 ± 16.7	64.5 ± 16.5	69.5 ± 4.9	72	20	56.1 ± 18.2
Lymphoma presentation						
Parotid gland swelling	7	0	0	0	0	7

Submandibular gland swelling	2	0	0	0	0	2
Cervical lymphadenopathy	1	3	0	0	1	5
Pelvic lymphadenopathy	0	1	0	0	0	1
Diffuse lymphadenopathy	0	0	1	0	0	1
Weight loss	1	0	0	0	0	1
Respiratory failure	0	0	1	0	0	1
Left anterior orbit mass	0	0	0	1	0	1
Years to lymphoma*	5.7 ± 3.3	13 ± 2.7	26 ± 15.6	12	-33	9.9 ± 8.1†

* From onset of sicca symptoms to lymphoma diagnosis

† Excluding patient who developed sicca symptoms after lymphoma diagnosis

Conclusion: These findings are the largest description to date of lymphomas in a North American SS population defined by the AECG criteria. Consistent with other reports, MALT and diffuse large B cell lymphomas were most commonly observed. T cell lymphomas or fatalities were not noted. Pathologic diagnoses usually paralleled the initial organs involved. Patients with salivary gland swelling usually had MALT lymphoma while those with localized or diffuse lymphadenopathy usually did not. Although lymphomas are a significant and at times fatal complication of SS, awareness of warning signs and prompt diagnosis may ensure a good prognosis in the North American SS population.

Disclosure: J. Kang, None; **L. Fisher**, None; **F. B. Vivino**, Digitas Health, 5, Daiichi Pharmaceutical, 5 .

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A Double-Blind, Placebo-Controlled, Crossover Study Using a Latin Square Design to Evaluate the Safety, Tolerability, and Efficacy of NGX267 Oral Capsules in Patients with Xerostomia Associated with Sjögren's Syndrome. Naoto Yokogawa[1], Jonathan S. Dunham[1], Lytia Fisher[1], Sue Mellberg, Frederick B. Vivino[1], Walter Chase[2], A. Kivitz[3] and Michael Murphy, [1]University of Pennsylvania, Philadelphia, PA, [2]Austin, TX, [3]Altoona Arthritis & Osteo Ctr, Duncansville, PA

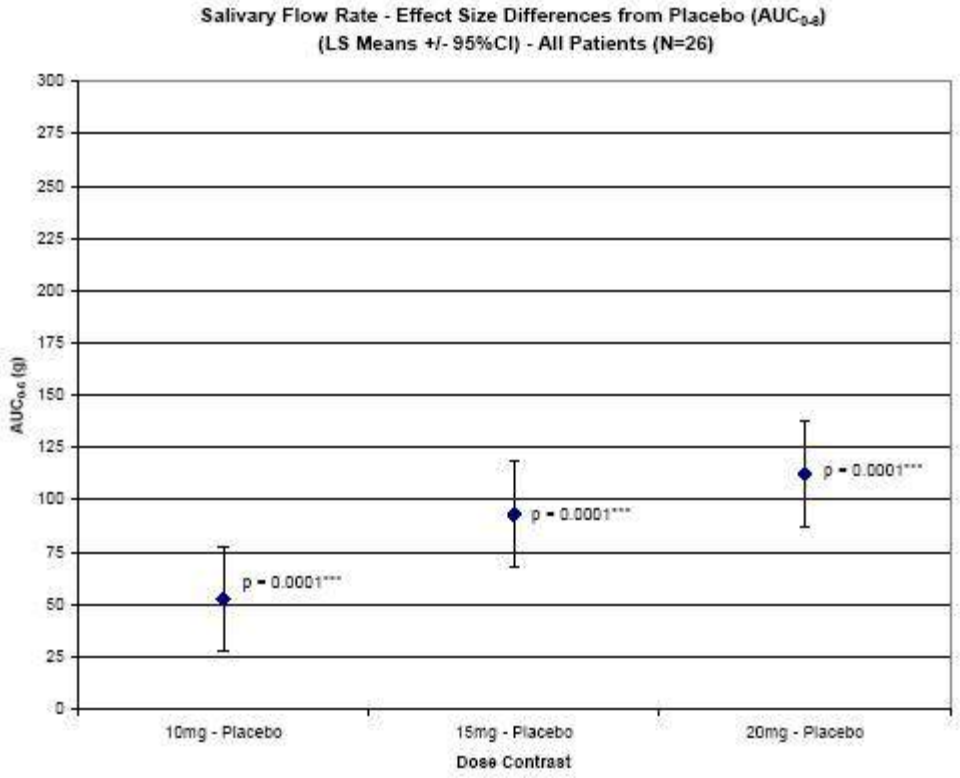
Purpose: To evaluate the efficacy and safety of NGX267 oral capsules for treatment of xerostomia due to Sjögren's syndrome.

Background: Muscarinic agonists may stimulate salivary flow and improve oral symptoms in patients with Sjögren's syndrome. However, the clinical utility of these agents is sometimes limited by dosing frequency and cholinergic side effects. NGX267 (Torrey Pines Therapeutics, Inc., La Jolla, CA) is a novel acetylcholine analog that is relatively M1 receptor selective (M1> M3>> M5> M4> M2). Prior phase I clinical studies documented increased salivary flow and tolerability of doses up to 20 mg/ day in normal elderly (age ≥ 65 years) men and women and, in doses up to 35 mg/ day in normal young adult males.

Methods: Twenty-six patients, aged 21 to 55 years with 1º or 2 º Sjögren's syndrome, diagnosed by American European Consensus Group criteria with subjective/objective salivary gland hypofunction were enrolled at 3 different centers for this 6 week protocol. After screening, patients were randomized to one of four different treatment sequences to receive single doses of NGX267 10mg, 15mg, 20mg or placebo in four separate 24 hour treatment periods interspersed by washout periods (6±2 days). A 4 x 4 Williams Latin Square crossover design was balanced for treatment order and carryover effects. Following an overnight fast, whole mouth sialometry was performed at baseline and 0.5, 1, 2, 4, 6, 12, 14 and 24 hours post dose. Subjects remained NPO except for water for the first 4 hours post dose. Unanesthetized Schirmer's tests were measured at baseline and 2, 12, 14 and 24 hours post dose. Oral symptoms including xerostomia, dry throat, dysphonia, dysphagia, cheilosis, dry tongue, level of thirst and sensation of saliva in the mouth were assessed with 100 mm visual analog scales (VAS). Safety was monitored by vitals, labs, EKGs/Holter monitors and patient diaries. The primary outcome was the cumulative salivary flow during the first six hours post-dosing of the study drug, AUCpd 0-6 (g).

Results: All doses of NGX267demonstrated a statistically significant dose-dependent ƒ¢ salivary flow over baseline compared to placebo for AUCpd 0-6 (g) (p=0.0001) **(Fig. 1):** 10mg- 52.5 (27.5-77.6), 15 mg- 93 (67.9-118.1), 20 mg-112.5 (87.3-137.7) that persisted for 24 hours: AUCpd 0-24 (g) (p=0.0025). All symptoms (24 hour post dose pooled- contrast VAS data) using the 15 and 20-mg doses improved over baseline compared to placebo. Lacrimal flow did not significantly change.

Figure 1



There were no dropouts for adverse effects or other reasons. Side effects included headaches, cold sweats, hyperhidrosis, nausea, flushing and URI's. Only one serious adverse event was noted in a patient who developed appendicitis after protocol completion.

Conclusion: NGX267 is safe and efficacious in Sjögren's syndrome patients during short-term use. Further, long-term placebo controlled trials are justified.

Study Sponsor Statement: This study was sponsored by Torrey Pines Therapeutics, Inc.

Disclosure: N. Yokogawa, None; **J. S. Dunham**, None; **L. Fisher**, None; **S. Mellberg**, TorreyPines Therapeutics, 5 ; **F. B. Vivino**, Digitas Health, 5, Daiichi Pharmaceutical, 5 ; **W. Chase**, None; **A. Kivitz**, takeda, novartis, roche, 8, Thru clinical trials, details of which sponsors can be provided , 2 ; **M. Murphy**, TorreyPines Therapeutics, 5 .

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Diagnostic Algorithm for Pediatric Sjögren's Syndrome. Naoto Yokogawa[1], Scott M. Lieberman[2], Sharon Bout-Tabaku[3], Faizan Alawi[1], Juan P. Palazzo[4], Marta Guttenberg[2], Frederick B. Vivino[1] and David D. Sherry[2], [1]University of Pennsylvania, Philadelphia, PA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, [3]The Children's Hospital of Philadelphia, Philadelphia, [4]Thomas Jefferson University, Philadelphia

Purpose: To develop a new diagnostic algorithm for childhood Sjögren's syndrome (SS).

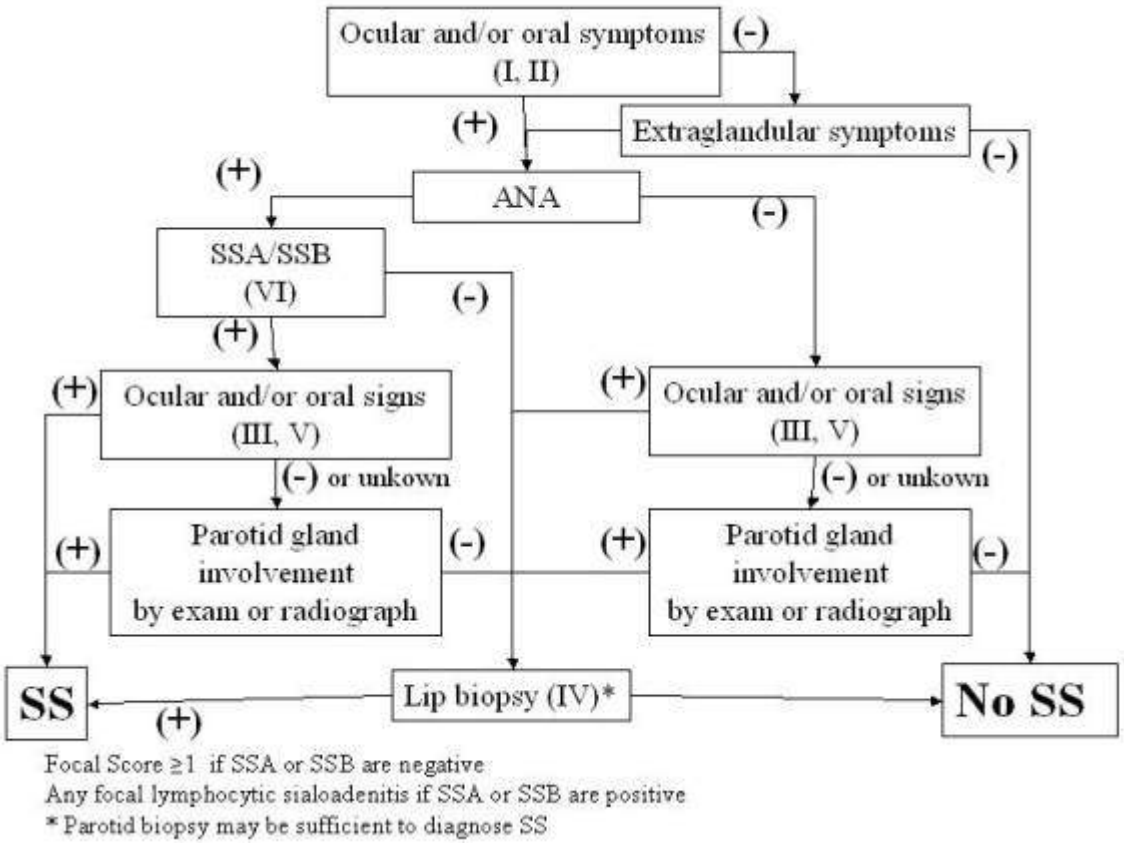
Background: The diagnosis of pediatric SS is challenging because sicca symptoms such as dry mouth/ dry eyes are often absent at the time of initial presentation. Adult classification criteria have not been validated in children and currently proposed pediatric criteria lack diagnostic sensitivity.

Methods: Retrospective review of medical records was performed at Children's Hospital of Philadelphia and the Penn Sjögren Center to identify patients (pts) with suspected pediatric SS. Inclusion required 1) diagnosis or symptom onset at age <20 yrs, 2) consensus agreement on diagnosis by pediatric and adult rheumatologists and 3) exclusion of other diseases based on diagnostic testing and/or long-term follow-up. Pts with overlapping autoimmune disease were not excluded. Information on clinical presentation, serologies, objective tests for sicca and histopathology was reviewed. All available salivary gland biopsies were blindly reviewed by oral pathologists to calculate a focus score (FS) and compared to biopsy findings from nonSS pts. Pts were classified as pediatric SS, nonSS or unclassifiable according to three criteria sets: 1) American-European Consensus Group (AECG) criteria (Vitali et al, 2002), 2) Japanese Criteria (Fujibayashi et al, 2004) and 3) pediatric criteria (Bartunkova et al, 1999) . A novel diagnostic algorithm was devised based on a modification of the adult AECG criteria. Sensitivity of various classification schemes was compared.

Results: Thirty-five children followed over a 10-15 year period met inclusion criteria. Pts met varying % of the 6 diagnostic categories for AECG criteria: I xerophthalmus 63% (22/35), II xerostomia 71% (25/35), parotid swelling 66% (23/35), III abnormal Schirmer's test 36.4%(8/22), abnormal corneal staining 23% (5/22), IV histopathology FS≥1/4 mm^2 75%(18/24), V abnormal salivary flow 46% (7/13), abnormal scintigraphy 100%(7/7), VI positive SSA or SSB (83%).

Antinuclear antibodies (ANAs) were the most sensitive diagnostic test (91%). Salivary gland biopsies demonstrated focal lymphocytic sialadenitis (FLS) in 84%(21/24). Modification of AECG criteria by inclusion of ANA positivity, parotid gland involvement and FLS irrespective of FS improved sensitivity (97%) compared to other classification schemes.

Pediatric SS, n=35	SS	Non SS	Unclassifiable	Excluded
Philadelphia algorithm	97%(34)	3%(1)	0%(0)	0%(0)
AECG criteria	54%(19)	3%(1)	42%(15)	0%(0)
Japanese criteria	60%(21)	3%(1)	37%(13)	0%(0)
Pediatric criteria	77%(27)	6%(2)	0%(0)	17%(6)



Conclusion: Criteria for childhood SS can be modified to maximize diagnostic sensitivity (97%) in order to facilitate earlier treatment and prevent long-term complications. The presence of ANAs and any FLS is more clinically significant in children than adults.

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Manifestations of Pediatric Sjögren's Syndrome: Comparison to Adult Sjögren's Syndrome. Naoto Yokogawa[1], Sharon Bout-Tabaku[2], Scott M. Lieberman[3], Faizan Alawi[1], Juan P. Palazzo[4], Lytia Fisher[1], Frederick B. Vivino[1] and David D. Sherry[3], [1]University of Pennsylvania, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]Thomas Jefferson University, Philadelphia

Purpose: To compare clinical and serologic features of childhood and adult Sjögren's syndrome (SS).

Methods: A retrospective chart review was performed at the Children's Hospital of Philadelphia (CHOP) and Penn Sjögren's Syndrome Center (PSSS) to identify patients (pts) with childhood SS. Diagnosis (DX) of pediatric SS was based on: 1) Dx or symptom onset at age <20 yrs 2) consensus agreement on DX by pediatric and adult rheumatologists and 3) exclusion of other DX based on other testing and long term follow-up. We compared clinical manifestations, serologies and SS Disease Damage Index (Vitali, et al, 2007) of the pediatric pts to adult pts from the PSSS database.

Results: The pediatric cohort included 30 cases from CHOP, the largest single institution series, and 5 pts from the PSSS diagnosed from 1994-2008. Twenty-eight had 1°SS and 7 had 2° SS (3 SLE, 3 UCTD, 1 JIA). Presenting manifestations included parotid swelling 43%, polyarthralgias 20%, neurological symptoms 11%, and sicca 11%. Sicca symptoms were present in 37% at time of diagnosis and occurred in 44% during follow-up. Complications included fetal heart block during teen pregnancy (n=1) and non Hodkins B cell lymphoma (n=1).

Adult pts (n=410, DX by AECG criteria) included 378 with 1°SS and 32 with 2° SS (13 CREST, 10 RA, 4 SLE, 2 UCTD, 1 Diffuse SCL, 1 MCTD, 1 DM). Sicca symptoms were more common in adults but parotitis was more common in children. Extraglandular manifestations such as fever, lymphadenopathy, neurological, renal disease, cutaneous vasculitis, inflammatory eye disease and, serological abnormalities such as SSA/SSB, ANA, RF, and □« C3/C4 were all more common in pediatric than adult SS. The SS Disease Damage Index was not statistically different between the two groups.

Parameter	**Pediatric (n=35)**	**Adult (n=410)**	**p**
Mean age(95%CI)	13.1(8.9-17.4)	54.7(41.3-68.1)	
Female	85.7	92.7	0.142
Caucasian	57	83.9	<0.001
Dry eyes	62.9	84.6	0.001
Xerostomia	71.4	88.5	0.004
Parotitis	65.7	23.1	<0.001
□« Schirmer	36.4(8/22)	49.1(113/230)	0.252
lip biopsy (FS ≥1)	75(18/24)	78(103/132)	0.743
Salivary flow (<0.1ml/min)	46.2(7/13)	43.4(141/325)	0.456
Abn. Scintigraphy	100(7/7)	74.1(157/212)	0.119
Fever	17.1	2	<0.0001
Joint pain	54.3	57.1	0.749
Adenopathy	45.7	15.1	<0.001
Neurological	20	9.3	0.043
Renal	14.3	3.9	0.005
Interstitial lung dis.	2.9	1.2	0.42
Inflammatory eye dis.	11.4	2	0.001
+SSA/SSB	82.9(29/35)	56.3(189/336)	0.003
+ANA	91.4(32/35)	68.6(203/296)	0.005
+RF	72.4(8/29)	40.7(112/189)	0.001
□« C3 or C4	42.3(11/26)	23.1(43/186)	0.035
ESR>20	48.6(17/35)	29.5(67/227)	0.025
wbc<4 or lymph<1.5	22.9(8/35)	50.6(166/328)	0.002
Damage index (95%CI)	0.97(0.52-1.42)	1(0.87-1.13)	0.55

Conclusion: Like the adult disease pediatric SS can cause significant organ damage but sicca symptoms are typically absent in the majority of patients at the time of diagnosis.

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Uncoupling Salivary Gland Dysfunction From Inflammation in a Large Cohort of Primary Sjögren's Syndrome Patients. Nikolay P. Nikolov[1], Ilias Alevizos[1], Margaret Grisius[1], Jane Atkinson[1], Ana Cotrim[1], Bruce J. Baum[1], Jaime Brahim[2], David Kleiner[3], Lolita Bebris[1] and Gabor G. Illei[4], [1]NIH/NIDCR, Bethesda, MD, [2]University of Maryland, Baltimore, MD, [3]NCI, Bethesda, MD, [4]NIDCR, NIH, Bethesda, MD

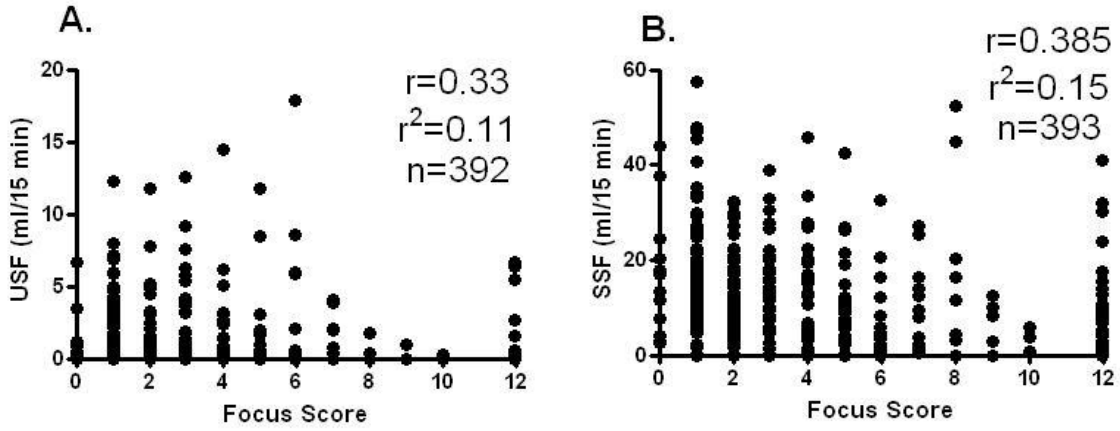
Purpose: To evaluate the association between salivary gland inflammation and hypofunction in a large cohort of primary Sjögren's syndrome (pSS) patients.

Background*:* Many theories of SS pathogenesis embrace the concept that glandular inflammation is the central event that leads to loss of glandular function even though the evidence for this assumption is circumstantial.

Method: A cohort of 393 well characterized patients with pSS underwent concomitant evaluation of salivary gland inflammation and function. Salivary gland inflammation was quantified by focus score (FS) on minor salivary gland (MSG) biopsy. Salivary gland function was quantified by calculating salivary flow rates (ml/15min) after standardized collection from individual parotid, submandibular and sublingual glands in the unstimulated state (total glandular unstimulated salivary flow, USF) and after 2% citric acid stimulation (total glandular stimulated salivary flow, SSF). Data were analyzed using Spearman correlation test. To account for confounders such as concomitant medications, duration of sicca symptoms and age a multiple regression model was used (SAS Institute, Cary, NC).

Results: A statistically significant but very weak negative correlation was observed between FS and glandular USF (r^2=0.11, p<0.0001, Figure 1A) and stimulated salivary flow (r^2=0.15, p<0.0001, Figure 1B). A similar negative correlation was observed between whole unstimulated salivary flow and FS (r^2=0.21, p<0.0001, n=87). These results demonstrate that salivary gland inflammation as measured by minor salivary gland focus score explains only 11-21% of the loss of glandular function. Multiple regression analyses showed no significant contribution of the potential confounders to the model.

Figure. Scatterplot of FS vs USF (A.) and SSF (B.) Abbreviations: r-coefficient of correlation; r^2-coefficient of determination, n-number of observations



Conclusion: Our findings show a statistically significant, but not clinically meaningful, negative correlation between the degree of salivary gland inflammation, as measured by FS on MSG biopsy, and glandular dysfunction, as measured by both USF and SSF, in a large cohort of pSS patients. These data suggest that salivary inflammation and dysfunction may be two different processes in the pathogenesis of SS. This observation may have significant implications for evaluating disease models, selecting appropriate outcome measures and designing clinical trials of pSS.

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Increased Immune Reactivity towards Human hsp60 in Patients with Primary Sjögren Syndrome Is Associated with Increased Cytokine Levels and Glandular Inflammation. Huib de Jong[1], Wilco de Jager[1], B. Prakken[2], Aike A. Kruize[1], Floris P.J.G. Lafeber[1], Johannes W.J. Bijlsma[1] and Joel A.G. van Roon[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University Medical Center, Utrecht, Netherlands

Purpose: Although the etiology of primary Sjogren syndrome (pSS) is largely unknown a predominant role for T cells and B cells in the immunopathology of pSS is indicated. Since self heat shock proteins are immunogenic proteins that are involved in different auto-immune diseases, the expression of and immune response to human hsp60 in patients with pSS compared to patients with non-SS sicca syndrome (nSS) was analyzed

Method: Hsp60 expression in glandular tissue of patients with pSS (n=7) and nSS (n=9) was assessed by immunohistochemistry. Anti-hsp60 specific antibodies in serum of pSS and nSS patients (both n=10) were assessed and correlated to disease parameters and circulating cytokines (assessed by Luminex). In addition, the capacity of hsp60 molecules to induce in vitro proliferation and cytokine production by PBMC of patients with pSS and nSS were measured.

Results: Hsp60 expression in salivary gland biopsies of pSS patients was increased compared to nSS sicca patients. Hsp60 expression significantly correlated with a decreased % of IgA+ plasma cells ($r=0.775$, $p=0.041$). Total serum IgG and IgG1 anti human hsp60 levels were significantly increased in pSS (both $p<0.05$), while the opposite was true for IgG2. The increased anti-hsp60 IgG and IgG1 titers and the decreased IgG2 titers correlated significantly with increased local and systemic disease parameters (all $p<0.01$). Human hsp60 induced IL-1β, IL6 and IL10 production by mononuclear cells (all $p<0.01$). Serum IL-1β, IL-6 and IL-10 concentrations significantly correlated with increased anti-human hsp60 IgG1 but decreased IgG2 levels. In addition serum IL1α, IL10, IL12, IL15, MIG, IP10, sRANKL and sVCAM levels in pSS patients were significantly increased and correlated with increased anti-hsp60 IgG1 and decreased anti-hsp60 IgG2 levels (all $p<0.05$).

Conclusion: The local expression of hsp60, the increased anti-human hsp60 antibody levels and the correlation of these antibodies with cytokine levels and disease parameters in patients with pSS suggest that immune reactivity towards this self antigen significantly contributes immunopathology in pSS. As previously demonstrated this immune reactivity might be exploited to regulate the local inflammatory response, e.g. by nasal or oral tolerization towards human hsp60 or hsp60-derived epitopes.

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Association of C8orf13-BLK and TNFSF4 Gene Variants with Primary Sjögren's Syndrome. Gunnel Nordmark[1], Gudlaug Kristjansdottir[2], Silke Appel[3], Lilian Vasaitis[1], Marika Kvarnström[4], Per Eriksson[5], Elke Theander[6], Per Lundmark[2], Christopher Sjöwall[5], Johan G. Brun[3], Peter Söderkvist[7], Erna Harboe[8], Lasse Gøransson[8], Leonid Padyukov[4], Maija-Leena Eloranta[1], Gunnar Alm[9], Eva Baecklund[1], Marie Wahren-Herlenius[4], Roald Omdal[8], Lars Rönnblom[1], Roland Jonsson[3] and Ann-Christine Syvänen[2], [1]Rheumatology clinic, Uppsala, Sweden, [2]Molecular Medicine, Uppsala, Sweden, [3]Broegelmann research laboratory, Bergen, Norway, [4]Rheumatology unit, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology clinic, Linköping, Sweden, [6]Rheumatology clinic, Malmö, Sweden, [7]Cell biology, Linköping, Sweden, [8]Clinical Immunology unit, Stavanger, Norway, [9]Biomedical Sciences, Swedish University of Agricultural sciences, Uppsala, Sweden

Purpose: Genetic factors are thought to contribute to the etiology of primary Sjögren's syndrome (pSS). The aim of this investigation was to perform a large scale candidate gene association study in patients with pSS from Sweden and Norway, to identify single nucleotide polymorphisms (SNPs) in genes with a putative role in the immune pathogenesis of pSS and in genes that have shown an association with SLE in genome wide association studies (GWA).

Method: Genotyping was performed with the GoldenGate assay from Illumina Inc., San Diego, USA, and 1121 SNPs in 83 genes passed quality control filters and remained for association analysis. A total of 541 patients, 345 Swedish and 196 Norwegian, and 531 controls, 318 Swedish and 213 Norwegian, had a genotype success rate of >90% and were analyzed. All patients fulfilled the AECC criteria and all were Caucasians. Allele counts and genotype frequencies were compared between patients and controls by Fisher's exact test and combined p-values and OR for the Swedish and Norwegian cohorts were calculated with Cochran-Mantel-Haenzel Chi square test.

Results: We found an association between pSS and SNPs in the C8orf13-BLK gene region and the TNFSF4 gene with a p-value of < 0.001 in the combined Swedish and Norwegian cohorts. The SNP rs12549796 in C8orf13-BLK showed an association with $p = 5.8 \times 10^{-4}$ and OR 1.36 (95% CI 1.15-1.63) and the SNP rs1234315 in TNFSF4 was associated with $p = 7.2 \times 10^{-4}$ and OR 1.35 (1.14-1.59). In addition we found an expected association between the TNPO3 gene SNP rs13246321, $p = 1.2 \times 10^{-5}$, OR 1.67 (1.33-2.10) which is in perfect LD with the IRF5 3´SNP rs10488631 and confirms our previous results. We found no association of these SNPs in C8orf13-BLK, TNFSF4 or TNPO3 with autoantibody status. There was no association with the BANK1, ITGAM-ITGAX, KIAA1542 or PXK genes that have shown an association with SLE in GWA studies.

Conclusion: We identified new candidate genes for pSS. Since BLK (B lymphoid tyrosine kinase) is only expressed in B-cells and activates nuclear transcription factors upon B cell receptor signaling and TNFSF4 (Tumor necrosis factor superfamily 4) = Ox40L, is expressed on antigen presenting cells including B cells and plasmacytoid dendritic cells, we conclude that genes involved in B cell activation are important in the pathogenesis of primary SS.

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Development and Preliminary Validation the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): A New Consensual Disease Activity Index That Detects Changes Accurately. Raphaèle Seror[1], Philippe Ravaud[1], Simon J. Bowman[2], Gabriel Baron[1], Athanasios G. Tzioufas[3], Elke Theander[4], Jacques-Eric Gottenberg[5], Hendrika Bootsma[6], Xavier Mariette[7], Claudio Vitali[8] and EULAR Sjögren's Task Force, [1]University of Paris VII, Bichat Hospital, Paris, France, [2]University Hospital Birmingham, Birmingham, United Kingdom, [3]Medical School-Univ of Athens, Athens, [4]Rheumatology clinic, Malmö, Sweden, [5]University Hospital of Strasbourg, Strasbourg, France, [6]University Medical Center Groningen, Groningen, Netherlands, [7]Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France, [8]"Villamarina" Hospital, Piombino, Italy

Purpose: To develop and assess sensitivity to change the EULAR Sjögren's Syndrome (SS) Disease Activity Index (ESSDAI).

Methods: Thirty-nine SS experts identified 12 organs (domains) contributing to disease activity. For each domain, features of disease activity were classified in 3 or 4 levels (items) according to their severity. 96 real profiles of patients with systemic complications of SS, including 3 successive visits were abstracted from medical charts. These data were used to generate 702 realistic vignettes. Real patient profiles were scored with the ESSDAI, the SS disease activity index (SSDAI) and the Sjögren's Systemic Clinical Activity Index (SCAI). Each expert, blinded to disease activity scores, assessed disease activity of 5 real profiles and 20 realistic vignettes using the 0-10 physician global assessment (PhGA), and determined for real profiles whether disease activity had improved, worsened or remained stable at visits 2 and 3. Realistic vignettes were used to develop the ESSDAI; domain weights were estimated using multiple regression modelling, with PhGA as gold standard. Real patient's profiles were used for validation; sensitivity to change was assessed by the standardized response mean (SRM) in each sub-group of improved, worsened, or stable patients.

Results: All 12 domains were significantly associated with disease activity in the multivariate model, domain weights ranged from 1 to 6. The ESSDAI scores were significantly correlated with PhGA in real patient profiles ($r=0.61$;, $p<0.0001$). For improved patients, the SRMs for all scores did not differ, and ranged from -1.08 to -1.38 between visits 1 and 2 and from -0.50 to -0.76 between visits 2 and 3. For patients with worsened activity, the SRMs, between visits 1 and 2 and between visits 2 and 3, were, respectively, +0.46 and +1.10 for the ESSDAI, -0.03 and +0.79 for the SSDAI, and +0.17 and +1.02 for the SCAI. For patients with stable activity, the SRMs, between visits 1 and 2 and between visits 2 and 3, were, respectively, 0.00 and -0.13 for the ESSDAI, -0.44 and -0.11 for the SSDAI, and -0.36 and +0.34 for the SCAI.

Conclusion: The ESSDAI is a consensual clinical index designed to measure disease activity in patients with primary SS. For patients with improved disease activity, ESSDAI has large sensitivity to change similar to that of SCAI and SSDAI. However, the ESSDAI detects changes in activity more accurately than other disease activity indexes, notably, for patients with stable disease activity.

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Autonomic Nervous Dysfunction Development in Patients with Primary Sjögren's Syndrome – a 5 Year Follow-up. Thomas Mandl, Malmö University Hospital, Malmö, Sweden

Purpose: To investigate autonomic nervous dysfunction development over a 5-year period in patients with primary Sjögren's syndrome (pSS).

Materials: 15 pSS patients, previously studied for autonomic dysfunction, were included. Autonomic nervous function test (ANT) and Autonomic Symptom Profile (ASP) controls consisted of 56/80/238/200 previously investigated individuals.

Methods: The patients were studied at baseline and after a 5 year follow-up by 5 ANTs (deep-breathing test (E/I-ratio), orthostatic heart rate test (AI), finger-skin blood flow test (VAC-index), and orthostatic blood pressure test (SBP & DBP-ratios)). Patients also filled out the ASP questionnaire on autonomic dysfunction symptoms.

Results: The E/I-ratio and SBP- & DBP-ratios were decreased in pSS patients both at baseline and follow-up.The orthostatic intolerance, urinary dysfunction, gastroparesis, secretomotor, pupillomotor and ASP total score were increased in pSS patients both at baseline and at follow-up. When comparing ANT and ASP results between baseline and at follow-up, the E/I- and DBP-ratios were decreased and the vasomotor score increased at follow-up.

Conclusion: Both objective and subjective signs of a parasympathetic and a sympathetic dysfunction were seen in pSS patients at baseline and after a 5 year follow-up. The E/I- and DBP-ratios and vasomotor score were found to significantly deteriorate during the 5-year follow-up.

Table 1 – Results of the ANTs and ASP, at baseline and after a 5 year follow-up. ANT results were age-corrected and expressed as z-scores (SD). Most ASP scores were age-, gender-, height- and weight-corrected and expressed as z-scores (SD).

	pSS patients Baseline	pSS patients Year 5	Controls	p-value pSS patients Baseline vs Year 5
ANT				
E/I-ratio	-0.82 (-1.30, 0.07)*	-1.32 (-1.76, -0.67)**	-0.25 (-0.62, 0.60)	**0.04**
AI	-0.14 (-1.32, 0.33)	0.15 (-0.94, 1.10)	0.03 (-0.67, 0.65)	0.09
VAC-index	0.54 (-0.85, 1.61)	0.39 (0.02, 1.48)*	0.09 (-0.67, 0.62)	0.38
SBP-ratio	-0.96 (-1.96, -0.06)**	-0.88 (-1.28, 0.64)*	0.00 (-0.61, 0.70)	0.26
DBP-ratio	-0.76 (-1.05, -0.22)**	-2.46 (-3.04, -1.64)***	0.00 (-0.47, 0.54)	**0.00**
ASP				
Orthostatic intol	1.21 (-0.64, 2.46)*	1.25 (0.22, 2.54)**	-0.39 (-0.78, 0.79)	0.83
Urinary	0.29 (-0.49, 2.34)*	0.12 (-0.45, 2.73)**	-0.51 (-0.71, 0.32)	0.25
Gastroparesis	0.75 (0.00, 1.50)*	0.00 (0.00, 1.50)*	0.00 (0.00, 0.00)	0.61

Autonomic diarrhea	0.62 (-0.51, 1.90)	0.65 (-0.52, 2.10)	-0.42 (-0.60, 0.68)	0.88
Constipation	0.45 (-0.54, 2.65)	1.05 (-0.54, 2.65)	-0.30 (-0.52, -0.18)	0.86
Secretomotor	2.30 (2.12, 4.66)***	4.25 (2.11, 5.07)***	-0.45 (-0.72, 0.52)	0.98
Pupillomotor	1.57 (-0.24, 3.23)**	1.73 (0.48, 3.07)***	-0.42 (-0.71, 0.55)	0.88
Vasomotor	-0.45 (-0.56, 2.39)	-0.26 (-0.54, 2.71)	-0.33 (-0.49, -0.20)	**0.02**
Reflex syncope	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.32
Sleep disorder	-0.42 (-0.83, 1.17)	0.44 (-0.16, 1.67)*	-0.05 (-0.79, 0.35)	0.22
Total score	1.92 (0.40, 3.32)***	2.44 (0.90, 3.11)***	-0.21 (-0.82, 0.72)	0.51

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Disclosure: T. Mandl, None.

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Utility of Whole Versus Total Glandular Unstimulated Salivary Flows for the Classification of Sjögren's Syndrome. Nikolay P. Nikolov[1], Margaret Grisius[1], Ilias Alevizos[1], Jane Atkinson[1], Ana Cotrim[1], Bruce J. Baum[1], Lolita Bebris[1] and Gabor G. Illei[2], [1]NIH/NIDCR, Bethesda, MD, [2]NIDCR, NIH, Bethesda, MD

Purpose: American-European Consensus Group (AECG) classification criteria for Sjögren's syndrome (SS) include documentation of objective signs of xerostomia such as salivary hypofunction defined as whole unstimulated salivary flow (WUSF) of ≤1.5 mL in 15 minutes. However, WUSF is contaminated with non-salivary fluids and proteins. Historically our clinic has used total glandular unstimulated salivary flow (TGUSF) as the standard method of saliva collection but TGUSF does not include saliva from minor salivary glands. This study compared TGUSF and WUSF to determine their impact on the SS classification.

Method: Salivary gland function was quantified in 292 consecutive subjects (156 pSS, 21 secondary SS and 115 non-SS) by calculating salivary flows using the WUSF method followed by standardized unstimulated collections from individual parotid, submandibular and sublingual glands (TGUSF). Data were analyzed using the non-parametric Spearman correlation test. To account for confounders such as concomitant medications, duration of sicca symptoms, age and glandular inflammation (focus score) a multiple regression model was used (SAS Institute, Cary, NC).

Result: Collections from all 292 subjects were analyzed. Good correlation between WUSF and TGUSF was observed (Figure, r=0.66, p<0.0001, n=292) but 18% (54/292) were discordant using 1.5 mL/15 minutes as a cutoff (AECG classification criteria). The discrepancy went equally in both directions: in 54% (29/54) WUSF overestimated and in 46% (25/54)-underestimated the TGUSF. Among the discrepant cases, documenting objective salivary hypofunction was critical for the SS classification of only 12 subjects (4% of the cohort) (Table). Of these, 11 would have met AECG criteria for SS using WUSF and 1-using TGUSF. In the multiple regression model, only focus score remained significantly associated with both WUSF and TGUSF.

Figure. Scatterplot of WUSF and TGUSF; r-coefficient of correlation, n-number of observations; AECG cutoff of 1.5 ml/15 min (dashed line).

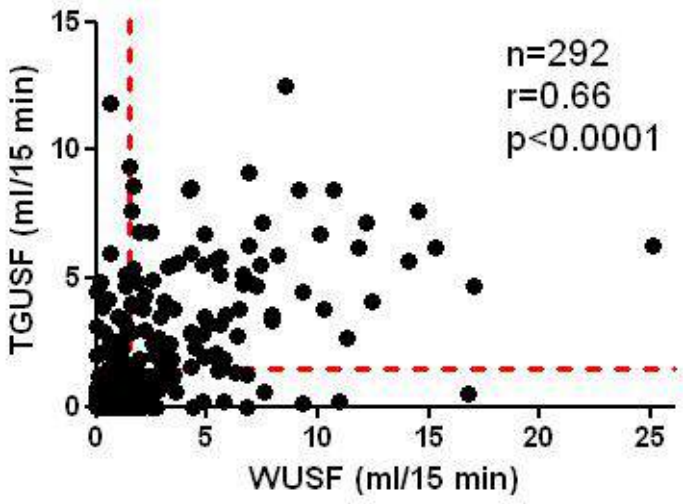

Table. Subject characteristics and impact of TGUSF and WUSF on the SS classification. n-number of observations.

	Primary SS	
Saliva collection method	**TGUSF (n=156)**	**WUSF (n=146)**
Age, years (mean, ±SD)	**51 (±14.2)**	**51 (±14.4)**
Females, %	**90**	**90**
Symptoms Duration, y (median, ±SD)	**6 (±9)**	**6 (±9)**
TGUSF, mL/15 min (mean, ±SD)	**1.092 (±1.877)**	**1.107 (±1.94)**
WUSF, mL/15 min (mean, ±SD)	**1.731 (±3.15)**	**1.552 (±2.95)**
Focus Score (median, ±SD)	**3 (±3)**	**3 (±3)**
Concomitant Meds, n (median, ±SD)	**2 (±3)**	**2 (±3)**

Conclusion: This is the first study to compare WUSF and TGUSF data for evaluation of salivary dysfunction and assess their utility for the classification of SS. Our results demonstrate a statistically significant and clinically meaningful correlation between whole and total glandular unstimulated salivary flows. The observed discrepancies did not suggest that one method is superior to the other in the assessment of salivary gland function. Ultimately the discordance between WUSF and TGUSF did not have a significant impact on the classification of SS.

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Degree of Modification of Ro 60 by the Lipid Peroxidation Byproduct 4-Hydroxy-2-Nonenal May Differentially Induce Sjögren's Syndrome or Systemic Lupus Erythematosus in BALB/c Mice. Biji T. Kurien[1], Andrew Porter[2], Yaser Dorri[2], Saqib Iqbal[2], Sima Asfa[3], Anil Dsouza[2], Kenneth Hensley[2] and R. Hal Scofield[4], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]OMRF, Oklahoma City, OK, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Oklahoma Med Res Foundation, Oklahoma City, OK

Purpose: Our earlier studies showed that immunization of rabbits with 4-hydroxy 2-nonenal (HNE) modified Ro 60 (SS-A) resulted in accelerated epitope spreading and autoimmunity. We determined to extend this model into mice and hypothesized that the degree of modification of Ro 60 with HNE might determine severity of disease and possibly bring about differential induction of Sjögren's syndrome (SS) and SLE in BALB/c mice.

Materials and Methods: Fifty BALB/c mice were divided into five groups with 10 mice in each group. Group I was immunized with purified Ro 60 treated with 1 mM sodium cyanoborohydride ($NaCNBH_3$) alone. Groups II to IV were immunized with Ro 60 modified with 0.4 mM (low HNE), 2 mM (medium HNE) and 10 mM (high) HNE respectively in the presence of 1 mM $NaCNBH_3$. Group V control mice received only Freund's adjuvant. Primary immunization was with Freund's Complete Adjuvant, with subsequent boosts in Freund's Incomplete Adjuvant. The first, second and third boosts were given on day 14, 35 and 63. Post-immune sera were collected on day 21, 42, 56, 70, 84, 98, 105, 126 and a final exsanguination bleed two days later. The anti-sera were used to determine binding to Ro60, HNE-modified Ro 60, La and dsDNA (*C. Lucillae*).

Results: Antibodies to ds DNA were found only in mice immunized with medium HNE-modified Ro 60 (Group III) in bleeds 7 and 9 (4/4 mice in each bleed). Anti-dsDNA was not present in any of the groups in the 6th bleed. Salivary flow, collected 120 days after immunization, decreased 31, 11 and 37% in Groups II, III and IV respectively compared to Freund's immunized controls while Group I mice did not have any reduction in salivary flow. Lymphocytic infiltration was seen in (Group IV-1/1) but not in Freund's immunized group. A rapid abrogation of tolerance to Ro 60 and La antigens was observed in mice immunized with HNE-modified Ro, especially the low and medium HNE-Ro immunized groups. Control mice immunized with Freund's did not make antibodies to Ro, La or other autoantigens studied. Anti-Ro 60 and anti-HNE Ro 60 was detected in the saliva of mice in Groups 1-4, but not in the control Group V mice. Anti-HNE Ro was highest in the saliva of the group immunized with medium HNE-Ro 60.

Conclusion: Immunization with oxidatively modified Ro60 accelerates autoimmunity. Immunization with Ro 60 modified with medium HNE induces an SLE like phenotype while high HNE Ro60 induces a Sjogren's like syndrome in experimental mice.

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Population-Based Prevalence of Primary Sjögren's Syndrome: A 5-Source Capture–Recapture Estimate. Carla Maldini[1], Raphaèle Seror[1], Olivier Fain[2], Robin Dhote[3], Xavier Mariette[4], Michel De Bandt[5], Jean-Luc Delassus[5], Géraldine Falgarone[3], Véronique Le Guern[1], François Lhote[6], Olivier Meyer[7], Jacky Ramanoelina[8], Karim Sacré[7], Yurdagül Uzunhan[3], Jean-Louis Leroux[9], Loïc Guillevin[1] and Alfred Mahr[1], [1]Hospital Cochin, Paris, France, [2]Hospital J. Verdier, Bondy, France, [3]Hospital Avicenne, Bobigny, France, [4]Hospital Bicêtre, Kremlin-Bicêtre, France, [5]Hospital R. Ballanger, Aulnay-sous-Bois, France, [6]Hospital Delafontaine, Saint-Denis, France, [7]Hospital Bichat, Paris, France, [8]Hospital Montfermeil-Le Raincy, Montfermeil, France, [9]Service médical Assurance-Maladie, Bobigny, France

Purpose: The prevalence of primary Sjögren's syndrome (pSS) is not well known. Most earlier studies based on small numbers of identified pSS cases yielded widely divergent prevalence estimates of 0.02–3% for general populations. This population-based study aimed at estimating the year 2007 prevalence of pSS.

Method: The cross-sectional study concerned Seine–Saint-Denis County, a Parisian suburb (France), with 1,093,515 adult inhabitants (□15 yr old). Case ascertainment used 5 sources: 1) hospitals; 2) community-based practitioners; 3) positive anti-SSA/SSB antibody testing by private laboratories; 4) a nationwide patient support group; and 5) a national health insurance database. Recorded case diagnoses were verified against the American–European Consensus Group (AECG) criteria; to account for inconsistent availability of information on objective ocular or oral dryness, we also defined "enlarged AECG criteria" (based on the presence of □3/4 remaining AECG items). Five-source capture–recapture analyses (CRA) using log-linear modeling was performed to estimate the number of cases missed by any source. Confidence intervals were calculated using the Poisson method.

Results: The 5 sources yielded 1,385 notifications of potential pSS cases; among them, 343 charts could not be accessed for detailed examination. After exclusion of non-pSS diagnoses, pSS cases diagnosed after 2007, and cases not meeting classification criteria, residing outside the study area or for whom no follow-up data were available for the study period and thereafter, we retained 122 subjects meeting the

AECG criteria and 183 subjects meeting the enlarged AECG criteria. Numbers of missed cases calculated by CRA were 18.0 and 37.6, respectively. The year 2007 prevalence estimate, adjusted for missed cases, was 128.0 per million adults (95% CI: 107.7–150.1) for AECG criteria and 201.7 per million adults (95% CI: 176.3–229.6) for enlarged AECG criteria.

Conclusion: This population-based study estimated pSS prevalence at 128–202/million (0.013–0.020%) adults. Although this rate must be interpreted with the possibility of undiagnosed pSS in mind, it agrees with the low prevalences obtained by the few other large population-based surveys and might represent a more accurate indication of the true pSS prevalence.

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Rheumatoid Factor and High Titer ANA Are More Strongly Associated with Focal Lymphocytic Sialoadenitis Than SS-A Antibodies. Alan N. Baer, Don R. Martin, Esen K. Akpek, Julius Birnbaum, James M. Christian and Gary R. Warnock, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: The diagnosis of Sjögren's syndrome (SS) requires the presence of SS-A/SS-B antibodies or a labial gland biopsy showing focal lymphocytic sialoadenitis (FLS) with a focus score ≥1. However, SS-A/SS-B antibodies are present in only 40-50% of SS patients. We sought to determine whether there are clinical or laboratory abnormalities that are more strongly associated with a "positive" labial gland biopsy in SS than SS-A antibodies.

Method: During the period of 2002-2009, 117 patients seen in the Rheumatology Clinics at Johns Hopkins University had labial gland biopsies performed at the discretion of the clinician to establish a diagnosis of primary SS. The biopsies were graded as to the presence of FLS with a focus score ≥1 (positive, n=63) or <1 (negative, n=54). The charts of these pts were reviewed to determine positive Schirmer's I (≤5 mm wetting) test results, the highest recorded ANA titer and "ever" presence of positive tests for SS-A or SS-B antibodies, rheumatoid factor (RF), and hypergammaglobulinemia.

Results: The group of patients with positive biopsies did not differ significantly from the group with negative biopsies in terms of age (53.4 vs 52.5 yrs) or female gender (92 vs 87%). There were a significantly greater number of African-American patients in the group with positive biopsies (9 vs 0, p=0.004). Among the 107 patients who had objective measures of sicca, 50 met the American-European Consensus criteria for SS.

Correlates	No. positive/ Total available (%)	Odds Ratio (95% CI)	P value[1]	Sens.	Spec.	+LR[2]
SS-A	19/27 (70)	2.5 (1.0-6.4)	0.05	0.31	0.85	2.1
SS-A or SS-B	19/29 (66)	1.9 (0.8-4.7)	0.20	0.31	0.82	1.7
ANA≥1:640	17/22 (77)	4.5 (1.5-13.4)	<0.01	0.33	0.90	3.3
ANA≥1:320	24/34 (71)	3.6 (1.5-8.8)	<0.01	0.47	0.80	2.4
RF	18/20 (90)	9.5 (2.1-43.6)	<0.01	0.32	0.95	6.8
Hypergammaglobulinemia	14/18 (77)	2.98 (0.9-9.9)	0.11	0.26	0.9	2.5
Abnormal Schirmer's	34/60 (56)	1.1 (0.3-3.7)	1.0	0.83	0.19	1.0
SS-A or RF	26/34 (76)	3.7 (1.5-9.4)	<0.01	0.46	0.81	2.4
SS-A or ANA≥1:640	21/29 (72)	3.8 (1.5-9.8)	<0.01	0.42	0.84	2.6

ANA≥1:640 or RF	22/28 (79)	5.7 (2.0-16.2)	<0.01	0.50	0.85	3.3
[1]Fisher exact test, with p<0.05 considered statistically significant [2]positive likelihood ratio						

Conclusion: In patients suspected of having SS, rheumatoid factor, a high titer ANA test, or the combination of these two were more strongly associated with a positive lip biopsy than SS-A antibodies alone. Additionally, these tests had greater sensitivity and specificity than SS-A antibodies. Rheumatoid factor and high titer ANA tests should be considered important serologic markers of SS and may serve as an adjunct to SS-A antibodies in future diagnostic criteria.

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Salivary Gland Tissue Expression of Interleukin-21 in Patients with Primary Sjögren's Syndrome. Kwi Young Kang[1], Hyun-Ok Kim[2], Sung Soo Kim[3], Ji-Min Kim[1], Ho-Sung Yoon[1], Chang-Hun Lee[1], Seung-Ki Kwok[1], Ji-Hyeon Ju[1], Kyung-Su Park[4], Sung-Hwan Park[5] and Ho-Youn Kim[1], [1]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Gyongsang University, Jinju, South Korea, [3]Ulsan Univ Med Sch Gangneung, Gangneung, [4]Seoul St Mary's Hospital, Seoul, South Korea, [5]Kangnam St Mary's Hosp, Seoul, South Korea

Purpose: To assess the levels of serum interleukin (IL)-21 in patients with primary Sjogren's syndrome (pSS) and to investigate salivary gland expression of IL-21 in pSS patients.

Method: The serum IL-21, IL-17, IL-23 and IL-6 in 40 pSS, 40 RA, 38 SLE patients and 20 healthy controls were measured by sandwich enzyme-linked immunosorbent assay. Laboratory data such as anti-nuclear antibody (ANA), anti-Ro/La antibody, anti-dsDNA antibody, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and globulin were tested. The relationship between serum IL-21 level and other laboratory data was analyzed. Minor salivary glands from 16 patients with pSS and 4 control with sicca symptom were evaluated for IL-21 and IL-21 receptor (IL-21R) expression by immunohistochemistry.

Results: The level of serum IL-21 in patients with pSS (646±637 ng/l) was higher than that in healthy control (71±132 ng/l) ($p<0.001$). The serum IL-21 in pSS patients was higher than that in RA patients (342.6±322 ng/l, $p=0.01$), but it was not significantly different with that in SLE patients (454.32±534 ng/l, $p=0.147$). The serum level of IL-21 was not correlated with that of IL-17, 23 and 6. There was no significant correlation between level of IL-21 and ANA, anti dsDNA antibody, RF and ESR. The level of serum IL-21 in pSS patients showed positive correlation with globulin ($r=0.482$, $p=0.002$) and immunoglobulin G (IgG) ($r=0.438$, $p=0.009$). Immunohistochemical staining of minor salivary glands biopsy specimens from pSS patients revealed positive staining for both IL-21 and IL-21R within lymphocytic foci and periductal area whereas only minimal expression was seen in samples from control. IL-21 was more strongly stained than IL-21R.

Conclusion: The elevated level of IL-21 in pSS patients has positive correlation with that of globulin and IgG. IL-21 and IL-21R is expressed in Salivary gland from pSS patients, which suggests that IL-21 may play a critical role in the pathogenesis of pSS.

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Establishment of New Murine Model for Sjögren's Syndrome Like Sialoadenitis Using M3 Muscarinic Acethylcholine Receptor Knockout Mice. Mana Iizuka, Ei Wakamatsu, Isao Matsumoto, Hiroto Tsuboi, Yumi Nakamura, Taichi Hayashi, Daisuke Goto, Satoshi Ito and Takayuki Sumida, University of Tsukuba, Tsukuba, Japan

Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of salivary glands, in which $CD4^+$ T cells are predominant. These infiltrating T cells play a crucial role in the generation of SS. Previous studies showed that autoantibodies and auto-reactive T cells against M3 muscarinic acethylcholine receptor (M3R) were detected in patients with SS. In this

study, to reveal the pathological mechanisms underlying immune response against M3R, we tried to establish the new murine model for SS like sialoadenitis as a target of M3R.

Method: 1) C57BL/6J mice and M3R knockout mice were immunized intradermaly with synthesized peptides, which were coded the extracellular domains of murine M3R (N-terminus, 1st, 2nd, and 3rd extracellular loops), in CFA. On day 10, these mice were boosted with intradermal injection. Ten days after booster immunization, spleens were isolated, the immune response to M3R was examined in vitro, and them were transferred to Rag1 knockout mice (C57BL/6J → $Rag1^{-/-}$ and $M3R^{-/-}$ → $Rag1^{-/-}$). 2) After inoculation, anti-M3R antibodies and amount of saliva flow were measured on day 0, 15, 45. 3) Salivary glands were investigated histologically by H&E staining on day 45 after the cell transfer to Rag1 knouckout mice. Infiltrated lymphocytes in the salivary glands were evaluated using anti-Thy1, anti-B220, anti-CD4 and anti-CD8 antibodies by immunohistochemical study.

Results: 1) IL-17 and IFNg were highly produced in splenocytes of immunized M3R knockout mice compared with C57BL/6J mice. 2) In $M3R^{-/-}$ → $Rag1^{-/-}$ mice, anti-M3R antibodies was increased and saliva flow were decreased. 3) On day 45, the sialoadenitis with remarkable mononuclear infiltration was observed in the salivary glands of $M3R^{-/-}$ → $Rag1^{-/-}$ mice, but not in the C57BL/6J → $Rag1^{-/-}$ mice. Moreover, $Thy1^{+}CD4^{+}$ cells predominantly infiltrated in salivary glands of $M3R^{-/-}$ → $Rag1^{-/-}$ mice .

Conclusion: We established the new murine model for SS like sialoadenitis using M3R knockout mice immunized with M3R. These findings support the possibility that autoimmune response to M3R molecule plays a crucial role in the generation of sialoadenitis in patients with SS.

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Novel Brain Biomarkers for Fatigue and Cognitive Function in Primary Sjogren's Syndrome. Barbara M. Segal[1], Bryon A. Mueller[1], Brian Pogatchnik[2], Erin Holker[2], Xiaochun Zhu[2], Rachel Prosser[3] and Sriharsha Veeramachaneni, [1]Univ of Minnesota, Minneapolis, MN, [2]University of Minnesota, [3]Hennepin County Medical Center

Purpose: To assess the degree of brain tissue injury in primary Sjogren's syndrome (PSS) subjects with minimal cognitive dysfunction. We hypothesized that microstructural abnormalities detectable with quantitative high resolution brain MR imaging would be correlated with neuropsychological measures.

Methods: Female PSS subjects who met AECG criteria were compared with age and education matched healthy volunteers. Subjects were evaluated who had no history of CNS disorder other than “mental fatigue" (subjective memory and concentration difficulties.) Subjects underwent an extensive neuropsychometric evaluation and completed validated questionnaires to assess symptoms of fatigue (FSS), pain (BPI), depression (CES-D), sleep quality (PSQI) and subjective cognitive function (Prof-M). Based on the results of cognitive tests, PSS subjects were classified as impaired or non-impaired. 7 PSS subjects with evidence of cognitive impairment, 7 PSS subjects with no impairment and 7 controls underwent MR imaging. MRI parameters assessed included diffusion tensor fractional anisotropy (FA) and mean diffusivity (MD), FLAIR imaging for white matter (WM) hyperintensities and T1 weighted MP-Rage lobar volume and cortical thickness. Analysis of variance was used to compare cognitive test scores, symptom measures and MR parameters between groups (significance threshold p=.05.) Mancova with Tukey correction for multiple comparisons was used to compare groups on MR measures of brain pathology. Spearman correlation coefficients were calculated to test for correlations between neuropsychological outcomes and MR parameters.

Results:19 female PSS patients mean age 47.6(10.8) and 18 controls mean age 50.9(5.4) were evaluated with a neuropsychometric battery. 18% of patients versus 6% of controls were impaired on measures of attention, 21 % of the PSS patients and 5.6% of the controls were <1.5 SD below age adjusted norms one or more measures of verbal learning. Impaired PSS subjects differed significantly from non-impaired PSS and control groups in DTI parameters localized to the inferior frontal lobe WM. There was no difference in regional cortical thickness,volume, WM lesion severity or lesion load between PSS subjects and controls. Pychological measures and tests of verbal memory correlated with DTI parameters in the inferior frontal region.

Conclusion: The present study suggests that DTI could be a sensitive biomarker for CNS pathology and mild cognitive dysfunction in pSS. Larger studies are needed to assess the contribution of microstructural brain abnormalities to neuropsychological symptoms and cognitive performance in PSS.

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The Role of Anti-2nd Extra-Cellular Loop-M3R Polypeptide (anti-M3R) in Sjogren's Syndrome. He Jing[1] and Li Zhanguo Sr.[2], [1]Peking University People's Hospita, Beijing, China, [2]Professor, Beijing, China

Purpose: M3 muscarinic acetylcholine receptor (M3R) plays a crucial role in Sjogren's syndrome. Resent studies have shown that autobodies against the 2 nd extra-cellular loop in M3R were detected in serum from Primary Sjogren's syndrome (pSS) patients.

Objective: To determine the role of 2 nd extra-cellular loop-M3R polypeptide antibodies in diagnosis of patients with pSS.

Method: (1)We synthesized 2 nd extra-cellular loop-M3R polypeptide by two ways: Linear and cyclic. (2) The prevalence of anti-M3R antibodies was examined by ELISA in 148 patients with pSS, 84 patients with systemic lupus erythematosus (SLE), 95 patients with rheumatoid arthritis (RA), and 64 healthy subjects. (3) The association between anti-M3RP antibodies and other autoantibodies of SS was also investigated.

Results: (1)The prevalence of anti-cycle-M3RP antibodies in the SS, SLE, RA, and health controls were 62.2%, 7.1%, 5.3% and 1.6%. The prevalence of anti-lined-M3RP antibodies in the SS, SLE, RA, and health controls were 56.1%, 20.0%, 14.7% and 9.4%. (2) The specificity of the anti-cycle-M3R antibodies in the diagnosis of SS was 95.1%, much higher than lined polypeptide (84.7%). (3) Anti-M3R antibodies were highly prevalent even in SS patients lacking anti-SSA, anti-SSB antibodies.

Conclusion: 2nd–M3RP may be the most important epitome in M3R, which may play the pathogenic role in SS. Anti-2nd–cycled M3RP antibody may be a good diagnositic marker in serum of SS patients.

Disclosure: H. Jing, None; **L. Zhanguo**, None.

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New Epitopes and Functions of Anti-M3 Muscarinic Acetylcholine Receptor Antibodies in Patients with Sjögren's Syndrome. Hiroto Tsuboi, Isao Matsumoto, Ei Wakamatsu, Yumi Nakamura, Mana Iizuka, Taichi Hayashi, Daisuke Goto, Satoshi Ito and Takayuki Sumida, University of Tsukuba, Tsukuba, Japan

Purpose: M3 muscarinic acetylcholine receptor (M3R) plays a crucial role in the secretion of saliva from salivary glands. Data from a recent study have suggested some patients with Sjögren's syndrome (SS) carried inhibitory auto-antibodies (Abs) against M3R. We reported a subgroup of SS patients had anti-M3R Abs recognizing the 2nd extracellular loop of M3R. In functional assays using salivary gland cells, IgG fractions from SS patients (SS-IgG) inhibited the rise in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) induced by carbachol. The precise epitopes of anti-M3R Abs and the relationship between the functions and epitopes are currently unknown. To clarify the precise B cell epitopes and the functions of anti-M3R Abs in patients with SS, we carried out this study.

Methods: 1) We synthesized four different peptides encoding the extracellular domains of human M3R such as N terminal region, 1st, 2nd, and 3rd extracellular loops. Abs against those regions of M3R were examined by ELISA in the sera from 42 SS patients and 42 healthy controls (HC). We assessed the correlation between anti-M3R Abs and various clinical features.

2) Human salivary gland (HSG) cells were pre-cultured with IgG fractions (1.0 mg/ml) separated from sera of anti-M3R Abs positive SS, negative SS, and HC for 12 h. After loading with Fluo-3, HSG cells were stimulated with cevimeline hydrochloride (20 mM), and then $[Ca^{2+}]_i$ was measured by the fluorescence plate reader.

Results: 1) Abs to N terminal region were detected in 42.9% (18/42) of SS patients and 4.8% (2/42) of HC. Abs to 1st extracellular loop were detected in 47.6% (20/42) of SS and 7.1% (3/42) of HC. Abs to 2nd were found in 54.8% (23/42) of SS and 2.4% (1/42) of HC. Abs to

3rd were detected in 45.2% (19/42) of SS and 2.4% (1/42) of HC. The titers of anti-M3R Abs against all extracellular domains were significantly higher in SS patients than HC. Some SS patients carried anti-M3R Abs that recognized several extracellular domains of M3R. The positivity for anti SS-A antibody was significantly higher among anti-M3R Abs positive SS than negative SS ($P<0.05$). In contrast, there was no difference in other clinical features between anti-M3R Abs positive and negative SS.

2) Anti-M3R Abs to the 2nd extracellular loop positive SS-IgG inhibited the increase of $[Ca^{2+}]_i$ induced by cevimeline hydrochloride. Abs to the N terminal positive SS-IgG and Abs to the 1st extracellular loop positive SS-IgG enhanced it, while Abs to the 3rd extracellular loop positive SS-IgG showed no effect on $[Ca^{2+}]_i$ as well as anti-M3R Abs negative SS-IgG.

Conclusion: These findings indicated the presence of several B cell epitopes on M3R in SS patients and some SS patients were reactive to several extracellular domains of the M3R. Influence of anti-M3R Abs on the secretion of saliva might differ with these B cell epitopes on M3R.

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Development of P552-02 to Treat Xerostomia in Sjögren's Syndrome. M.L. Singh[1], A.S. Papas[1], P.C. Fox[2], A.L. Stevens[3], R.C. Boucher[4], B.T. Thelin[3] and M.R. Johnson[3], [1]Tufts University, Boston, MA, [2]PC Fox Consulting, LLC, Spello (PG), Italy, [3]Parion Sciences, Durham, NC, [4]University of North Carolina at Chapel Hill, NC

Purpose: Sjögren's syndrome (SS) is an autoimmune inflammatory disorder characterized by diminished exocrine secretions, xerostomia and oral health deterioration. Evidence suggests that oral mucosal hydration is regulated, in part, via transepithelial salt (and water) transport. Transepithelial absorption of sodium through the epithelial sodium channel (ENaC) drives absorption of water through the oral mucosa reducing mucosal hydration. We predict inhibition of ENaC in the oral mucosa will increase oral hydration and improve xerostomia symptoms. A novel potent small-molecule inhibitor of ENaC, P552-02 (552), is being developed by Parion Sciences and Kainos Medicine for treatment of xerostomia. It is designed to be a safe and effective topical agent with little to no oral bioavailability.

Method: Safety and exploratory efficacy of 552 were evaluated in a randomized, double-blind, placebo-controlled, crossover study of 552 oral rinse vs. placebo (PBO) in 30 subjects with primary SS (study 205S). Subjects received 6 doses of 552 oral rinse (10mL of 5µg/mL solution) or PBO daily for 28 days. Visual analogue scales (VAS) were used to assess xerostomia symptoms on days 7 and 28. Also, a pharmacokinetic (PK) study evaluating systemic exposure of 552 was completed as part of an ongoing randomized, double-blind, placebo-controlled, parallel clinical trial evaluating safety and efficacy of a higher dose of 552 oral rinse (25 µg/mL solution) in 120 subjects with SS (study 207S). Blood samples were taken 15 minutes before the last dose on Treatment Day 7 and at 5 time points during the 2-hour steady-state dosing interval. A validated LC/MS/MS method was used to determine concentrations of 552.

Results: In study 205S, significant improvements from baseline were seen between 552 and PBO for mouth dryness on Days 7 and 28 ($p=0.039$, 0.033, respectively) and the ability to sleep on Day 28 ($p=0.042$). The differences between treatments in global assessment of dry mouth and tongue dryness approached statistical significance ($p=0.056$, both variables) on day 28. No clinically relevant differences between 552 and PBO were seen for adverse events, clinical laboratory parameters, vital signs, or physical examination findings. In the PK study, 552 was "below limit of quantification" (<20 pg/mL) in all samples from all subjects (8 active; 8 PBO), confirming lack of oral bioavailability when administered by oral rinse.

Conclusion: 552 (5 µg/mL) was well tolerated when given 6 times daily for 28 days to subjects with SS. Despite a small sample size, subjects' assessment of changes from baseline indicated that 552 was effective in improving the key symptoms of oral dryness and the ability to sleep. Furthermore, the PK sub-study of a larger second study found no systemic exposure following oral rinsing with 552 (25µg/mL).

Disclosure: M. L. Singh, Parion Sciences, 2 ; **A. S. Papas**, Parion Sciences, 5 ; **P. C. Fox**, Parion Sciences, 5 ; **A. L. Stevens**, Parion Sciences, 3, Parion Sciences, 1 ; **R. C. Boucher**, Parion Sciences, 6, Parion Sciences, 1 ; **B. T. Thelin**, Parion Sciences, 3, Parion Sciences, 1 ; **M. R. Johnson**, Parion Sciences, 6, Parion Sciences, 3, Parion Sciences, 1 .

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Frequency of Neurologic Disease in Sjogren's Patients Versus Controls. Julius Birnbaum, Douglas Kerr and Alan N. Baer, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Neurologic disease is a devastating extraglandular manifestation of Sjögren's syndrome. Comparing the frequency of neurologic syndromes in Sjögren's versus non-diseased controls can highlight specific syndromes highly relevant to Sjögren's patients. Therefore, we sought to assess the frequency and potential diagnostic utility of different neurologic syndromes in discriminating between Sjögren's patients and clinically relevant controls.

Method: Retrospective, case-control study, characterizing the frequency of neurologic syndromes, seen in 268 consecutively evaluated outpatients, referred for diagnostic suspicion of Sjögren's syndrome.

Results: Neurologic Syndromes in Sjögren's patients versus non-diseased controls

Variable	Sjögren's syndrome (N=157)	Controls (N=111)	Sensitivity/ Specificity	Positive/Negative Predictive value for neuropsychiatric syndromes	p-value[1]
DEMOGRAPHICS					
Age onset Neuro Sx, years	46.2	42.5	N/A	N/A	p=0.91
Sex, %Female (#)	90% (142)	89% (99)			p=0.83
Race Caucasian % (#) African-American %(#) Other	84%(133) 11% (17) 5% (7)	84% (93) 12% (13) 4% (5)	N/A	N/A	p=0.84
AUTOANTIBODIES					
SS-A antibodies % (#)	66% (95)	27% (27)	69%/71%	75%/66%	p<0.01
SS-B antibodies % (#)	33% (48)	9% (9)	37%/87%	77%/55%	p<0.01
NEUROLOGIC SYNDROMES					
Any neurologic syndrome % (#)	76% (119)	37% (41)	76%/63%	74%/65%	p<0.01
CNS Syndromes					
Diffuse Syndromes					
Cognitive complaints % (#)	10% (14)	0% (0)	10%/98%	89%/44%	p<0.01
Headache % (#)	25% (39)	16% (18)	25%/82%	68%/50%	p=0.10
Demyelinating Syndromes					
Neuromyelitis Optica (NMO), or NMO-Spectrum of syndromes	6% (9)	0% (0)	6%/100%	100%/43%	p=0.02
Multiple Sclerosis (MS)-type Demyelinating Syndrome % (#)	10% (16)	2% (2)	10%/98%	83%/43%	P=0.02
Focal Syndromes					

Cerebrovascular Disease % (#)	5% (7)	4% (4)	4%/96%	64%/42%	p=1.00
Seizures % (#)	4% (6)	1% (1)	4%/99%	85%/42%	p=0.25
PNS Syndromes					
Small-fiber neuropathy % (#)	7% (11)	1%(1)	7%/99%	92%/43%	p=0.02
Ganglionopathy % (#)	3% (5)	0% (0)	3%/100%	100%/42%	p=0.08
Axonal, symmetric polyneuropathy % (#)	1% (2)	1% (1)	1%/99%	67%/42%	p=1.00

(1) Assessed by student's t-test for continuous variables, and by chi-squared analysis or Wilcoxon rank sum test for categorical variables

Conclusion: (1) The frequency and positive predictive value (PPV) of neurologic disease in discriminating between Sjögren's versus controls, was similar to the seroprevalence and predictive value of the SS-A and SS-B antibodies.

(2) In contrast to lupus, "focal" CNS syndromes (strokes, seizures) are uncommon and not statistically associated with Sjögren's patients.

(3) Although demyelinating syndromes and neuropathies are uncommon, these syndromes are statistically associated with Sjögren's, and exhibit high PPV in distinguishing between Sjogern's patients versus controls.

(4) As a major, multi-center, NIH funded study is underway to revise diagnostic criteria for Sjogren's syndrome, this study suggests that the aggregated presence of neurologic disease, as well as the presence of demyeinating syndromes and neuropathies, may have potential diagnostic utility in discriminating between Sjogren's versus controls.

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Proteomic Analysis of Whole Saliva as a Promising Tool to Identify Novel Disease Biomarkers in Primary Sjögren's Syndrome.

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Purpose: To characterize the salivary proteomic profile of patients affected by primary Sjögren's syndrome (pSS) in order to identify novel diagnostic biomarkers for the disease.

Method: Forty patients with a diagnosis of pSS made according to the AECC criteria (50.86 ± 9.41 years, mean age ±SD) were enrolled in this study. Forty healthy subjects, sex and age matched (48.45 ± 7.56 years, mean age ±SD) were included as controls. Unstimulated whole saliva was collected by draining under standard conditions, and samples were analysed by two-dimensional electrophoresis (2DE) combined with matrix-assisted laser desorption ionisation time of flight mass spectrometry (MALDI-TOF-MS) The same samples were also analysed by surface enhanced laser desorption ionisation time of flight mass spectormetry (SELDI-TOF-MS) which was carried out on different chip arrays (CM10, Q10, IMAC30, H50).

In order to verify the ability of the candidate potential biomarkers to distinguish pSS from other non-SS sicca syndromes, serial salivary samples from 24 patients who were routinely subjected to minor salivary gland biopsy (MSGB), were also analyzed. MSGB was employed as the gold standard test to differentiate pSS from other non-SS sicca syndromes.

Results: Eleven proteins resulted differently expressed in the 2DE-MALDI-TOF-MS analysis of pSS vs healthy subjects. Poly-Ig receptor, alpha-salivary amylases, carbonic anhydrase VI, cystatin SN and prolactine-inhibitor protein precursor were significantly reduced, while enolase, Ig kappa light chain, beta-2-microglobulin, Zn alpha 2 glycoprotein, calgranulin A and B resulted increased. SELDI-TOF-MS detected 57 peaks differently expressed in pSS vs healthy controls. The longitudinal prospective study of the biopsied patients revealed that 36 peaks were also differently expressed in pSS patients compared with non-SS sicca sydrome patients. Noteworthy, 9/36 increased peaks corresponded exactly to 9/57 peaks increased in the comparison between pSS and healthy subjects (m/z 3371, 7511, 10852, 11586, 11740, 12697, 13470, 21721, 77961). Moreover, 3/36 decreased peaks were identical to 3/57 peaks (m/z 4928, 13825, 14266) which were decreased in pSS vs healthy volunteers. The EPO-KB database identified the m/z 3371 and the m/z 11740 peaks as corresponding to neutrofil defensin

1 and beta-2-microglobulin respectively. In addition, the m/z 10852, 11586, 13470 resulted vey close to the molecular weight of calgranulin A, Ig kappa light chain and calgranulin B, apparently validating the results obtained by using 2DE-MALDI-TOF-MS.

Conclusion: This study demonstrated that 2DE-MALDI-TOF-MS and SELDI-TOF-MS might be valid complementary techniques able to identify a pannel of potential novel diagnostic biomarkers for pSS.

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Heat Solubilized Curcumin/Turmeric Inhibits Autoantigen-Autoantibody Interaction in Sjögren's Syndrome (SS)/SLE and in a Mouse Model of SS. Biji T. Kurien[1], Anil Dsouza[2] and R. Hal Scofield[3], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]OMRF, Oklahoma City, OK, [3]Oklahoma Med Res Foundation, Oklahoma City, OK

Purpose: Curcumin, derived from Curcuma longa, is the most active component in the Indian curry spice turmeric. Curcumin has emerged as a new "nutraceutical" agent that can ameliorate multiple sclerosis, RA, psoriasis, and inflammatory bowel disease in human or animal models by regulating inflammatory cytokines and related signaling pathways in immune cells. Curcumin levels upto 8 g/day is non-toxic to humans. Insolubility of curcumin limits its biological utility. However, we found that heat treatment increased curcumin solubility 12-fold. We report here that heat-solubilized curcumin/turmeric binds to proteins. We therefore hypothesized that heat-solubilized curcumin/turmeric would bind to antigen and/or antibody and thus inhibit their interaction. Such an intervention would be of therapeutic potential to prevent autoantibody targeting of cognate antigen to ameliorate autoimmune diseases.

Method: BSA or HeLa cell antigens were resolved by SDS PAGE and stained with heat-solubilized curcumin. Antibody/antigen (Ro60, Ro multiple antigenic peptide (MAP)-274 or human spectrin) was determined by ELISA in SLE/SS patients and a mouse model of SS in the absence or presence of heat-solubilized curcumin/turmeric. Surface plasmon resonance was used to determine binding of curcumin to Ro MAP 274antigen interaction as well as inhibition of autoantibody binding to specific antigens. Primary SS (n=20) and SLE (n=20) sera were used in this study along with age and sex matched controls. In addition sera were obtained from 5 mice each immunized with Ro 274 peptide (LQEMPLTALLRNLGKMT) or Freund's.

Results: Curcumin was found to interact significantly with proteins. Anti-Ro 60 antibodies or anti-Ro 274 peptide antibodies bound significantly ($p < 0.001$) to Ro 60 or Ro 274 MAPs compared to controls. Anti-Ro 60 binding to Ro 60 (in SS patients with significant anti-Ro 60 activity) was inhibited 24-43% (35 ± 5.8%; n=9) by curcumin. However the inhibition ranged from 26-74% in SS patients (58 ± 13.5%; n=9) when turmeric extract was used. In the case of SLE patients the range was 36-52% (43 ± 6.6; n=4) and 61-70% (65 ± 4) respectively when curcumin or turmeric respectively was used. Anti-Ro 274 mice sera bound significantly to Ro MAP 274 (p=000) compared to Freund's immunized. Curcumin inhibited binding of anti-Ro 274 antibodies to Ro MAP 274 by 35-50% (46 ± 8.9; n=5) while turmeric inhibited by 55 to 60% (58 ± 2.7%; n=5). Heat-solubilized curcumin/turmeric also inhibited binding of polyclonal anti-spectrin to spectrin by 50/56 % respectively.

Conclusion: Heat mediated curcumin and turmeric significantly inhibited the interaction of human anti-Ro 60, anti-Ro 274 or anti-spectrin peptide antibodies with respective cognate antigens. Turmeric inhibited better than curcumin. Curcumin/turmeric could prove useful as a therapeutic intervention in SS or SLE to minimize autoantibody/antigen interaction and reduce severity of disease manifestation.

Disclosure: B. T. Kurien, None; **A. Dsouza**, None; **R. H. Scofield**, None.

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Perturbations in B-Cell Homeostasis in Primary Sjögren's Syndrome. Mustimbo Roberts[1], Chungwen Wei[2], James Roger[3] and Iñaki Sanz[4], [1]University of Rochester, Rochester, NY, [2]University of Rochester, [3]University of Rochester School of Medicine and Dentistry, Rochester, NY, [4]University of Rochester School of Medicine and Dentistry., Rochester, NY

Purpose: To elucidate abnormalities in B cell homeostasis with pathophysiological and diagnostic implications for primary Sjogren's Syndrome (pSS). Multicolor flow cytometry was used in a cross-sectional analysis of patients that meet AECG criteria for the diagnosis of pSS as compared to patient with a clinical diagnosis of pSS and patients with sicca symptoms referred to our Rheumatology clinics for the evaluation of possible pSS. We also initiated longitudinal analysis to identify biomarker candidates that could be then validated for their predictive value for the development of full-blown pSS.

Method: B-cells from pSS (n=17), SLE (n=26), RA (n=26), healthy controls (n=24) and longitudinal pSS (n=11) patients were analyzed by multicolor flow cytometry for expression of CD24, CD27, CD38, IgD, B220, CXCR3 and CXCR5 in C19+ B cells.

Results: As reported by others, pSS patients feature decreased frequencies of switched memory (SM) (IgD-/CD27+) and unswitched memory (UM) (IgD+/CD27+) cells as compared to healthy controls (HC) ($p=0.0007$, $p=<0.0001$). In contrast CD27-/IgD- switched cells, a population we reported expanded in SLE, were significantly increased in pSS ($p=0.0142$). We also report that similar to SLE, there is a significant decrease of UM cells in pSS but not RA. Our use of multicolor flow cytometry revealed a relative expansion within the IgD-, CD27+ and CD27-, population of a novel B220+/CXCR3+/CXCR5- subset with a phenotype suggestive of effector B cells. Our preliminary data also indicate that the reported expansion of pre-GC cells (Bm2') may be explained partly by increased transitional B cells (CD24hi/CD38hi). Finally, longitudinal analyses indicate that a decrease in the frequency of UM cells may constitute a valuable indicator of clinical progression to pSS.

Conclusion: Our data provide greater understanding of B-cell homeostasis in pSS and identify more discreet memory subsets that might be implicated in the pathogenesis of the disease and serve as biomarkers for diagnosis and disease progression. The decrease in UM B-cells appears to be the earliest change in the progression to pSS and may bear substantial pathophysiological significance as equivalent marginal zone-like cells have been postulated to play protective roles against autoimmunity in animal models. The CXCR3+/CXCR5-/B220+ population of B-cells is hypothesized to represent effector B cells with enhanced ability to migrate to inflamed target tissues and contribute to disease. Our data suggest a model of clinical autoimmunity onset triggered by an imbalance of regulatory/effector B cell functions mediated by a decrease in regulatory B-cells which may represent an early biomarker in the development of pSS. The presented results also identify the expansion of new candidate effector B cells.

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Blocking LFA-1 with Efalizumab Promotes Inflammation, T Cell Activation and Autoimmunity in Primary Sjögren's Syndrome (pSS). Nikolay P. Nikolov[1], Kanneboyina Nagaraju[2], Svetlana Ghimbovschi[2], Maria Alba[1], Larissa Lapteva[3], David Kleiner[4], Janine Clayton[5], Ilias Alevizos[1], Margaret Grisius[1], Lolita Bebris[1] and Gabor G. Illei[6], [1]NIH/NIDCR, Bethesda, MD, [2]Children's National Medical Center, Washington, DC, [3]FDA, Silver Spring, MD, [4]NCI, Bethesda, MD, [5]NIH, Bethesda, MD, [6]NIDCR, NIH, Bethesda, MD

Purpose: The LFA-1/ICAM-1 interaction is important in lymphocyte migration to inflammatory sites, T cell activation and antigen presentation. In SS, activated lymphocytes have increased expression of LFA-1 whereas activated endothelial cells in the salivary and lacrimal glands have increased ICAM-1 expression. In this pilot study we evaluated the safety, clinical efficacy and biology of blocking this interaction in primary SS (pSS) subjects with weekly efalizumab (EFLZ) (1mg/kg), a recombinant humanized monoclonal antibody against the alpha subunit of LFA-1.

Method: The study had three phases (Table). Primary outcome was measured by objective improvement in salivary and lacrimal flows and minor salivary gland (MSG) inflammation (focus score) at the end of Phase 1. Gene expression was profiled from PBMC total RNA collected at baseline and at the end of the double blinded, open label and follow-up phases. Data were analyzed using GeneSpring GX and Ingenuity Pathways Analysis (IPA) software.

Results: After 9 pSS subjects were enrolled (Table) the study was terminated due to reports of fatal JC viral infection in psoriasis patients.

Table. Summary of study accrual and outcomes:

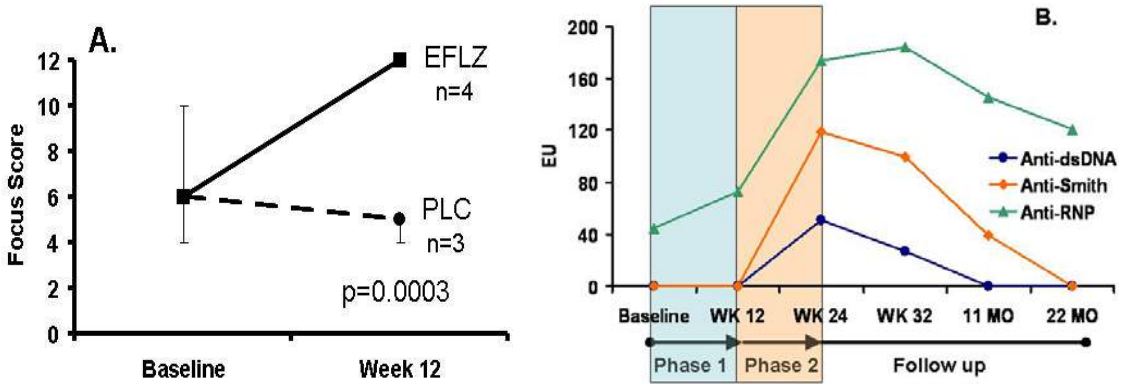
Phase 1 (Week 1-12), Randomized, Double Blinded, Placebo Controlled	**EFLZ , (n=6)**	**Placebo, (n=3)**
Gender	5 Females	All Females

Age, years (median, ±SD)	54 (±4)	54 (±14)
Completed Phase 1	4	3
Responded	0	1
Withdrawn, study terminated	1, Week 08	0
Withdrew, personal reasons	1, Week 09	1, Week 12
Phase 2 (Week 13-24), Open Label	**EFLZ , (n=4)**	**EFLZ , (n=2)**
Responded	0	0
Withdrawn, worsening of SS	1, Week 13	0
Withdrawn, worsening of SS and study termination	1, Week 21	0
Completed Phase 2	2	2

Phase 3 (Week 25-32), Follow up

Repeat MSG biopsy at the end of Phase 1 showed significant increase in inflammation in EFLZ treated subjects (Figure A). Two subjects developed anti-dsDNA antibodies (Abs) during EFLZ treatment one of whom developed multiple auto-Abs and lupus like syndrome which resolved after EFLZ discontinuation (Figure B). Serum Immunoglobulins (IgG) increased significantly in 3 subjects, 2 developed IgG monoclonality and one oligoclonality.

Figure. EFLZ-induced exacerbation of MSG inflammation (A) and de novo auto-antibody secretion (B)



GeneSpring analysis showed 582 genes significantly differentially expressed after EFLZ treatment. IPA identified CD86-CTLA4, IL-2 and Wnt/Beta-catenin signaling pathways to be the most significantly altered in EFLZ treated subjects.

Conclusion: EFLZ exacerbates SS and induces significant increase in local inflammation and systemic autoimmunity. The gene expression data suggest that hyperactivation of peripheral T cells may be responsible for the systemic B cell activation and auto-Abs generation. Further studies may elucidate how inhibition of LFA-1/ICAM-1 signaling drives this profound immune system perturbation.

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Differential Expression of MicroRNAs Not Related to Inflammation in Minor Salivary Glands of Primary Sjögren's Syndrome Identify Novel Pathogenesis Related Pathways. Ilias Alevizos[1], Siddhartha Bajracharya[2], Roy J. Turner[3] and Gabor G. Illei[2], [1]NIH/NIDCR, Bethesda, MD, [2]NIDCR, NIH, Bethesda, MD, [3]Bethesda, MD

Purpose: The etiology of salivary gland dysfunction (SGDF) in Sjögren's syndrome (SS) is poorly understood but most likely includes both inflammatory and non-inflammatory mechanisms. It is likely, that changes in the regulation of gene expression may also play a role. MicroRNAs (miRNAs), are master regulators of gene expression. They exert their effects by mRNA degradation and inhibition of translation. A single miRNA is capable of regulating the translation of a multitude of genes involved in certain functions. We hypothesized that miRNA patterns, which are different from healthy controls but do not correlate with inflammation may identify potentially pathogenic processes underlying SGDF.

Methods: Minor salivary gland (MSG) microRNA expression profiles were compared between healthy volunteers (n=8) and primary SS patients (n=16) with minimal (n=8, focus score 1 or 2) or extensive inflammation (n=8, focus score 12). Half of the patients in both pSS groups had preserved and half had decreased salivary flow. MicroRNA expression profiles of minor salivary glands were generated using Agilent microarrays. We developed a novel method to normalize the array data by identifying a set of housekeeping miRNAs. We used validated and bioinfomatically predicted mRNA targets to identify networks and pathways altered by the differential expression of the microRNAs with the Ingenuity Pathway Analysis software.

Results: We identified 30 miRNAS which were overexpressed in the entire SS cohort compared to controls but did not correlate with inflammation. To test if they targeted pathways that are related to non-immunologic aspects of the disease process we used the Ingenuity Pathway Analysis to predict the networks and pathways they might be targeting. Because each microRNA has potentially hundreds of mRNA targets, to reduce the chance identification of pathways that may result from the multiple predicted targets of each microRNA, we only included those predicted mRNAs which were targeted by at least 25% of miRNAS. Pathway analysis identified 20 statistically significant canonical pathways. The six most significant ($p<0.01$) included FGF signaling, pathways related to signaling in neurons (ephrin receptor signaling, reelin signaling in neurons), O-glycan biosynthesis, T cell receptor signaling and proteasomal degradation (PTEN signaling).

Conclusion: Pathway analyis of differentially expressed microRNAs not related to inflammation in MSG of SS patients predicted target pathways related to neurogenesis, FGF signaling and lysosome degradation as the top targets of microRNAs. These pathways may play an important role in the pathogenesis of SS.

Disclosure: I. Alevizos, None; **S. Bajracharya**, None; **R. J. Turner**, None; **G. G. Illei**, None.

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MicroRNA Differential Expression in Minor Salivary Glands of Primary Sjögren's Syndrome with High Focus Scores and Normal or Decreased Function Identifies Altered Salivary Gland Function Related Pathways. Ilias Alevizos[1], Siddhartha Bajracharya[2], Roy J. Turner[3] and Gabor G. Illei[2], [1]NIH/NIDCR, Bethesda, MD, [2]NIDCR, NIH, Bethesda, MD, [3]Bethesda, MD

Purpose: Salivary gland dysfunction in Sjögren's syndrome (SS) is poorly understood as it is not always associated with structural damage of the salivary gland parenchyma by lymphocytes. It is likely, that changes in the regulation of gene expression in the lymphocytic infiltrate may also play a role. MicroRNAs (miRNAs), are master regulators of gene expression. They exert their effects by mRNA degradation and inhibition of translation. A single miRNA is capable of regulating the translation of a multitude of genes involved in certain functions. We hypothesized that miRNA expression differences exist between the functional and non-functional minor salivary glands with very high focus score (FS of 12) and that those differences can reveal differences in the type of infiltrating cells

Methods: Eight minor salivary glands from primary Sjögren's syndrome patients with high focus score were used for this study. Half of the patients had normal and half had decreased salivary flow. microRNA expression profiles of minor salivary glands were generated using Agilent microarrays. We developed a novel method of normalizing microRNA microarrays by generating minor salivary gland specific housekeeping miRNAs.. We used validated and bioinfomatically predicted mRNA targets to identify networks and pathways altered by the differential expression of the microRNAs with the Ingenuity Pathway Analysis software.

Results: We identified 21 miRNAs upregulated in the samples with normal salivary flow. Using Targetscan we identified the predicted mRNA targets of those miRNAs and kept only the mRNAs that are targeted by 7 or more of the miRNAs. The list of those genes was then

explored with the Ingenuity Pathway Analysis software and revealed 28 statistically significant pathways. The top 5 of those pathways are: PPARα/RXRα Activation, Glycosphingolipid Biosynthesis – Neolactoseries, Aldosterone Signaling in Epithelial Cells and Clathrin-mediated Endocytosis.

Equally important was the discovery that three of the 21 microRNAs, namely hsa-mir-18a, hsa-mir-19a and hsa-mir-19b, belong to the mir-17-92 cluster which has been associated with specific types of lymphocytes and lymphocytic pathologies. More specifically, decrease of the mir-17-92 has been associated with accumulation of pro-B cells with a marked reduction of pre-B and more mature B cells, and overexpression of it has been linked to lymphoproliferative disease and autoimmunity.

Conclusion: MicroRNA expression differences between MSGs with high focus score suggest that qualitative rather than quantitative differences in the infiltrating lymphocytes are associated with loss of function. Further exploration of the pathways associated with decreased salivary flow will provide insight in the pathophysiology of SS and may identify novel therapeutic targets.

Disclosure: I. Alevizos, None; **S. Bajracharya**, None; **R. J. Turner**, None; **G. G. Illei**, None.

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Aquaporin Expression in Interstitial Lung Diseases Related to Sjögren Syndrome. Carmen Navarro[1], Alfonso Salgado[2], Miguel Gaxiola[3], Mayra Mejia[3] and Moises Selman[3], [1]National Institute of Respiratory Diseases, Mexico City, Mexico, [2]National Institute of Respiratory Diseases, [3]National Institute of Respiratory Diseases, Mexico

Purpose: Aquaporins (AQP) are molecular water channels expressed in many epithelia and endothelia involved in fluid transport, such salival and lacrimal gland or lung. It has been shown down-regulation of AQP in salivary glands in patients with Sjögren´s syndrome (SS) and altered expression on lacrimal gland in animal models of the disease suggesting AQP may play a crucial role in the pathology and clinical manifestations of the disease. To assess abnormalities in the expression of AQP in lung tissue of SS patients who develop interstitial lung disease (ILD).

Method: We analyzed 7 lung biopsy obtained with diagnosis proposal from SS patients who develop ILD. Pattern of AQP 1, 4 and 5 mRNA expression in both, total lung tissue and epithelial cells obtained by laser captured microdissection, were examined by quantitative real-time PCR. We used RNA from normal lung commercial available (StratageneÒ, ClontechÒ, AmbionÒ) as control group.

AQP localization in lung tissue was evaluated by standard immunohistochemistry using antibodies commercial available (Santacruz Ò). Clinical data were collected from clinical charts.

Results: The data we have obtained showed that 5 of the 7 SS-ILD patients had lower expression of AQP-1 than the average expression in the control group; 6 of the 7 SS-ILD patients had lower expression of AQP-4 than the control group; and all the patients had higher expression of AQP-5 than the control group. Similar results were found on the mRNA obtained from epithelial cells and total lung tissue. Localization of AQP-1 and AQP-4 were similar to normal tissue. However expression of AQP-5 was diminished compared with normal tissue.

Conclusion: Expression of AQP is modified in lung parenchyma of SS patients who develop interstitial lung diseases. Although the full implications of these findings remain to be determined, may be AQP could be involved in the lung damage of SS patients.

Disclosure: C. Navarro, None; **A. Salgado**, None; **M. Gaxiola**, None; **M. Mejia**, None; **M. Selman**, None.

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Anti-Aquaporin-4 Antibodies Are Highly Specific for Neuromyelitis Optica and Show No Association with Sjögren's Syndrome and Other Autoimmune Diseases. Alessandra Dellavance[1], Rossana R. Alvarenga[2], Silvia H. Rodrigues[2], Fernando Kok[3], Alexandre W. S. Souza[2] and Luis Eduardo C. Andrade[2], [1]Fleury Health and Medicine, São Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [3]Universidade de Sao Paulo, Sao Paulo, Brazil

Purpose: Neuromyelitis optica (NMO; Devic's syndrome) is a severe CNS demyelinating syndrome characterized by optic neuritis (ON) and acute myelitis. Anti-aquaporin 4 antibodies have been recently reported as a biomarker for NMO with specificity over 90% in patients with optic-spinal syndrome and other demyelinating conditions. The specificity of anti-aquaporin 4 antibodies for NMO has not been tested

against a wider spectrum of systemic autoimmune diseases but a recent report has suggested that patients with Sjögren's syndrome may present anti-aquaporin 4 antibodies. Therefore we set to screen anti-aquaporin 4 antibodies in a wide clinical spectrum of systemic and organ-specific autoimmune diseases, demyelinating neurological diseases and infectious diseases.

Method: Serum was obtained from patients regularly followed at specialized outpatient clinics at Federal and State University of São Paulo, Brazil: 37 with NMO, 22 with other demyelinating conditions, 28 with primary Sjögren's syndrome, 32 with rheumatoid arthritis, 80 with systemic lupus erythematosus, 38 with systemic sclerosis, 40 with myasthenia gravis, 37 with primary biliary cirrhosis, 23 with hepatitis C virus, 12 with miscellaneous infectious disease (CMV, dengue, herpes simplex), and 200 samples from patients from the general outpatient clinic without any suspicion of neurological disease. IgG anti-aquaporin 4 antibodies were determined by indirect immunofluorescence on rat cerebellum at a screening dilution of 1/10 as previously established (Lennon VA et al, JEM 2005, 202:473). Slides were read by two blinded independent observers at x200 and x400 magnification.

Results: The characteristic staining pattern of anti-aquaporin 4 antibodies was observed in 30 of 37 samples from patients with neuromyelitis optica (81% sensitivity) and in none of 549 samples not related to this disease (100% specificity). Detailed clinical data was available for 15 patients with documented primary Sjögren's syndrome and revealed neurologic involvement in 4 of them. Peripheral polyneuropathy occurred in two and cranial neuropathy in two other patients. No patient had central nervous system involvement. Cutaneous small vessel vasculitis was observed in two patients and in one of them it was associated with cryoglobulinemia.

Conclusion: Anti-aquaporin 4 antibodies are highly specific for the diagnosis of NMO in the context of several autoimmune and infectious diseases. There was no association of anti-aquaporin 4 antibodies with neurological manifestations in Sjögren's syndrome.

Disclosure: A. Dellavance, None; **R. R. Alvarenga**, None; **S. H. Rodrigues**, None; **F. Kok**, None; **A. W. S. Souza**, None; **L. E. C. Andrade**, None.

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Clinical, Radiographic, and Autoantibody Features Are Associated with Distinct Patterns of Demyelinating Syndromes in Sjögren's Patients. Julius Birnbaum, Douglas Kerr and Alan N. Baer, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Demyelination in the Central Nervous System (CNS) can be a severe neurologic manifestation of Sjögren's syndrome. In recent years, "idiopathic" demyelinating syndromes (i.e. Multiple Sclerosis versus Neuromyelitis Optica/NMO) are increasingly recognized as heterogeneous entities, which exhibit distinct demographic, clinical, radiographic, and autoantibody patterns. We sought to characterize whether the demyelinating syndromes in Sjögren's may similarly exhibit distinct clinical and radiographic features, and to characterize the autoantibody patterns in these CNS demyelinating syndromes.

Method: We reviewed the medical records of 157 consecutive patients with Sjögren's syndrome, presenting for evaluation between January, 2002 and May 2009. Demyelinating attacks required both symptoms and exams suggestive of a clinically relevant lesion, with evidence of demyelination on spine or brain MRI neuroimaging.We investigated whether demyelinating episodes satisfied revised diagnostic criteria for Neuromyelitis Optica/NMO, the Neuromyelitis Optica-Spectrum of Syndromes (NMOS), or had multifocal brain lesions similar to Multiple Sclerosis.

Results: Of 157 patients, 25 experienced CNS demyelinating syndromes. Patients with demyelinating syndromes reported earlier onset of sicca symptoms (mean 39.7 years, compared to 47.3 years, $p<0.01$). Sjögren's patients with demyelinating attacks, were also younger at time of first flare, compared to Sjögren's patients experiencing other neurologic syndromes (mean of 38.8 years, versus 48.3 years $p<0.01$).

Two patients satisfied diagnostic criteria for NMO; 7 patients satisfied suggested criteria for NMOS, having recurrent myelitis attacks without optic neuritis, but with inflammation on spinal cord MRI spanning at least 3 vertebral segments. Seven of the nine patients (77%) with NMO/NMOS were seropositive for the NMO-IgG autoantibody. Sixteen patients had symptomatic and/or radiographic multifocal brain disease which was phenotypically similar to Multiple Sclerosis. Patients with demyelinating episodes had a non-statistically higher seroprevalence of anti-Ro antibodies (75% versus 64%, $p=0.35$), but a lower seroprevalence of anti-La antibodies (17% versus 37%, $p=0.06$)

Conclusion: Demyelinating syndromes in Sjögren's syndrome are clinically and radiographically heterogeneous syndromes, which can be distinguished as being more similar to NMO/NMOS versus MS. Patients with demyelinating syndromes are younger, and are more likely to have an autoantibody profile showing isolated SS-A positivity with SS-B negativity

Disclosure: J. Birnbaum, None; **D. Kerr**, None; **A. N. Baer**, None.

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Effect of Rituximab Treatment On Cytokine/ Chemokine Profile in Patients with Primary Sjögren's Syndrome. R.P.E. Pollard, W.H. Abdulahad, J.M. Meijer, M.G. Huitema, F.K.L. Spijkervet, C.G.M. Kallenberg, A. Vissink and H. Bootsma, University Medical Center Groningen, Groningen, Netherlands

Purpose: To assess the effect of rituximab (anti-CD20) treatment on the cytokines/ chemokines profile in patients with primary Sjögren's syndrome (pSS)**.**

Method: In a randomised double-blinded placebo-controlled trial patients were treated on days 1 and 15 with either rituximab (n= 20) or placebo (n= 10). Fresh blood samples were collected at various time points (before, 5, 12, 36 and 48 weeks following treatment). In addition, age- and sex-matched blood samples were collected from healthy controls (n=10). B and T-cells were examined by four-color cytometry. A multiplex-25 bead array cytokine assay was used enabling simultaneous measurement of (1) proinflammatory cytokines (GM-CSF, IL-1β, IL-1RA, IL-6, IL-8, TNF-α); (2) Th1/Th2 distinguishing cytokines (IFN-γ, IL-2, IL-2R, IL-4, IL-5, IL-10); (3) nonspecific acting cytokines (IFN-α, IL-7, IL-12p40/p70, IL-13, IL-15, IL-17); and (4) chemokines (Eotaxin, IP-10, MCP-1, MIP-1α, MIP-1β, MIG, RANTES).

Results: Depletion of B-cells was observed in the rituximab treated group after first infusion, while B-cell levels remained unchanged after placebo treatment. The B-cells reappeared in the rituximab treated group within 24 to 48 weeks after treatment. Regarding CD4+ and CD8+ T cells no changes were observed between the rituximab and placebo treated patients at all time points. When compared to healthy controls, except for IL-8 and IFN- γ, an increase was seen in the levels of the other cytokines at baseline. After rituximab treatment, a decrease and subsequent (partial) recovery within 24 to 48 weeks was observed for IL-1β, IL-1RA, IL-2R, IL-4, IL-5, IL12, IL-15, IL-17, TNF-α, GM-CSF, MIP-1α, MIP-1β, MIG, Eotaxin, MCP-1. As compared to placebo, the most striking early decrease was observed in IL-10 levels.

Conclusion: These preliminary data show a variation in cytokine/ chemokine profile before and after rituximab therapy in conjunction with a depletion and reappearance of B-cells. Related to the observed changes in cytokine profiles, specific cytokines are noted that may play a role in pathogenesis of pSS. This observation will be correlated with clinical data. Extended data are in progress.

Disclosure: R. P. E. Pollard, None; **W. H. Abdulahad**, None; **J. M. Meijer**, None; **M. G. Huitema**, None; **F. K. L. Spijkervet**, None; **C. G. M. Kallenberg**, None; **A. Vissink**, None; **H. Bootsma**, None.

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Peripheral Neuropathy Is An Uncommon Cause of Neuropathic Symptoms in Sjögren's Patients. Julius Birnbaum, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Sjögren's patients frequently describe sensory symptoms, ranging from numbness to excruciating, lancinating pain. Different cohorts have reported discrepant rates of peripheral neuropathy in Sjogren's syndrome, ranging from 3 to 60 percent. We sought to understand the frequency of sensory symptoms in Sjogren's patients, the attribution of these symptoms to peripheral neuropathies, and to understand the autoantibody patterns of Sjogren's patients with sensory symptoms and peripheral neuropathies

Method: We reviewed the medical records of 157 patients presenting with Sjogren's syndrome. We considered the patients as having neuropathic symptoms if they complained of numbness, or other sensory descriptors contained in the LANSS neuropathy questionnaire. Patients were considered as having neuropathic pain if they satisfied the 2007 consensus redefinition for neuropathic pain, which requires pain in a plausible neuroanatomic distribution; a potential history of a CNS or PNS cause of such neuropathic pain; and confirmation (either by neurologic exam, or other corroborating studies) of both topographic distribution and cause of neuropathic pain.

Results: A considerable number of Sjögren's patients (55%, 86/157) had neuropathic symptoms. However, of these 86 patients with sensory symptoms, a diagnosis of neuropathic pain was only achieved in 66% (57/86) patients. In Sjögren's patients with neuropathic symptoms, only 21% (18/86) had peripheral neuropathies: CNS structural disease (i.e. cervical spondylosis) and demyelinating syndromes were causes of neuropathic symptoms in 16% (14/86) and 29% (25/86) of patients. Seropositivity to anti-La was seen less commonly in Sjögren's patients with neuropathic symptoms (24% versus 43%, OR=.41 [95% CI [0.20, 0.83], p=0.02) There was no difference in seropositivity for SS-A, comparing Sjögren's patients without versus having neuropathic symptoms (63% versus 70%)

Conclusion: A considerable number of Sjogren's patients with neuropathic symptoms, will not have plausible CNS or PNS identifiable etiologies allowing the diagnosis of neuropathic pain. Only a minority of Sjogren's patients with neuropathic symptoms will have a neuropathy. The lower seroprevalence of anti-La antibodies in Sjogren's patients with neuropathic symptoms suggests that immunologic mechanisms may modulate the perception of neuropathic pain in Sjogren's patients.

Disclosure: J. Birnbaum, None.

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B-Cell Reconstitution and T-Cell Balance After Rituximab Treatment of Active Primary Sjögren's Syndrome. Wayel H. Abdulahad[1], Jiska Meijer[1], Rodney Pollard[1], F.K.L. Spijkervet[1], C.G.M. Kallenberg[1], A. Vissink[1], Frans Kroese[2] and Hendrika Bootsma[1], [1]University Medical Center Groningen, Groningen, Netherlands, [2]Groningen, Netherlands

Purpose: To analyze the phenotype and the state of activation of reconstituting B-cells after B-cell depletion, and to assess the effect of reconstitution on regulatory (T_{Reg}) and effector (T_{eff}) T-cell numbers in patients with active primary Sjögren's syndrome (pSS).

Method: Twenty-nine patients with pSS were treated on days 1 and 15 with either rituximab (RTX, n=20) or placebo (PLC, n=9). B-cell numbers and phenotypes were examined in fresh blood samples by four-color cytometry at baseline and at 5, 12, 24, 36, and 48 weeks after infusions. The distribution of plasma cell/blast ($CD38^{High}CD27^{High}CD19^{+}$), post-switches memory ($IgD^{-}IgM^{-}CD27^{+}CD19^{+}$), pre-switches memory ($IgD^{+}IgM^{+}CD27^{+}CD19^{+}$), naïve ($CD38^{-/Low}CD27^{-}$), and transitional ($CD38^{High}CD27^{-}$) B-cells subsets were examined. In addition, numbers of both T_{Reg} cells ($CD3^{+}CD4^{+}CD25^{High}CD127^{-}$) and T_{eff} cells ($CD3^{+}CD4^{+}CD25^{+}CD127^{+}$) were also analyzed at all time points.

Results: At baseline, patients with pSS displayed several abnormalities in B-cell homeostasis, including a significant reduction of pre-switched memory B-cells and expansion of immature- and mature naïve B-cells, compared with healthy controls (n=10). Following RTX-treatment (at week 48), a majority of emerging B-cells revealed a phenotype of transitional B-cells. Although the recovery of memory B-cells was delayed, a significant increase in post-switched and a significant decrease in pre-switched memory B-cells was observed in post-RTX when compared with pre-RTX and post-PLC. Remarkably, no significant differences in the percentages of plasma cells were found at 48 weeks compared to pre-RX-treatment. Furthermore, percentages and absolute counts of T_{Reg} and T_{eff} cells, as well as T_{Reg}:T_{eff} ratios, showed no significant changes after RTX compared to baseline.

Conclusion: B-cell reconstitution after RTX-treatment starts with transitional B-cells followed by post-switched memory B-cells that probably include autoreactive B-cells. RTX-treatment did not alter the numbers of circulating T_{Reg} and T_{eff} cells.

Disclosure: W. H. Abdulahad, None; **J. Meijer**, None; **R. Pollard**, None; **F. K. L. Spijkervet**, None; **C. G. M. Kallenberg**, None; **A. Vissink**, None; **F. Kroese**, None; **H. Bootsma**, None.

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Associatioin of Primary and Secondary Sjögren's Syndrome in Lupus Families. Rachna Aggarwal[1] and R. Hal Scofield[2], [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, University of Oklahoma HSC, Dept Veterans Affaris Med Cnt, Oklahoma City, OK

Purpose: Systemic lupus erythematosus (SLE) and Sjögren's syndrome are closely related diseases, but the relationship of primary and secondary Sjögren's syndrome within families with SLE is not known. We undertook this study to determine whether primary Sjögren's syndrome is increased among SLE-unaffected, and whether primary and secondary Sjögren's syndrome are associated within families with SLE.

Methods: Families were collected through the Lupus Family Registry and Repository. All SLE patients met the 1982 revised classification criteria for SLE, and all families had at least one member with SLE.. All subjects completed a standardized questionnaire, and had autoantibodies determined by ELISA and double immunodiffusion. Sjögren's syndrome was considered present when subjects met the combined US-European Sjögren's classification criteria for dry mouth as well as dry eyes and had anti-Ro (or SSA).

Results: Among a total of 2537 SLE patients, there were 505 (19.9%) SLE patients with secondary Sjögren's syndrome. There were 65 SLE-unaffected relatives of SLE patients who had primary Sjögren's syndrome, while none of 1304 age and sex matched healthy controls

had Sjögren's ($\chi 2$=12.7, p=0.02). Seventeen (26.2%) of the 65 subjects with primary Sjögren's had an SLE-affected relative with secondary Sjögren's syndrome, compared to 493 (7.1%) of 6922 SLE-unaffected family members without primary Sjögren's ($\chi 2$=34.8, p<0.00001, odds ratio=5.0).

Conclusion: We find that primary Sjögren's is found among relatives of SLE patients statistically more often than in healthy controls. Furthermore, within these SLE families primary Sjögren's syndrome in SLE-unaffected members was associated with secondary Sjögren's. That is, there was a familial distribution of primary and secondary Sjögren's. Primary Sjögren's affected family members were about 5 times more likely to have an SLE-affected relative with secondary Sjögren's than family members without primary Sjögren's. These data suggest common susceptibility factors, possibly genetic, for primary and secondary Sjögren's syndrome.

Disclosure: R. Aggarwal, None; **R. H. Scofield**, None.

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Memory T Cells Require the Continuous Presence of B Cells in a Mouse Model of Sjögren's Syndrome. Yongmei Li[1], Robert Dunn[2], Marilyn R. Kehry[2], Jennifer Resling[1], Ammon B. Peck[3], Robert A. Eisenberg[4] and Philip L. Cohen[1], [1]Temple University, Philadelphia, PA, [2]Biogen Idec, San Diego, CA, [3]University of Florida College of Dentistry, Gainesville, FL, [4]University of Pennsylvania, Philadelphia, PA

Purpose: To use B-cell depletion with a monoclonal anti-mouse CD20 as a tool to understand the mechanism of T-cell activation in C57BL/6.NOD.Aec1Aec2 (AEC) mice, which spontaneously develop Sjögren's syndrome.

Method: Splenic B and T cell subsets were analyzed in B-cell depleted and untreated 10 week, 16 week and 14 month-old AEC mice and B6 controls.

Results: We found expanded numbers of CD3+ T cells in spleens of AEC mice starting at 10 wk of age, mostly reflecting an increase in CD4+ memory T cells ($CD62L^{lo}$ $CD44^{hi}$). Na•ve and activated CD4+ subsets, as well as CD8 T cells, were not different between AEC and B6 controls. B-cell numbers were initially lower in AEC mice at 10 wk of age but became comparable to B6 controls at 16 wks of age. To investigate the role of B cells in this accumulation of CD4+ memory T cells, we depleted B cells in 9-12 month old AEC females by injecting i.p. anti-mouse CD20 (0.25mg, clone 18B12 IgG2ak, weekly, for three or four weeks). In two separate experiments, anti-mCD20 significantly reduced peripheral blood B cells, and splenic follicular, marginal zone B cells, as well as spontaneous IgM- and IgG-antibody forming B cells. Anti-mCD20-treated AEC mice also had significantly reduced numbers of CD4+ memory T cells (46% reduction, p=0.025) compared to mice treated with control antibodies or PBS. Other T-cell subsets were unaffected.

Conclusion: Our findings suggest that the proliferation of a substantial number of CD4+ memory T cells is dependent on the continuous presence of B cells. The perpetuation of a T-cell immune response, which seems to be of critical importance in mediating SS tissue damage, may require B-cell presentation of autoantigens and/or B-cell derived cytokines. These studies provide an experimental framework for ongoing trials of B-cell depletion in human SS.

Disclosure: Y. Li, None; **R. Dunn**, Biogen Idec, 3 ; **M. R. Kehry**, Biogen Idec, Inc., 3 ; **J. Resling**, None; **A. B. Peck**, None; **R. A. Eisenberg**, None; **P. L. Cohen**, None.

ACR Poster Session A

Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment I

Sunday, October 18, 2009, 9:00 AM - 6:00 PM

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Comparison of RAPID3, BASDAI and BASFI in Ankylosing Spondylitis Patients in Routine Care: RAPID3, Composed of Patient Measures Only, Is Strongly Correlated with BASDAI and BASFI. Duygu Kurtulus[1], Cengiz Bahadir[1], C.J. Swearingen[2] and Yusuf Yazici[3], [1]Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, [2]MUSC, Charleston, SC, [3]NYU Hospital for Joint Diseases, New York, NY

Purpose: The Bath ankylosing spondylitis disease activity index (BASDAI) and Bath AS Function Index (BASFI) were developed as outcome measures to assess and monitor patients with ankylosing spondylitis (AS). Although widely used in clinical trials and other clinical research, these questionnaires are not commonly used in routine clinical care. It is complex to distribute multiple questionnaires to different patients in a reception area. A single questionnaire for all patients with rheumatic diseases may present advantages to introduce quantitative measurement into routine care. A multidimensional health assessment questionnaire (MDHAQ) has been developed to be used as part of the infrastructure of routine care and has been used in the clinics of the senior author for close to 10 years in every patient with any diagnosis. Routine assessment of patient index data 3 (RAPID3) is a composite index based on 3 MDHAQ components, patient function, pain and patient global assessment, each scored 0-10 for a total of 0-30. The MDHAQ has been shown to be useful in RA, OA, fibromyalgia and Behçet's syndrome.

Method: Consecutive AS patients seen at Haydarpasa Numune Training and Research Hospital, Physical Medicine and Rehabilitation Outpatient Clinic in Istanbul, Turkey, between May 18 and June15, 2009 were enrolled. All patients completed a BASDAI (score range 0-10), BASFI (score range 0-10) and MDHAQ and had medical records reviewed for additional demographic information, disease characteristics, medication use and selected laboratory test results. Spearman correlations were computed for components of MDHAQ and RAPID3 (score range 0-30) with BASDAI and BASFI.

Results: 51 AS patients were assessed (mean (SD) age:30 (10.9) 69% male, disease duration: 5.0 (6.7) years). Mean scores for BASDAI, BASFI and RAPID3 were 4.9 (2.5), 3.6 (2.5) and 12.9 (7.0), respectively. RAPID3 was strongly correlated with BASDAI and BASFI (r:0.77, and 0.72, $p<0.001$). Individual components of the MDHAQ (pain r:0.72, 0.6) patient's global assessment (r:0.8, 0.65), function (r:0.5, r:0.73), MD global assessment (r:0.7, r:0.76) and fatigue (r:0.62, r: 0.53) (all $p<0.01$), were also correlated significantly with both BASDAI and BASFI, respectively.

Conclusion: RAPID3, on an MDHAQ was strongly correlated with the outcome measures of BASDAI and BASFI in AS patients. Additional measures in the MDHAQ were also correlated. This extends findings that an index of patient measures, RAPID3, may provide a user-friendly index and an effective measure in clinical care of individual patients with AS.

Disclosure: D. Kurtulus, None; **C. Bahadir**, None; **C. J. Swearingen**, None; **Y. Yazici**, BMS, Celgene, Centocor, Genentech, Roche, UCB, 5, BMS, Pfizer, 8 .

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Maintained Clinical Response of Infliximab Treatment in Ankylosing Spondylitis: A 6-Year Long-Term Study. Ioanna Saougou[1], Theodora E. Markatseli[1], Paraskevi V. Voulgari[2], Niki Tsifetaki[2], Evripidis Kaltsonoudis[2] and Alexandros A. Drosos[3], [1]Trainee in Rheumatology, Ioannina, Greece, [2]Assistant Professor of Rheumatology, Ioannina, Greece, [3]Ioannina Medical School, Ioannina, Greece

Purpose: To investigate the efficacy, safety and drug discontinuation in patients with ankylosing spondylitis (AS) treated with infliximab, as well as the drug survival over a period of 6 years.

Method: Forty patients with AS treated with infliximab were included in this prospective, open label study. All patients fulfilled the New York revised criteria for AS. Infliximab was given intravenously (5 mg/kg/body weight) at weeks 0, 2, 6 and every 8 weeks thereafter for a period of 6 years. Data concerning infliximab efficacy, tolerability, adverse events and drug discontinuation, were recorded. Clinical improvement according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50% and the Ankylosing Spondylitis Assessment Study Group (ASAS) 20% and 40% were also recorded.

Results: A significant improvement in the BASDAI and ASAS scores was noted in the first year which sustained through the sixth year of treatment. More specifically, after the sixth year of treatment, BASDAI 50% was achieved by 65% of patients (26/40), ASAS 20% by 72.5% (29/40) and ASAS 40% was reached by 70% (28/40) of patients. Clinical improvement was associated with the reduction of acute phase reactants, such as C-reactive protein levels. After the first and the second year of treatment, the survival rate of infliximab reached 95%, after the third year it was 80%, while after the fourth year it was 72.5%, which was maintained throughout the fifth and sixth year of therapy. Five patients were increased the dose of infliximab and 3 of them had shortened the interval infusion. Overall, 11 patients were withdrawn during the observational period, 3 because of adverse events, 2 because of lack of efficacy, while 6 were lost from follow-up.

Conclusion: Infliximab was effective, safe and well-tolerated in patients with AS. The clinical response was maintained for a period of six years, with high infliximab survival rate, reaching the percentage of 72.5% .

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Golimumab, ANew, Human, TNF Alpha Antibody, Administered Subcutaneously Every 4 Weeks in Psoriatic Arthritis Patients: 104-Week Efficacy and Safety Results of the Randomized, Placebo-Controlled GO-REVEAL Study. A. Kavanaugh[1], P. Mease[2], G.G. Krueger[3], D. Gladman[4], J. Zrubek[5], A. Beutler[5], B. Hsu[5], S. Mudivarthy[5], M. Mack[5] and Iain B. McInnes[6], [1]UCSD, San Diego, CA, [2]Swedish Med Ctr/U of Washington, Seattle, WA, [3]U of Utah Hlth Sciences Ctr, Salt Lake City, UT, [4]The Toronto Western Hosp., Toronto, ON, [5]Centocor R&D, Inc, Malvern, PA, [6]University of Glasgow, Glasgow, United Kingdom

Purpose: To assess long-term efficacy & safety of golimumab (GLM) in active PsA.

Methods: PsA pts with ≥3 swollen and ≥3 tender joints and psoriasis were randomized to SC PBO or GLM (50 or 100 mg) q4wks. At wk 16, pts with inadequate arthritis response entered early escape (EE). All pts received GLM from wk 24. Investigators could dose-escalate pts receiving GLM 50 mg to 100 mg based on clinical judgement after all pts reached wk 52. The results for pts who remained on the same dose of GLM 50 to 100 mg are described. Analyses were based on observed data.

Results: 405 pts with active PsA were randomized (113 PBO, 146 GLM 50 mg, 146 GLM 100 mg). GLM was significantly better than PBO in improving signs and symptoms of PsA at wk 24, and GLM efficacy was maintained through wk 52.Through wk 104, pts continuing on the same dose of GLM 50 or 100 mg maintained high levels of response. GLM 50 mg pts who switched to 100 mg in EE or via dose escalation also achieved clinically meaningful responses (Table). 8.6% (34/394) of GLM-treated pts experienced SAEs through wk 104. Injection site reactions occurred in 8.9% (35/394) of pts. There was 1 case of histoplasmosis in a pt (GLM 100 mg) that was successfully treated. Malignancies reported through wk 104 include basal cell skin (1 pt), colon (1 pt), and small cell lung cancer (1 pt) in pts receiving GLM 50 mg, and basal cell skin (3 pts), prostate (1 pt), and small cell lung cancer (1 pt; fatal) in pts receiving GLM 100 mg. An additional pt died due to a climbing accident (GLM 50 mg).

Table:

Summary of efficacy in GO-REVEAL through wk 104

	GLM 50mg only[1]	**GLM 50 ≥100mg[2]**	**GLM 100mg only[3]**
Wk 52 ACR20	80/102(78.4%)	11/26(42.3%)	93/115(80.9%)
HAQ score, mean (SD) improvement	n=100, 0.49 (0.55)	n=26, 0.20(0.49)	n=113, 0.50 (0.54)
ACR50	58/102(56.9%)	7/26(26.9%)	68/115(59.1%)
ACR70	44/102(43.1%)	3/26(11.5%)	41/115(35.7%)
PASI75[4]	44/71(62.0%)	17/23(73.9%)	60/86(69.8%)
Wk 104 ACR20	64/70 (91.4%)	43/76 (56.6%)	95/130 (73.1%)
HAQ score, mean(SD) improvement	n=69, 0.54 (0.55)	n=76, 0.36 (0.57)	n=127, 046 (0.57)
ACR50	46/70 (65.7%)	27/76 (35.5%)	70/130 (53.8%)

ACR70	31/70 (44.3%)	17/76(22.4%)	48/130(36.9%)
PASI75	33/48 (68.8%)	35/56 (62.5%)	73/96 (76.0%)

[1] *Includes pts randomized to GLM 50mg and did not change dose;* [2] *Includes pts on PBO at baseline who entered EE or crossed over to GLM 50mg and later dose escalated to GLM 100mg and pts randomized to GLM 50mg who entered EE or dose escalated to GLM 100mg;* [3]*Includes pts randomized to GLM100 mg and did not change dose;* [4]*Among pts with ≥3% body surface area psoriasis involvement at baseline.*

Conclusion: Pts with active PsA treated with GLM 50 and 100mg SC q4 wks maintained high levels of improvement through wk 104. GLM was generally well-tolerated, with a safety profile similar to that observed for other anti-TNF agents.

Disclosure: A. Kavanaugh, Centocor Research and Development, Inc, 9 ; **P. Mease**, Centocor Research and Development, Inc ; **G. G. Krueger**, Centocor Research and Development, Inc, 9 ; **D. Gladman**, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Research and Development, Inc., Schering-Plough, Wyeth Pharmaceuticals , 5 ; **J. Zrubek**, Centocor Research and Development, Inc, 3 ; **A. Beutler**, Centocor, Inc., 3 ; **B. Hsu**, Centocor Research and Development, Inc, 3 ; **S. Mudivarthy**, Centocor Research and Development, Inc, 3 ; **M. Mack**, Centocor Research and Development, Inc, 3 ; **I. B. McInnes**, Centocor Research and Development, Inc .

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Both Structural Damage of the Spine (X-Rays) and Spinal Inflammation (MRI) Contribute to Impairment of Spinal Mobility in Patients with Ankylosing Spondylitis.

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Purpose: Structural damage in ankylosing spondylitis (AS) has been shown to impair spinal mobility. However, the contribution of spinal inflammation to potentially reversible impairment of spinal mobility is not well established. Our aim was to study the relationship between radiographic damage of the spine, spinal inflammation (MRI) and spinal mobility in patients with AS.

Method: In this investigator-performed sub-analysis of the ASSERT database at baseline, in total 214 patients, representing an 80% random sample, were investigated. MRI inflammation was assessed by the ASspiMRI-a score, structural damage by the mSASSS and spinal mobility by the linear definition of the BASMI (BASMI-lin). Independent associations between the variables of interest were investigated by linear regression analysis on van der Waerden-normalised variables. Because of a relevant statistical interaction between disease duration (in quartiles) and ASspiMRI or mSASSS, sub-analyses are presented in patients with low (≤3 years) *vs* high (>3 years) disease duration.

Results: BASMI-lin correlated moderately well with mSASSS (Spearman's rho=0.60) but only weakly with ASspiMRI-a (rho=0.30). A best-fit model for BASMI-lin included the variables presented in table I (sex included by default).

Table I: Best-fit model for BASMI-lin

	Beta	**B**	**95% CI**	**p-value**
mSASSS	0.544	0.863	0.675 to 1.052	<0.001
ASspiMRI-a	0.142	0.235	0.040 to 0.431	0.019
Sex (male)	-0.08	-0.303	-0.735 to 0.130	0.169

In patients with a disease duration ≤3 years, ASspiMRI-a (but not mSASSS) was the only contributory variable (B=0.594 (0.171 to 1.017); p=0.007), while in patients with a disease duration >3 years mSASSS (but not ASspiMRI-a) was contributory (B=0.923 (0.713 to 1.132); p<0.001).

Conclusion: Spinal mobility impairment in AS is independently determined both by irreversible spinal damage as well as by reversible spinal inflammation. Spinal mobility impairment is dominated by spinal inflammation in early disease, and by irreversible structural damage in later disease, which may imply that spinal mobility can better be maintained by early as compared to late intervention.

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The Prevalence of Co-Morbidities in a Psoriatic Arthritis Cohort. Majed M. Khraishi[1], Nadia Longo[2], Anthony Pellegrino[2] and John S. Sampalis[2], [1]Nexus Clinical Research, St Johns, NF, [2]JSS Medical Research, Westmount, QC

Purpose: Psoriatic arthritis (PsA) is a serious chronic condition that affects 10-35% of patients with skin psoriasis (PSO) and is associated with progressive joint damage and significant morbidity. Co-morbidities associated with PsA are still not fully defined specifically in early stages of the disease compared to the general population.

Method: Data was collected from a rheumatology clinic specializing in patients with PSO and PsA diagnosed greater than 2 years (Established PsA) compared to cohort of PsA patients diagnosed less than 2 years (Early PsA) in Newfoundland. Data for controls with no history of PSO or PsA were collected from the Newfoundland and Labrador Center for Health Information (NLCHI). Controls were matched 3:1 to the Established PsA cohort. Co- morbidities associated with PsA will be compared to the general population using age adjusted standardization rates by gender.

Results: 148 patients with PsA were identified, of which 38 were in the Early PsA group. Mean (SD) age of the established group was 53 (11.0) and 48 (11.3) for the early group. Mean (SD) duration of PsA was 12.6 (9.4) months for the Early PsA cohort and 8.0 (9.1) years in the Established PsA cohort. There were more females in the Early PsA group compared to the Established PsA (60.5% vs. 42.6%) respectively. The table summarizes the prevalence rates of co-morbidities, showing that hypertension, obesity, diabetes and depression are more prevalent in the PsA population in comparison to the general population.

Gender	Co- morbidities	Early PsA Cohort			Established PsA Cohort		
		Observed (PsA cohort)	Expected (Control cohort)	Prevalence Rate	Observed (PsA cohort)	Expected (Control cohort)	Prevalence Rate
Males	Hypertension	5	0.6	8.2	17.5	3.6	4.9
	Coronary Heart Disease	0	0.6	0	6	3.7	1.6
	Diabetes	1	1	1	6	5.9	1
	Obesity	0	1	0	14	5.9	2.4
	Depression	1	0.2	5.1	3	0.6	4.9
Female	Hypertension	7	0.4	16.9	24	1.3	17.8
	Coronary Heart Disease	1.0	0.4	2.3	1	1.4	0.7
	Diabetes	5	1.1	4.4	6	3.6	1.7
	Obesity	7	0.4	18.2	18	1.3	14.1
	Depression	1	1.1	0.9	8	3.5	2.3

Conclusion: Patients with PsA have a high prevalence of cardiovascular disease and metabolic abnormalities even when age is adjusted to the general population. These co-morbidities are present in patients with short disease duration suggesting that the predisposition of cardiovascular and metabolic abnormalities in PsA patients may precedes the development of joint disease.

Disclosure: M. M. Khraishi, Abbott Laboratories, 2, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **N. Longo**, Nexus Clinical Research, 5 ; **A. Pellegrino**, Nexus Clinical Research, 5 ; **J. S. Sampalis**, Nexus Clinical Research, 5 .

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The Impact of Psoriatic Arthritis (PsA) According to the International Classification of Functioning, Health and Disability (ICF).
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Purpose: To determine the categories of the ICF-Checklist (an abbreviated form of the ICF augmented by categories in the ICF Core-sets of rheumatoid arthritis and ankylosing spondylitis), affected in at least 30% of people with PsA and to compare the number of affected categories with scores on self-report measures of disability and health related quality of life.

Method: Data was collected from 94 patients with PsA attending rheumatology clinics in Wellington, Maroochydore, Melbourne, Barnsley, Toronto and Seattle using the extended ICF-Checklist interview. For ICF categories affected by PsA in at least 30% of patients, the percentage of patients affected were determined under the headings of Body Structures, Body Functions, Activities & Participation and Environmental Factors. A count of affected categories in the Activities & Participation section was compared to the SF-36 scales, HAQ, and PsAQOL using Spearman correlation.

Results: Thirty-eight percent were male, mean (SD) age was 51 (11) years and the mean (SD) disease duration was 10 (8) years. There were 25 categories in the Body Functions section, 6 categories in the Body Structures section and 51 categories in the Activities & Participation section that were affected by PsA in at least 30% of participants. There were 13 facilitating Environmental Factors and 1 Environmental Factor (climate) that was a barrier in at least 30% of participants. The number of affected Activities & Participation categories correlated highly ($r>0.6$) with SF-Physical Function, SF-Role Physical, SF-Social Functioning, HAQ-DI, and PsAQOL.

Conclusion: PsA is associated with a wide range of impairments, limitations and restrictions across the ICF categories. People with PsA find Environmental Factors more often to be helpful than a barrier to good health. Standardised self-report measures of functioning correlate highly with the number of affected Activities & Participation categories, suggesting that these instruments measure a similar concept to the ICF concept of functioning. The large number of affected categories in the Activities & Participation domain (51 of 97 categories that were assessed, 53%) highlight the importance of this concept in PsA and compares with 16 of 48 (33%) categories listed as affected in a methodologically similar study of patients with rheumatoid arthritis and 35 of 78 (45%) in ankylosing spondylitis.

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Increased Prevalence of Obstructive Sleep Apnea in Patients with Psoriatic Arthritis and Ankylosing Spondylitis.
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Purpose: To determine the prevalence of Obstructive Sleep Apnea (OSA) in psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients in the Salt Lake City Veterans Affairs rheumatology clinics.

Methods: Polysomnography (PSG) data was collected from consecutive AS (n=13) and PsA (n=17) Salt Lake City veterans enrolled in the Program to Understand the Longterm Outcomes in Spondyloarthritis registry between July 2008 and April 2009. Home four channel PSG was used in 23 of 30 patients. Seven patients received conventional sleep lab studies. The apnea hypopnea index (AHI) at 4% was used to

measure the severity of OSA. Fisher's exact test and 2 tailed t-tests were used to compare variables. Patients were excluded if they smoked in the week prior to PSG or if they refused PSG.

Results: OSA was diagnosed in 23 of 30 (77%) patients, and 14 (47%) patients had moderate to severe OSA. The prevalence of OSA in patients taking TNF-inhibitors was significantly lower compared to those not taking TNF-inhibitors. There was a trend toward higher disease activity measures in the OSA group compared to the no OSA group. There were no statistically significant differences in patient characteristics or disease features between the OSA and no OSA groups. Demographics and AHI were similar in the PsA and AS groups.

Conclusion: The prevalence of OSA in these patients was substantially higher than both the 1-9% prevalence reported in the general population and the 12% and 23% prevalence reported in two small AS studies[1,2]. The age, BMI, and male predominance were higher in this study than in the general population and the aforementioned AS studies. However, these differences were not statistically significant between the OSA and no OSA groups. The lower prevalence of OSA in patients taking TNF-inhibitors is consistent with data demonstrating elevated serum levels of TNF-α and IL-6 in OSA patients and with a pilot study showing improvement in AHI after treatment with etanercept[3]. OSA is under-recognized in veterans with PsA and AS, and alterations of inflammatory cytokines with biologic therapy may positively impact OSA.

Characteristics of patients with & without OSA

	OSA		**No OSA**		
	n (%) or ± SD	**n**	**n (%) or ± SD**	**n**	**p value**
Age	63 ± 11	23	54 ± 15	7	0.108
Male	22 (96%)	23	7 (100%)	7	NA
BMI	30.1 ± 5.1	23	28.2 ± 6.4	7	0.425
Disease duration, yrs	21 ± 15	23	18 ± 18	7	0.694
BASDAI	4.6 ± 2.9	13	2.5 ± 1.8	6	0.058
BASFI	4.4 ± 2.7	13	2.6 ± 2.5	6	0.116
ESR	22.2 ± 14.3	11	9.3 ± 13.7	3	0.190
CRP	11.4 ± 12.0	9	1.5 ± 2.3	3	0.196
Modified Schober's	3.5 ± 2.4	16	4.6 ± 2.3	6	0.287
Lateral bending	12.4 ± 7.6	16	13.7 ± 7.1	6	0.653
OTW	5.2 ± 5.5	16	2.2 ± 2.5	6	0.234
Chest expansion	1.8 ± 1.3	16	2.3 ± 1.3	6	0.399
Biologic therapy	9 (39%)	23	6 (86%)	7	0.037
Nonbiologic DMARD	9 (39%)	23	1 (14%)	7	0.228

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Value of PET/CT in Clinical Practice in Patients with Possible Spondyloarthropathy. Hiroyuki Yamashita, Kazuo Kubota, Yuko Takahashi, Junwa Kunimatsu, Arisa Shimizu, Toshiki Eri, Kenji Itoh and Akio Mimori, International Medical Center of Japan, Tokyo, Japan

Purpose: Seronegative spondyloarthropathy (SNSA) is a disease group characterized by enthesopathy, sacroiliitis, synovitis, and spinal inflammation. Its diagnosis based on clinical and plain x-ray findings is not always easy, especially at early stages or in cases of undifferentiated spondylitis. We aimed to evaluate the utility of 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for diagnosing SNSA, which to our knowledge has been little described in the literature of rheumatology.

Method: Nine patients suspected of having SNSA were hospitalized at our institute between 2006 and 2008 for diagnosis or to start initial therapy for the diseases. The mean age of the patients was 48.9+/-20.3 (range 19-73) years old. All 9 patients were examined by PET/CT, magnetic resonance imaging (MRI), and bone x-rays. We evaluated whether or not each patient met the European Spondyloarthropathy Study Group criteria of SNSA (ESSG), Amor's criteria of SNSA (Amor), or the modified New York criteria of ankylosing spondylitis (NY/AS). The evaluation was based on either clinical and plain x-ray findings or on those findings combined with PET/CT findings. Some of the patients received additional imaging tests, including x-ray CT and/or bone scintigraphy.

Result: PET/CT revealed positive results (the number of patients) in all 9 patients including enthesopathy (7), spondylitis (6), and/or sacroilitis (3). These lesions were partially detected by MRI in 7 patients but totally negative in 2 patients, and were never detected by bone x-ray. The ratios of positive results were 1/3 in bone scintigram and 0/1 in x-ray CT. More patients met the diagnostic criteria of SNSA when the positive results of PET/CT were considered, as shown in Table, and PET/CT was more sensitive than MRI to detect lesions.

Conclusion: PET/CT is quite useful for diagnosing seronegative spondyloarthropathy (SNSA) by virtue of its high sensitivity in detecting inflammation at SNSA disease-specific sites.

Table: Diagnosis according to the criteria of SNSA in reference to PET/CT

case	1	2	3	4	5	6	7	8	9
Dx	USpA	USpA	USpA	USpA	ReA	ReA	ReA	AS	AS
ESSG	-	+*	+	+*	+*	+*	+*	+	+*
Amor	+	+	+*	+*	+	+*	+*	+	+
NY/AS	-	-	-	-	-	-	-	+*	+*

Abbreviations: Dx, diagnosis; USpA, undifferentiated spondyloarthritis; ReA, reactive arthritis; AS, ankykosing spondylitis; +, met the diagnositic criteria based on clinical and x-ray findings; +*, met the diagnostic criteria when positive results of PET/CT were considered.

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Analysis of Factors Associated with Obesity in Psoriatic Arthritis. Allen P. Anandarajah[1] and Christopher T. Ritchlin[2], [1]Univ of Rochester Med Ctr, Rochester, NY, [2]University of Rochester, Rochester, NY

Purpose: To examine the relationship between environmental factors and obesity in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) and to determine factors associated with the outcome variable body mass index (BMI).

Method: Patients were selected from the Consortium Of Rheumatology Researchers Of North America (CORRONA) database and matched for age, sex and disease duration. Univariate analysis was performed to determine if the matched PsA and RA cohorts differ in their

association with several variables. These same covariates were examined in matched PsA and RA patients stratified by the categorical outcome variable BMI (<30 or >30) and logistic regression was then performed in the two cohorts using the same covariates.

Results: Frequency matching (age, sex and disease duration) yielded 2389 RA and PsA pairs. Logistic regression revealed that the number of tender joints, non-smoking status, absence of exercise, depression, age, shorter disease duration and female gender were associated with an elevated BMI in PsA whereas only lack of exercise, non-smoking status and shorter disease duration were associated with obesity in the RA cohort. Stepwise logistic modeling revealed that after controlling for exercise, older age, shorter disease duration, depression and the presence of PsA were associated with an elevated BMI. Increased tender joint counts and female gender also increased the likelihood of obesity in the PsA but not the RA cohort.

Conclusion: These findings support a multiplicative model of obesity in PsA that results from interplay between the environment and factors related to the disease process that remain to be identified.

Disclosure: A. P. Anandarajah, None; **C. T. Ritchlin**, None.

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Adalimumab in Crohn's-Related Spondylitis Patients Resistant or Intolerant to Infliximab. Marco Antivalle, Luca Bertani, Michele Battellino, Alberto Batticciotto, Alessandra Mutti, Fabiola Atzeni and Piercarlo Sarzi-Puttini, L. Sacco University Hospital, Milano, Italy

Purpose: : Limited evidence shows that switching anti-TNF therapy in ankylosing spondylitis may be effective. However, there are no data on the switch from infliximab (IFX) to adalimumab (ADA). In Crohn's patients, ADA therapy in patients resistant or intolerant to IFX has been studied by several authors. Aim of the study was to assess the clinical response to the treatment with ADA in Crohn's-related spondylarthritis in patient resistant or intolerant to IFX.

Methods: ADA was administered 40 mg sc eow in patients diagnosed with Crohn's disease and spondylarthritis, who had stopped the treatment with IFX due to intolerance or non-responsiveness, starting at least after 8 weeks from the last injection of IFX. Concurrent therapies were continued during the study, and dose adjustments allowed. Patients were followed-up to one year, and clinic visits were performed at baseline, and after 4, 12, 24, and 52 weeks of treatment with ADA. At each visit spondylitis activity and function were assessed by the BASDAI, and the BASFI scores. The response to treatment was evaluated by the ASAS20 score. Crohn's disease activity was assessed by the CDAI score, and quality of life by the SF-36 questionnaire. The variation of clinical measures was evaluated by Wilcoxon test, and differences in proportions by chi-square test.

Results: 18 patients entered the study (12 F 6 M, mean age 43.55 ± 13.1 yrs). Mean duration of IFX treatment was 92.09 (range 2 - 256) weeks. Reason for IFX discontinuation were inefficacy (N=12) or intolerance (N=6). Crohn's disease activity was low in all patients (CDAI < 150). 13 patient had active spondylitis, (BASDAI score > 4). 15 patients completed the week 24 visit, and 12 the week 52 visit. ADA was discontinued in 3 patients, due to Crohn's related complications or articular flare-up (N=1). The variation of BASDAI and BASFI clinical scores are reported in Figures 1 and 2. During the study, both the BASDAI and the BASFI improved as compared to study entry levels, significant differences vs baseline values being recorded only up to the 6^{th} month for BASDAI, and up to the 3^{rd} month for BASFI. BASDAI reduction > 50% and ASAS20 responses were recorded in 3/18, 7/18, 3/15, and 2/15 patients, and in 3/18, 4/18, 3/18, and 2/18 patients at month 1, 3, 6, and 12 respectively. Only patients with BASDAI > 4 at entry showed ASAS20 responses. However, the proportion of responders was not statistically significant by chi-square test. CDAI and SF-36 scores changed little during the study. Overall, the effect of treatment on all considered variables, reached a maximum at the 3^{rd} month, but was not maintained at subsequent assessments, being minimal at the 12^{th} month.

Fig. 1. Mean BASDAI variation during treatment with Adalimumab

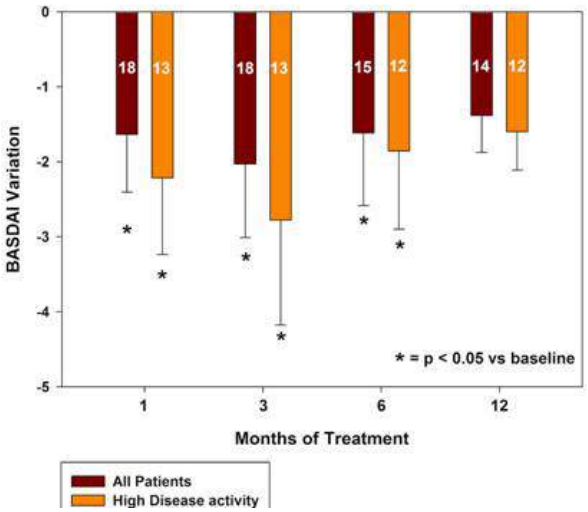
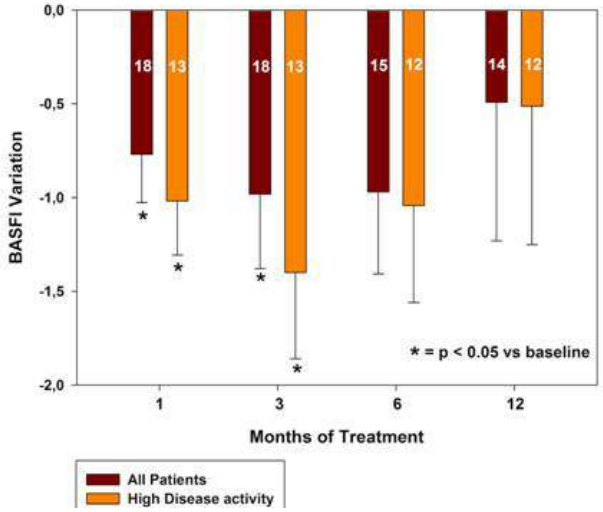


Fig. 2. Mean BASFI variation during treatment with Adalimumab



Conclusion: Our study is, to our knowledge, the first addressing the effectiveness of adalimumab in Crohn's-related spondylarthritis after failure of infliximab. Our results suggest that treatment with ADA may be a suitable option in these patients. However, the magnitude and duration of therapeutic effect should be further investigated.

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European Ankylosing Spondylitis Infliximab Cohort (EASIC): Long-Term (5 years) Efficacy of Infliximab On Disease Activity and Function - A Real Life Experience After the End of ASSERT. Frank Heldmann[1], Jan Brandt[2], Jürgen Braun[3] and EASIC study group, [1]Centre of Rheumatology, Herne, Germany, [2]Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany

Purpose: The knowledge about the clinical efficacy of long-term anti-TNF therapy in patients with ankylosing spondylitis (AS) is rather limited. This study has been performed to demonstrate that treatment with infliximab in patients with AS is efficacious after more than 5 years of therapy.

Method: AS patients from 6 European countries who had taken part in the 2 year RCT ASSERT were invited to take part in the open label investigator driven study EASIC where they were followed every 6-8 weeks. For pragmatic reasons patients could only be included several months after the end of ASSERT. In the meantime they were treated by the local standard of care. There were mainly two groups of patients: patients allocated to group 2 had received infliximab between ASSERT and EASIC, patients allocated to group 1 had not, these were divided into two subgroups: to group 1a in case of relapse (BASDAI > 4 and physician global VAS > 4) and to group 1b in case of remission. All patients of group 1a and group 2 were continuously treated with infliximab during EASIC (96 weeks) in a mean dosage of about 5 mg/kg and intervals of 6-8 weeks, this decision was left to the discretion of the investigator.

Results: A total of 103 of 149 (69.1%) ASSERT patients were included in EASIC 1.3 ± 0.9 years after ASSERT (9 in group 1a, 5 in group 1b, 89 in group 2). Data from 97 patients (14 in group 1, 83 in group 2) could be analyzed. The patients were 82.5% men and 17.5% women and had a mean age of 43.5 years (39 in group 1, 44 in group 2). There was no major difference to the ASSERT population. 81 patients completed the 96 weeks of the trial, 5 in group 1 (33.3%) and 76 in group 2 (86.4%). There were 6 drop-outs due to adverse events, 4 due to lack of efficacy, 3 due to a planned pregnancy, 7 due to other and 2 due to unknown reasons. The table summarizes the responses for the completers of group 2. The values of BASDAI, BASFI, BASMI, Patient VAS, CRP, Swollen joint count and enthesitis index were at week 96 significantly improved compared to the ASSERT baseline data. At the end of ASSERT 78.4% of patients had no arthritis and 84.9% had no enthesitis.

	Baseline ASSERT	End of ASSERT	Week 0	Week 48	Week 96
BASDAI 50 (%)	NA	68.4	59.5	60.5	67.1
ASAS 20 (%)	NA	82.9	78.9	84.2	82.9
ASAS 40 (%)	NA	67.1	57.7	67.1	61.8
ASAS partial remission (%)	NA	30.3	23.9	27.6	27.6
CRP (mg/dl)	2.9	0.6	0.7	0.6	0.5
BASDAI	6.4	2.4	2.9	2.7	2.5
BASFI	5.9	2.9	3.2	3.1	3.1
BASMI	4.0	2.7	2.1	2.0	2.2
Patient global disease VAS	7.0	2.7	3.3	2.7	2.8
Swollen joint count	1.6	0.6	0.6	0.4	0.6
Enthesitis Index	9.0	3.7	0.6	0.3	0.4

Conclusion: The majority of patients was continuously treated with infliximab between ASSERT and EASIC and during EASIC in a total of 5 years therapy. Attrition rates for any reason were lower than 10% per year in these patients. In the completer analysis, this was associated with a sustained high response rate, low disease activity, a good functional state, a very low prevalence of arthritis and enthesitis and a low CRP. Anti-TNF therapy with infliximab was clinically efficacious on a long-term basis.

Disclosure: F. Heldmann, None; **J. Brandt**, None; **J. Braun**, Centocor, Inc., 2, Abbott Laboratories, 2, Wyeth Pharmaceuticals, 2 .

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Diagnostic Utility of MRI in Early Spondyloarthritis: Do Rheumatologists Omit Diagnostic Information Provided by the T1-Weighted Sequence? Mikkel Ostergaard[1], Ulrich Weber[2], Susanne J. Pedersen[1], Juerg Hodler[2], Robert GW Lambert[3] and Walter P. Maksymowych[3], [1]Copenhagen University Hospitals, Copenhagen, Denmark, [2]University Clinic Balgrist, Zurich, Switzerland, [3]University of Alberta, Edmonton, AB

Purpose: There is increasing acceptance that MRI has diagnostic utility in early spondyloarthritis (SpA). Prior studies and a recent ASAS consensus-driven proposal have focused only on the presence of bone marrow edema on fat-suppressed (FS) sequences as the principle diagnostic feature and ignore the potential contribution of diagnostic abnormalities seen on T1-weighted (T1W) sequences. We aimed to compare the diagnostic utility of FS and T1W MRI in early SpA using a standardized approach to the evaluation of the sacroiliac joints (SIJ).

Method: Six experienced readers (4 rheumatologists, 2 radiologists) from 3 international centres, blinded to patient and diagnosis, independently assessed MRI scans (T1W and STIR) from the following subjects: 77 patients with AS and symptom duration < 10 years; 26 patients with mechanical low back pain, age <45 years and symptom duration < 10 years; 25 patients with pre-radiographic inflammatory back pain (IBP), mean symptom duration 26 months; and 59 healthy controls, age < 45 years. MRI scans of the SIJ were read systematically as described in a standardized online training module. We recorded bone edema, fat replacement, joint erosions, and ankylosis according to standardized definitions using an online data entry system. In addition to deciding on the presence/absence of SpA readers were asked to

record the following: 1. Whether their diagnostic conclusion was primarily based on abnormalities observed on the STIR, T1W, or both. 2. Which type of lesion was the primary basis for the diagnostic conclusion.

Results: Diagnostic utility of MRI in early AS was better for concordant data from radiologist (sensitivity 85.7%, specificity 100%) as compared to rheumatologist (sensitivity 79.6%, specificity 94.9%) reader pairs. The better performance of radiologists (sensitivity 48%/specificity 100%) as compared to rheumatologists (sensitivity 48%/specificity 94.9%) was also noted for pre-radiographic SpA. Although all readers considered both sequences as more important to the diagnosis of early AS than either T1W or STIR sequence alone, rheumatologists based their diagnostic conclusion on the STIR significantly more frequently than radiologists for both early AS and pre-radiographic SpA ($p<0.0001$ for both) and this difference was associated with a greater recognition of the importance of erosions on TIW by the radiologists.

	Sequence the diagnosis is based on (% of patients)			Primary feature the diagnosis is based on (% of patients)			
	STIR	**T1**	**T1+STIR**	**Bone edema**	**Fat**	**Erosion**	**Ankylosis**
AS/All readers	19.4	22.8	60.4	51.9	6.2	24.2	17.3
AS/Rheumatologists	27.7	18.9	57.4	68.1	4.1	10.6	17.2
AS/Radiologists	2.9	30.7	66.4	27.8	9.5	44.6	17.6
IBP/All readers	60.0	5,2	34.7	88.2	3.8	8.1	0
IBP/Rheumatologists	72.7	4.0	23.3	91.2	3.7	5.1	0
IBP/Radiologists	34.7	7.7	57.7	83.7	3.9	12.5	0

Conclusion: Rheumatologists rely primarily on the diagnostic information by the STIR sequence and de-emphasize the contribution of abnormalities on the T1W, such as erosions, which radiologists consider important to the diagnosis of SpA by MRI.

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Ultrasound-Guided Sacroiliac Joint Injection in Patients with Sacroiliitis: Precise i.a. Injection Does Not Predict Outcome. Wolfgang Hartung[1], Jürgen Schölmerich[2], Rainer H. Straub[2], Thomas Herold[3], Christian J. Ross[3], Stefan Feuerbach[3] and Martin Fleck[2], [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, Bad Abbach, Germany, [2]University Hospital Regensburg, Regensburg, Germany, [3]University Medical Center Regensburg, Regensburg, Germany

Purpose: Intraarticular injections of sacroiliac joints (SIJ) with corticosteroids are often performed in patients suffering from low back pain due to active sacroiliitis. However, SIJ injections are technically demanding, and therefore the clinical outcome of ultrasound-guided corticosteroid SIJ injections was analyzed in relation to the accuracy of the injection.

Method: Ultrasound-guided injections were performed with 40 mg triamcinolone and 0,78 mg gadolinium in 20 SIJ of 14 consecutive patients suffering from active sacroiliitis. Immediately following SIJ injection, MRI scanning was initiated to verify the correct placement of the drug. Clinical outcome of the intervention was determined using a numerical pain rating scale (NRS) at day 1 and 28.

Results: Despite ultrasound guidance, only 8 injections (40%) were exactly positioned into the SIJ-space, whereas the other 12 injections (60%) missed the SIJ. However, there were no significant differences observed in the clinical outcome between the intraarticular-injected group and the periarticular-injected group. There was a similar pain relief observed in both groups 24h and 28 days following the intervention (intraarticular injection group: mean NRS-baseline: 6,8 [range 4 - 9], NRS-24h: 4,3 [range 1 - 7], NRS-day 28: 3,5 [range 1 - 5]; periarticular injection group: mean NRS-baseline: 7,0 [range 5 - 10], NRS-24h: 4,1 [range 1 - 10], NRS-day 28: 4,5 [range 1 - 8]).

Conclusion: These results demonstrate that intraarticular SIJ-injections remain technically challenging despite ultrasound guidance. However, periarticular deposition of triamcinolone appears sufficient for pain and symptom control in patients suffering from inflammatory low back pain due to active sacroiliitis.

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Etanercept Benefits Skin, Joint, and Entheseal Symptoms in Patients with Psoriasis and Psoriatic Arthritis: The PRESTA Trial.

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Purpose: Etanercept (ETN) has been approved for the treatment of both psoriatic arthritis (PsA) and moderate-to-severe plaque psoriasis (PsO) based on its efficacy in treating both joint and skin symptoms. ETN can be used at 50mg twice weekly (BIW) in PsO *v* 50mg once weekly (QW) in PsA. Efficacy of 50 mg BIW for joint symptoms in PsA has not been previously investigated. The objective of this study was to determine the efficacy of 2 ETN regimens on skin, joint, and entheseal manifestations in subjects with both PsO and PsA at 12 and 24 weeks.

Methods: Subjects (n= 752) received either ETN 50mg BIW (n=379) or 50mg QW (n=373) for 12 weeks double-blind followed by open-label 50mg QW for 12 weeks. Eligibility criteria included stable, moderate-to-severe plaque PsO assessed by dermatologist and active PsA (≥2 swollen/painful joints) assessed by rheumatologist. Primary endpoint was % subjects achieving Physician Global Assessment (PGA) of psoriasis of clear/almost clear at week 12. Improvement in skin, joint and enthesitis/dactylitis manifestations of PsA were also evaluated. Subject assessed physical function and symptoms.

Results: See Table for efficacy results. In addition, subjects with enthesitis at baseline were found to have more extensive skin and joint involvement with more swollen/painful joints and higher mean PASI at baseline. The regimens had similar safety profiles with no new safety signals.

Conclusion: In this population of subjects with PsO and PsA, etanercept 50 mg BIW/QW provided faster relief of skin symptoms than 50 mg QW/QW at week 12, while either regimen appeared appropriate for relief of joint and soft tissue rheumatic symptoms at weeks 12 & 24. Both regimens were safe and effective at 24 weeks.

	ETN 50 mg BIW/QW n = 379		**ETN 50 mg QW/QW n = 373**	
Week	**12**	**24**	**12**	**24**
	% Subjects			
PGA psoriasis†	78*	80	71*	79
PASI ≥75%	55**	70	36**	62
PASI ≥90%	27**	46*	15**	35*
PsARC	77	82	76	80
ACR 20	66	69	61	72
ACR 50	45	52	41	54
No swollen jnts	41	55	37	52
Enthesitis‡	74	81	70	81

Dactylitis§	74	82	69	77
	% Improvement from Baseline			
PASI Mean % change	71	78	62	74
HAQ	47	51	47	54
SGA Joint Pain	56	57	51	59
SGA Arthritis activity	56	58	54	59

*p<0.05; **p< 0.001; †**% subjects achieving clear/almost clear/mild**; ‡% **subjects with improvement in at least 1 tendon/ligament insertion; §% change from baseline based on 60pt scale**; PGA=Physician Global Assessment; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria; ACR=American College of Rheumatology; HAQ=Health Assessment Questionnaire; SGA=subject global assessments

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Efficacy of Etanercept On Rheumatic Signs and Pulmonary Function Tests in Advanced Ankylosing Spondylitis. Results of a Randomized Double Blind Placebo-Controlled Study (SPINE). Maxime Dougados[1], J. Braun[2], S. Szanto[3], B. Combe[4], M. Elbaz[5], P. Geher[6], G. Thabut[7], V. Leblanc[8] and I. Logeart[8], [1]Hôpital Cochin, Paris, France, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]University of Debrecen medical and Health Sciences Center, Debrecen, Hungary, [4]Immuno-Rheumatology, Montpellier, France, [5]Medical center, Avignon, France, [6]Polyclinic of the Hospitaller Brothers of St. John of God, Budapest, Hungary, [7]Paris Diderot University, Bichat Hospital,Paris, [8]Wyeth Pharmaceuticals France

Purpose: TNF blockers have demonstrated their benefit in patients with active Ankylosing Spondylitis (AS) (1). Advanced AS patients are disabled because of reduced spinal mobility and respiratory functional impairment.

This study evaluated the effect of etanercept (ETN) not only on the rheumatic symptoms (pain, function) but also on signs (spinal mobility) and respiratory function tests.

Method: *Patients*: Definite AS patients (modified New York criteria) with active (BASDAI ≥40), refractory (at least 2 NSAIDs), severe (at least 2, 3 or 3 inter-vertebral radiological consecutive bridges at the lumbar, thoracic or cervical level respectively), anti-TNF naive. *Study design*: Multi-center, randomized, double blind, placebo-controlled trial of 12-week duration. *Study drugs*: ETN 50 mg OW and identical placebo (PBO). *Outcome measures*: BASDAI, BASFI, BASMI, CRP and respiratory function tests.

Results: Of the 95 screened patients, 82 (males: 95%, age: 47.3±10.4 y, disease duration: 16±10.4 y, B27 positive: 81.7%) were randomized to receive either ETN (n=39) or PBO (n=43). At baseline, patients had an active (BASDAI: 61±13.4, CRP: 20.7±25.5 mg/l) and severe (BASMI: 5.7±1.3, mSASSS: 36.5±20.5) disease. During the 12 weeks of the trial, 5 patients discontinued the treatment (4 in the PBO arm [due to lack of efficacy: 2, lost to follow-up:1, withdrawal of consent: 1) and 1 in the ETN arm [due to serious adverse event]). The adjusted mean BASDAI (primary outcome: normalized net incremental Area Under the Curve between baseline and W12) was significantly greater in the ETN vs PBO group: -19.8±16.5 vs -11.0±16.4, (p=0.019). Moreover, all the analyses evaluating the changes observed at 12 weeks were in favor of ETN (BASDAI -26.4±19.7 *vs* -14.4±19.7, p=0.008; Total back pain -29.2±24.0 vs -14.9±24.0, p=0.010; BASFI -21.7±17.6 *vs* -10.1±17.6, p=0.004; BASMI -0.6±0.6 *vs* -0.2±0.6, p=0.011; CRP -15.7±14.2 *vs* -1.3±14.2, p<0.001); pulmonary vital capacity +0.14±0.26 *vs* -0.05±0.26, p=0.003.

Conclusion: This prospective study conducted in advanced AS patients confirms the short term symptomatic efficacy of ETN previously reported in less advanced disease. Such efficacy has been observed on the main symptoms of the patients (*e.g.* pain) and on the markers of inflammation (*e.g.* CRP); this study also shows a significant effect on signs related to the severity of the disease such as spinal mobility and pulmonary capacities.

(1) Van der Heidje D et al. ARD 2006; 65:1572-1577.

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Folate Pathway Enzyme Gene Polymorphisms and the Efficacy and Toxicity of Methotrexate in Psoriatic Arthritis. Vinod Chandran[1], Fotios Siannis[2], Proton Rahman[3], Catherine T. Schentag[1], Vernon Farewell[4] and Dafna D. Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Athens, Greece, [3]St Clare's Mercy Hospital, St Johns, NF, [4]Medical Research Council (MRC) Biostatistics Unit, Cambridge, United Kingdom

Purpose: Our aim was to determine whether polymorphisms of genes coding enzymes of folate pathway are associated with effectiveness, toxicity and drug survival of methotrexate (MTX) in psoriatic arthritis (PsA).

Methods: Data was obtained from a longitudinal cohort of PsA patients. Patients are evaluated every 6 months according to a standard protocol. Data on drugs taken with start and stop dates, dose, side effects and reasons for discontinuation are systematically recorded. Response to MTX treatment was assessed at 6 months and was categorized as excellent if there was ≥50% decrease in joint counts from baseline at dose of ≤15 mg/wk, good if there was ≥50% decrease in joint counts from baseline at dose of >15 mg/wk and none if there was <50% decrease, no change, or an increase in joint counts. Patients treated with MTX after clinic entry and who had ≥3 swollen joints prior to initiating MTX therapy were selected for effectiveness evaluation. Data from all patients treated in the clinic with MTX was used in evaluation of toxicity and drug survival. The following SNPs were measured using the Sequenom platform from DNA isolated from peripheral blood: MTHFR 677C>T (rs1801133), MTHFR 1298A>C (rs1801131), DHFR –473T>C (rs1650697), DHFR 35289A>G (rs1232027), and RFC 80G>A (rs1051266). Fisher's exact test and logistic regression was used to determine association between heterozygote and homozygote of the minor allele of the SNPs tested with effectiveness, and toxicity of MTX. Cox proportional hazards analysis was used to determine association between these SNPs and drug survival.

Results: 281 patients (165 males, mean age 44 years, mean disease duration 10 years) treated with MTX were identified from the database. 119 patients (67 males) were included in the effectiveness analysis. After 6 months of therapy with MTX 52.4% patients had 50% reduction in their actively inflamed joint count. 31% had an excellent response, 16% had a good response and 53% had no response to MTX. The minor 'A' allele of DHFR gene at +35289 was the only SNP associated with an increased odds of 50% reduction in actively inflamed joint count (OR = 3.03, p=0.02) as well as an excellent/good response to MTX after 6 months of therapy (OR= 2.7, p=0.03). 156/281 (55.5%) experienced side effects to MTX. 45 (16%) had liver function test abnormalities and in 103 (36.7%) side effects led to drug discontinuation. Patients homozygous for the minor allele of MTHFR 677C/T (677TT) had more liver toxicity (Fisher p=0.04). None of the other SNPs tested were associated with response to MTX, toxicity or drug survival.

Conclusion: Polymorphisms of the DHFR gene are associated with MTX efficacy and that of the MTHFR gene are associated with MTX induced liver toxicity in PsA.

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The Fatty Romanus Lesion- A Non-Inflammatory Spinal MRI Lesion Specific for Axial-Spa. Alexander.N. Bennett[1], Amer Rehman[2], EM Hensor[3], Helena Marzo-Ortega[3], P. Emery[3] and Dennis McGonagle[3], [1]Defence Medical Rehabilitation Centre, London, United Kingdom, [2]American Hospital, Dubai, United Arab Emirates, [3]University of Leeds, Leeds, United Kingdom

Purpose: Fatty changes at vertebral corners have been reported on MRI in axial-SpA but the distribution or specificity of these lesions to axial-SpA has not been determined. This study assessed the diagnostic utility of Fatty Romanus Lesions (FRLs) for axial-SpA in a chronic back pain population.

Method: Axial-skeleton TI SE and fat-suppressed MRI were performed on 174-patients with back pain and 11-controls. MRI lesions including FRLs were scored blind. An imaging diagnosis was given on MRI findings alone and compared to the gold-standard treating physician diagnosis.

Results: Twenty-nine patients had FRLs. Thirty-one percent (20/64) of SpA, 13% (6/45) of degenerative arthritis, 4% (2/45) of spinal malignancy, 5% (1/20) of "other" diagnoses and 0/11 normals. . The majority of FRLs in SpA 59%(135/226) were present in the thoracic-spine. The diagnostic utility of FRLs for SpA(LR=4.7) was significantly ($p<0.05$) greater than for other diagnoses and increased further (LR=12.6,$p<0.05$) when >5 FRLs were present. Of note 5/20 (25%), of SpA patients with FRLs had no diagnostic bone-oedema lesions on fat-suppressed MRI suggesting that FRLs may be useful diagnostically in axial-SpA.

Conclusion: This study defines the FRL as a diagnostic imaging feature of axial-SpA which may be useful where inflammatory changes are absent on fat-suppression MRI and where radiography is normal.

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TNF Inhibitors in Ankylosing Spondylitis (AS) in the NOR-DMARD Register: Is Switching Useful? Elisabeth Lie[1], Désirée M.F.M. van der Heijde[2], T. Uhlig[1], M.S. Heiberg[1], E. Rødevand[3], C. Kaufmann[4], K. Mikkelsen[5], W. Koldingsnes[6] and T.K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]St Olavs Hospital, Trondheim, Norway, [4]Buskerud Central Hospital, Drammen, Norway, [5]Lillehammer Hospital for Rheumatic Diseases, Norway, [6]University Hospital of Northern Norway, Tromsø, Norway

Purpose: To assess the efficacy of switching to a second TNFi in patients failing the first TNF inhibitor.

Method: Data were extracted from a multi-center treatment registry where patients (pts) with inflammatory arthropathies starting treatment with DMARDs and biologicals are assessed at baseline and followed longitudinally. BASDAI and BASFI were included from 2006. Pts with AS who started on their 1st or 2nd TNFi were eligible for the current analyses. Mann-Whitney U and Chi-square tests were used to compare the effectiveness between patient groups and Wilcoxon signed rank and McNemar's tests were applied for the comparison within the same patient group.

Results: We identified a total of 514 pts with AS who started their first TNFi (etan(ercept) n=264, infl(iximab) n=180, ada(limumab) n=70). 71% were male, 92% HLA-B27 positive, median (IQR) age was 42 (35-50) yrs and disease duration 11 (4-20) yrs. A subgroup of 79 pts (etan n=32, infl n=43, ada n=4; switchers 1st TNFi) switched to a second TNFi (etan n=31, infl n=20, ada n=28; switchers 2nd TNFi). Median (IQR) time between stop of 1st and start of 2nd TNFi was 72 (0-308) days. Baseline variables and 3-month responses in non-switchers and the 1st and 2nd TNFi in switchers, respectively, are shown in the table. BASDAI/BASFI data were available for 58, 38 and 73% of pts in the respective groups. Switchers were on 1st TNFi for 252 (98-592) days, and for these pts the last recorded BASDAI/ASDAS/Patient global before switch were 6.1(3.1-7.5)/3.5(1.7-4.2)/59(27-75). Reasons for discontinuation of the 1st TNFi were insufficient response (IR) in 31, adverse events (AEs) in 45 and not reported in 3 pts. Baseline disease activity level and 3-month responses in IR-switchers and AE-switchers did not differ. As of Feb 2009, 40 of the 79 switchers were still on their 2nd TNFi after 533 (244-908) days, 32 pts had discontinued therapy (reason: 17 IR, 13 AEs, 2 other) while 7 pts were lost to follow-up.

Conclusion: Responses to the 2nd TNFi were generally similar to responses of the 1st TNFi within the same patient group and also similar to responses in pts who did not switch. This study supports that switching to a 2nd TNFi can be effective in AS pts and can be as useful as in RA pts.

Baseline variables and 3-month responses (medians [IQR])						
	Non-switchers		Switchers			
			1st TNFi		2nd TNFi	
	Baseline n=435	3 months n=333	Baseline n=79	3 months n=65	Baseline n=79	3 months n=58
BASDAI50 (%)	-	49	-	25*	-	30*
ASAS20 (%)	-	52	-	48	-	44
ASAS40 (%)	-	37	-	30	-	36
BASDAI (0-10)	5.7	-2.0 (-4.1; -0.6)	6.7#	-1.7 (-3.4; 0.2)	6.0	-1.9 (-3.4; 0)
BASFI (0-10)	4.5	-1.3 (-2.8; -0.3)	5.3	-0.9 (-3.3; 0.6)	5.4	-1.1 (-2.4; 0)
ASDAS	3.4	-1.4 (-2.1; -0.5)	3.7	-1.2 (-1.8; 0.1)	3.7	-1.2 (-2.5; -0.2)
Patient global VAS, mm	58	-29 (-52; -7)	60	-22 (-38; -4)§	60	-18 (-45; -1)
Physician global VAS, mm	36	-23 (-36; -11)	38	-21 (-31; -7)	37	-18 (-44; -3)
Pain VAS, mm	53	-28 (-45; -9)	59	-24 (-40; -5)	58	-26 (-46; 0)
Fatigue VAS, mm	62	-19 (-41; 0)	63	-16 (-35; -1)	63	-13 (-33; 11)
CRP, mg/L	12	-8 (-22; 0)	9	-4 (-17; 0)	10	-6 (-22; 0)
ESR, mm/h	18	-11 (-24; -2)	16	-8 (-18;-2)	20	-5 (-31; 0)

*p=0.03 vs. non-switchers, #p=0.003 vs. non-switchers, §p=0.04 vs. non-switchers

Disclosure: E. Lie, Abbott Immunology Pharmaceuticals, 5, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5 ; **D. M. F. M. van der Heijde**, Amgen, 5, Abbott Immunology Pharmaceuticals, 5, Centocor, Inc., 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5 ; **T. Uhlig**, None; **M. S. Heiberg**, None; **E. Rødevand**, None; **C. Kaufmann**, None; **K. Mikkelsen**, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Pierre-Fabre, 5, UCB, 5, Schering-Plough, 5, Nycomed, 5 ; **W. Koldingsnes**, Abbott Immunology Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Roche Pharmaceuticals, 5 ; **T. K. Kvien**, Wyeth Pharmaceuticals, 5, Roche Pharmaceuticals, 5, UCB, 5, Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Bristol-Myers Squibb, 5 .

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Psoriatic Arthritis in a Diverse Ethnic Cohort. Gail S. Kerr[1], John S. Richards[2], Hashem Vahabzadeh-Monshie[3], Chesahna Kindred[4], Iraj Sabahi[5], Annyce Treherne[3], Michael D. Alpert[3], George Cohen[6] and Richard Amdur[3], [1]VAMC, Georgetown and Howard University Hospitals, Washington, DC, [2]VAMC, Geogetown University Hospital, Washington, DC, [3]VAMC, Washington, DC, [4]Howard University Hospital, Washington, DC, [5]Washington Hospital Center, Washington, DC, [6]VAMC, Howard University Hospital, Washington, DC

Purpose: Present literature is sparse concerning psoriasis (PSO) and psoriatic arthritis (PsA) in minority populations, often retrospective and lacking current measures of disease burden and activity. Our objective was to determine the prevalence, disease severity and activity and quality of life of PsA in a diverse ethnic cohort of patients with PSO.

Method: Patients with confirmed PSO or PsA seen in dermatology and rheumatology clinics at 2 institutions during a12 month period were enrolled. Patient demographics, disease duration, smoking (never, former, current), anti-TNF therapy, and body mass index (BMI) were recorded. Patients were examined to ascertain type of psoriasis (plaque, guttate, pustular), psoriasis area and severity index (PASI), arthritis pattern (appendicular, axial) and tender, swollen joint counts. ESR, CRP, uric acid were obtained, and DAS28 calculated. Questionnaires were administered for functional status (MD-HAQ) , quality of life (SF-36, PSORIQoL, PsAQoL) and fatigue (Multidimensional

Assessment of Fatigue-MAF). Employment status (yes, no), education level (high school, college) and insurance coverage information (yes, no) were obtained.

Results: Eighty-four PSO patients (39 African Americans (AA), 45 Caucasians), predominantly males (91%), of mean age 59.9, years (11.7) were enrolled. PsA occurred in 27.9%, with mean disease duration of 21.6 (14.8) years. PsA followed the diagnosis of PSO by a mean of 6 years, but occurred earlier in AA (3.5 yrs vs 8.4 yrs). PsA was one third less prevalent in AA compared to Caucasians (13.9% vs 39.5%, p<.01). Appendicular arthritis and plaque psoriasis were the predominant patterns. AA and Caucasians differed significantly in PSO disease duration (20.6 ± 17.4 vs 32.4 ± 21.5, p<.05), insurance coverage (57.6 % vs 80.5%, p<.05), alcohol use (29.4% vs 69.3%, p<.01) and trended to lower mental component of SF-36 scores (38.7 ± 7.0 vs 41.7 ± 7.1, p=.06). Smoking, education level, employment status, BMI, uric acid levels, MAF and PSORIQoL were similar in both groups. In those with PsA, there was no ethnic difference in MD-HAQ, DAS28, or PsAQOL scores. Anti-TNF therapy was prescribed in 27.4% of the cohort, and despite less insurance coverage in AA, was not statistically different from Caucasians (20% vs 32.6%). PSO with and without PsA were similar in all variables.

Conclusion: In this study cohort, psoriatic arthritis occurred in approximately one third of patients with psoriasis. Psoriatic arthritis in African Americans was one third less prevalent than in Caucasians, but of equal disease burden. The diagnosis of psoriasis in African Americans appeared to have less psychological impact and the lack of medical coverage was not an impediment to receive biologic therapy. Enrollment continues to examine the validity of these findings.

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Predicting Major Quality of Life Improvement Via PASI or HAQ in Psoriatic Arthritis Patients. Bruce W. Kirkham[1], Wenzhi Li[2], Charles T. Molta[2], Amitabh Singh[2] and Arthur Zbrozek[2], [1]Thomas Guy House and University of New South Wales-Sydney, London, England, [2]Wyeth Research, Collegeville, PA

Purpose: Patients with psoriatic arthritis (PsA) suffer significant morbidity from both skin and joint disease. Biologic therapy has benefited both areas. However, the relative effects of skin or physical function morbidity reduction on the enhancement of health status is not presently understood, reducing our understanding of the value of clinical improvement. The objective of this analysis was to compare the predictive power *post hoc* of skin sign and physical function in major quality of life improvement ie, to the general population level, in a population with active PsA.

Method: A 12-week randomized double-blind study followed by a 12-week open-label extension; subjects received etanercept 50 mg BIW or 50 mg QW during the double-blind period followed by 50 mg QW during the open-label period. Key eligibility criteria included: age >18 y; stable, moderate-to-severe plaque psoriasis with ≥2 swollen/painful joints, and no previous anti-TNF therapy. PASI for psoriasis signs, HAQ for physical function, and EQ-5D VAS were measured at baseline, and Weeks 12 and 24. Logistic regressions predicted a change in EQ-5D VAS to at least 82 (0-100 scale), a level consistent with the general population. Meaningful changes from baseline as predictors: HAQ= 0.375, 0.5; PASI= 50%, 75%.

Results: At baseline, subjects (n=752) had a mean age 47 y, were 63% male, and 89% white. Mean number of tender joints= 19.2, and swollen joints= 12.5. Mean durations of psoriasis and PsA= 19 and 7 years, respectively. Baseline scores were not significantly different between the 2 groups; pooled baseline (mean±s.d.) PASI= 19.43 ±10.28, HAQ= 0.91±0.69, and EQ-5D VAS= 55.55 ±20.73. Only PASI change from baseline at Week 12 differentiated treatment groups. Pooled reductions from baseline to W24 (LOCF) were: PASI= 75.9%, and HAQ= 52.0%. Proportion achieving EQ-5D VAS (≥82)= 44.4%. HAQ change from baseline of ≥0.375 was most consistent change predictor in improving the quality of life score to the general population level, with HAQ change ≥0.375 at Week 12 being the strongest single predictor. Higher baseline HAQ scores reduced the odds for major quality of life improvements at both Weeks 12 and 24.

Odds ratios* of EQ-5D VAS to ≥82

Week 12 (N= 723) Week 24 (N= 723)

	Estimate (95% C.I.)	Estimate (95% C.I.)
EQ-5D VAS baseline	1.04 (1.03 – 1.05)	1.03 (1.02 – 1.04)
HAQ baseline	0.39 (0.26 – 0.59)	0.47 (0.32 – 0.67)
HAQ change ≥0.375	2.68 (1.37 – 5.25)	2.25 (1.20 – 4.24)
HAQ change ≥0.50	2.09 (1.10 – 3.98)	
PASI change ≥50%	2.03 (1.16 – 3.55)	
PASI change ≥75%	1.88 (1.25 – 2.85)	2.40 (1.54 – 3.75)
Asian		0.22 (0.08 – 0.62)

*Factors reported were those significant ($p<0.05$).

Conclusion: Patients with less advanced PsA could have better odds of achieving an improvement in quality of life to the level consistent with that of the general population when treated to reduce both skin and joint morbidity.

Disclosure: B. W. Kirkham, Abbott Laboratories, 2, Wyeth Pharmaceuticals, 9, Amgen, 9, Centocor, Inc., 9, Bristol-Myers Squibb, 9, Schering-Plough, 9 ; **W. Li**, Wyeth Research, 3 ; **C. T. Molta**, Wyeth Pharmaceuticals, 3 ; **A. Singh**, Wyeth Research, 3 ; **A. Zbrozek**, Wyeth Research, 3 .

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Cross-Sectional Evaluation of Different Retreatment Schedules with Infliximab in Daily Practice Treatment of Patients with Ankylosing Spondylitis. M. Devinck[1], H. Mielants[2] and F. Van den Bosch[3], [1]University hospital, Gent, Belgium, [2]University Hospital, Gent, Belgium, [3]Univ Hosp, Ghent, Belgium

Purpose: Since 2004, TNF blocking agents became available in Belgium for patients with active, NSAID-refractory ankylosing spondylitis (AS). The reimbursement criteria for infliximab stipulate that after a conventional loading dose regimen, all patients should be retreated with a dose of 5 mg/kg and an interval of 8 weeks. Only in case of repeated (on 2 consecutive retreatment visits) and significant raise of the BASDAI (increase with at least 50% or 20 points on a 0-100 scale), the retreatment interval can be decreased to every 6 weeks. To our knowledge, Belgium is the only country where this stepwise reimbursement system is used; in most other countries the decision on the retreatment interval is at the discretion of the treating rheumatologist. The objective of this study is to evaluate the efficacy of infliximab in daily practice treatment of patients with AS. **Methods:** A cross-sectional evaluation of all AS patients currently treated at our department was performed from the 1st of March until the 30th of April 2009. Values for BASDAI and BASFI were collected for all patients at time of retreatment. Retreatment regimen (every 8 weeks (q8w), every 6 weeks (q6w), other), age of the patient, and duration of treatment with infliximab (weeks) was recorded.

Results: A total of 102 patients was evaluated : 85 patients are retreated with an interval of 8 weeks, whereas only 15 patients are retreated with a shorter interval of 6 weeks. Of interest is the fact that there are 2 patients that are retreated with a longer interval (10 or 12 weeks). Results are summarised in the table (median value and range are presented). Both with regard to the BASDAI and the BASFI, a higher median value was observed in the patients that are retreated every 6 weeks. Of the 15 patients, 7 had a BASDAI value greater than 40.

	Q6w	Q8w	Q10/12w
Nr of patients	15 (15%)	85 (83%)	2 (2%)
Age (years)	52 (30/71)	47 (22-75)	44 (41-47)
Male/female ratio	10/5	70/15	2/0

Duration of treatment	204 wks (17-491)	243 wks (13-500)	355 wks (287-422)
BASDAI (0-100)	36 (3-70)*	20 (0-75)	24 (10-37)
BASFI (0-100)	49.5 (0-96)**	20 (0-85)	33 (0-65)

*p=0.084, ** p=0.008 comparison between q6w en q8w, using T-test

Conclusion: Low BASDAI and BASFI scores are observed in AS patients chronically retreated with infliximab every 8 weeks. Pharmacoeconomically, these data support the stepwise reimbursement approach where patients are only treated with the more intensive q6w regimen in case of documented high disease activity. In the group retreated every 6 weeks, the median values for these assessments are higher, reaching statiscal significance for the BASFI. Several interpretations are possible. The higher BASFI might suggest more structural damage, pointing towards a subgroup possibly needing more frequent treatment. On the other hand, the higher BASDAI could suggest that even with a shorter retreatment interval, the disease is still not adequately controlled in a number of patients, and that other treatment options should be considered.

Disclosure: M. Devinck, None; **H. Mielants**, Abbott Laboratories, 9 ; **F. Van den Bosch**, None.

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Higher Remission Rates in Psoriatic Arthritis: Cause and Effect. Tajvur P. Saber[1], Chin Teck Ng[1], Guillaume Renard[1], Bernadette M. Lynch[1], Alexia Grier[1], Patricia Minnock[2], Madeline O'Neill[2], Louise Moore[2], Marian Molloy[1], Barry Bresnihan[1], Oliver M. FitzGerald[1], Ursula Fearon[1] and Douglas J. Veale[1], [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Rheumatology Rehabilitation, Our Lady's Hospice, Dublin, Ireland

Background: Psoriatic arthritis (PsA) is an inflammatory arthritis with a higher male prevalence.TNF targeted drugs have proven efficacy in randomised controlled trials. Previous studies highlight an association between Testosterone and HLA B 27.

Purpose: To assess remission in a PsA compared to an RA cohort matched for disease activity and to identify possible factors associated with remission.

Methods: A prospective analysis of a biologic database 2004-08 was performed. Patients attend prior to commencing biologic therapy and at 3, 6 and 12 months. Baseline characteristics collected included age, gender, disease duration, smoking status, rheumatoid factor, previous DMARDS, 28 joint count, patient global assessment VAS, CRP, DAS 28 using CRP and HAQ score. Values are expressed as median, analysis used Wilcoxin Rank Sum, Oneway Anova and Chi-Square tests.

Results: 152 PsA patients completed 1 year follow up, 47% were male. Measures of disease activity significantly improved in PsA patients from baseline to 12 months post treatment (see table) TJC ($p<0.01$), SJC ($p<0.01$), CRP ($p<0.01$), HAQ ($p<0.01$). DAS28 remission (<2.6), validated for PsA, was achieved in 58% of PsA patients from baseline 4.86 to 2.23 ($p <0.001$). Male PsA patients attained significantly lower DAS28 scores than females 1.88 vs 2.65 at 1 year ($p <0.05$). To compare remission rates in PsA vs RA, we analysed a subset of patients matched for disease activity at baseline (n=41, in each group). Remission rates defined by DAS28 were significantly greater in PsA patients ($p=0.01$), 59% PsA patients vs 44% RA patients at 12 months.

Conclusion: PsA patients with significant disease activity at presentation achieved high levels of remission at one year. Male gender is significantly associated with a favourable outcome, this may be further evidence of an important association between testosterone, HLA B27 and spondyloarthropathy which deserves further study. Remission was significantly higher in PsA than RA patients in a disease activity matched cohort.

References: Lynch et al; Arthritis and Rheumatism, October 2008

W H James; Sex ratios and hormones in HLA related, Ann Rheum Dis. 1991 June; 50(6): 401–404.

Months	TJC			SJC			CRP			DAS28 4V CRP			HAQ		
	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F
0	7	6	8	5	4.5	5.5	9	8.5	11	4.86	4.65	5.03	0.875	0.625	1.25
3	2	0.5	2.5	1	0.5	2	4	4	4	2.99	2.75	3.37	0.5	0.375	0.625
6	0	0	2	0	0	1	4	4	4	2.44	1.81	2.84	0.25	0.625	0.5
12	0	0	0	0	0	0	4	4	4	2.23	1.88	2.65	0.25	0	0.375

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The Sensitivity of National Criteria to Assess Eligibility for Biologic Therapy in Patients with Ankylosing Spondylitis. Sarah M. Keidel[1] and Antoni Chan[2], [1]Dept. of Rheumatology, Royal Berkshire Hospital NHS Foundation Trust, Reading RG1 5AN, United Kingdom, [2]Royal Berkshire Hospital, NHS Foundation Trust, Reading RG1 5AN, United Kingdom

Background: Ankylosing spondylitis (AS) is an inflammatory arthritis primarily affecting the vertebrae. Anti-TNF therapy has been shown in randomized controlled trials to reduce composite measures of disease activity and is assumed to prevent the accumulation of structural damage. In the United Kingdom, the National Institute of Clinical Excellence (NICE) has developed guidelines for the treatment of AS with anti-TNF agents (May 2008, TA 143).

Purpose: To determine the cohort of AS patients in our hospital who would qualify for anti-TNF therapy under the NICE guidance, and to determine if this guidance is sensitive in selecting patients who would benefit from anti-TNF therapy.

Method: Patient cohort identified (251 AS patients) in August 2008 via patient database and updated by a review of clinic letters. Available case notes (174 patients, 69%) were reviewed retrospectively. Patient demographics, radiographic data and assessment scores (Bath AS scores) were recorded.

Results: 174 patients with AS were studied. Mean age was 46.8 years (SD 13.7) and disease duration 12 years. 13 patients (7%) were already on anti-TNF agents (n= 3 patients on Infliximab, 5 on Etanercept and 5 on Adalimumab). 4 patients (2%) fulfilled all 3 NICE criteria and were therefore eligible for anti-TNF therapy. 3 patients (2%) had a contraindication to anti-TNF therapy (coexistent multiple sclerosis and chronic sepsis). 53 patients (30%) did not qualify for anti-TNF therapy due to outright failure of at least 1 NICE criterion. Of these patients, 18 (10%) failed to satisfy the New York (NY) criteria due to normal sacroiliac radiographs, despite evidence of sacroiliitis on MRI.

28 patients (16%) fulfilled 2 out of 3 NICE criteria (26 patients met NY criteria and ≥ 2 NSAIDs, 2 patients met NY criteria and BASDAI ≥4). 65 patients (37%) fulfilled 1 out of 3 NICE criteria (56 patients met NY criteria, 9 patients were treated with ≥2 NSAIDs). These 101 patients are undergoing further assessment in a specialist AS clinic to determine whether the remaining NICE criteria are satisfied.

Conclusion: In our study, 4 patients with ankylosing spondylitis were eligible for anti-TNF therapy in accordance with the NICE guidelines, in addition to 13 patients already on treatment. These NICE-compliant patients represent 23% of our AS population where complete data are available. 58% of our patients require further assessment including follow-up Bath AS indices to determine their status against the NICE guidance. It is expected that approximately 23% of these patients will also qualify for anti-TNF therapy.

A significant proportion of our patients (10%) were ineligible for anti-TNF treatment due to failure to fulfill NY criteria despite sacroiliitis on MRI. This included patients with early AS. New diagnostic criteria for AS should include MRI to increase the sensitivity of screening for patients who may qualify for anti-TNF therapy, as radiographic change may take years to develop[1,2].

[1]Song I et al, *Ann Rheum Dis* 2008 Nov;67(11):1535-40, [2]Rudwaleit M et al, *Arthritis Rheum* 2005 Apr;52(4):1000-1008.

Disclosure: S. M. Keidel, None; **A. Chan**, None.

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Are Clinical and Radiologic Outcomes the Same for Patients with Moderate Vs. Severe Disease Activity at Baseline in Patients with Psoriatic Arthritis? - *Post-Hoc* Analysis of ADEPT. Philip Mease[1], Arthur Kavanaugh[2], Renee Perdok[3], Hartmut Kupper[4] and Frédéric Lavie[5], [1]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [2]University of California San Diego, La Jolla, CA, [3]Abbott Laboratories, Abbott Park, IL, [4]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [5]Abbott Laboratories, Rungis, France

Purpose: Patients (pts) in psoriatic arthritis (PsA) trials usually have severe disease activity at baseline, yet most pts in clinical practice have more moderate disease. This *post-hoc* analysis compared clinical and radiographic responses to placebo (PBO) and adalimumab (ADA) for pts with moderate vs. severe PsA.

Methods: Observed clinical data at Weeks 2, 12, 24, and 48 and radiographic data at Weeks 24 and 48 of the ADEPT study were analyzed.[1] Pts were classified by the 28-joint Disease Activity Score (DAS28) as having moderate (<5.1) or severe (≥5.1) PsA at baseline. Outcomes included ACR20, 50, and 70 responses at Weeks 2, 12, 24, and 48, and mean change in modified total Sharp score (ΔmTSS) between baseline and Weeks 24 and 48. Data from pts who received PBO or ADA during the first 24 weeks of ADEPT were analyzed separately. All pts were switched to ADA in an open-label extension after Week 24.

Results: Data from 288 ADEPT pts were analyzed (ADA, N=145; PBO, N=143). Of these 288 pts, 172 pts (ADA, n=86; PBO, n=86) had moderate PsA and 116 pts (ADA, n=59; PBO, n=57) had severe PsA at baseline. At Weeks 12, 24, and 48, no differences were observed in ACR20 and ACR50 responses between pts with moderate vs. severe PsA at baseline. Conversely, at Weeks 24 and 48, a statistically significantly greater ACR70 response was observed in the ADA-treated pts with moderate PsA at baseline ($p<0.05$). Similarly, we observed a trend for a greater radiographic outcome at Week 48 in pts with moderate PsA at baseline in both treatment groups. Results of clinical and structural evaluations at Week 48 are presented in the table.

Clinical and Radiographic Responses to ADA and PBO for Pts With Moderate vs. Severe PsA

Outcome at Week 48		**Baseline DAS28 <5.1**	**Baseline DAS28 ≥5.1**
ACR20, n (%)	ADA	77 (68.8)	51 (68.6)
	PBO/ADA	83 (54.2)	55 (58.2)
ACR50, n (%)	ADA	77 (53.2)	51 (51.0)
	PBO/ADA	83 (39.8)	55 (38.2)
ACR70, n (%)	ADA	77 (42.9)[a]	51 (23.5)
	PBO/ADA	83 (21.7)	55 (23.6)
ΔmTSS, mean (SD) [n]	ADA	–0.1 (1.35) [69]	+0.4 (2.66) [44]
	PBO/ADA	+0.3 (3.52) [75]	+1.7 (5.13) [50]

[a]$p<0.05$ compared with ADA-treated patients with severe PsA (DAS28>5.1) at baseline using Fisher's exact test.

Conclusion: Treatment with ADA resulted in greater ACR70 response rates and in a trend for greater inhibition of radiographic progression for pts with moderate disease activity at baseline compared with patients with severe disease activity at baseline.

Reference: [1]Mease PJ, et al. *Arthritis Rheum*. 2005;52:3279–89.

Disclosure: P. Mease, Abbott Laboratories, 2, Abbott Laboratories, 8, Abbott Laboratories, 5 ; **A. Kavanaugh**, Abbott Laboratories ; **R. Perdok**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **H. Kupper**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **F. Lavie**, Abbott Laboratories, 3 .

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Comparison of Conventional X-Ray with CT Using SASSS for as Patients. Sang-Hoon Lee[1], So-Hee Park[1], So-Young Park[2], In-Ah Choi[1], Ji-Na Park[1], Seong-Su Nah[3], Yeon-Ah Lee[1], Seung-Jae Hong[1], Wook Jin[2] and Hyung-In Yang[1], [1]Internal Medicine, School of Medicine, Kyung Hee University, Seoul, South Korea, Seoul, South Korea, [2]School of Medicine, Kyung Hee University, Seoul, South Korea, EAST-WEST Neo Medical Center, Sagngil-dong, Gangdong-gu, Seoul, South Korea, Seoul, South Korea, [3]Soonchunhyang University College of Medicine, Cheonan, South Korea

Purpose: To compare conventional radiography and Computed tomography for evaluation of radiolographic progression in ankylosing spondlitis

Methods: All patient fulfilled the modified New York diagnostic criteria for AS and visited at Neo Medical Center of Kyung Hee university from March. 1, 2008 to February .1 2009. Assessment of radiolographic progression in conventional x-ray and computed tomography was performed with Stoke Ankylosing Spondylitis Spinal Score. All images were read twice and blindly by two readers.

Results: total 339 patients with AS were examined. Disease duration is less than 10 years and the mean age is 30.5±5.7 years. The proportion of male to female is 3:1 and 90.1% was HLA-B27 positive. Total SASSS is 15.9± 11.6 in X-ray and 19.7 ± 8.3 in CT. In sclerosis, syndesmophyte and bridging CT detected more than X-ray, but did not in erosion and squaring, significantly. There were significant differences in SASSS of conventional radiography versus those of CT in all L-spine level. Especially bone bridge and syndesmophyte was significantly detected when 3 dimensional reconstruction.

Conclusion: Conventional X-ray overestimates Erosion and squaring and underestimates sclerosis, syndesmophyte and bridging. Our study suggests that the CT is more appropriate method than X-ray for assessing radiographic change in AS.

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Effect of Anti-Tumor Necrosis Factor–α Treatment On the Arterial Stiffness, Carotid Intima-Media Thickness and Rheological Parameters of Blood in Active Psoriatic Arthritis. Tatiana V. Korotaeva[1], Elena Yu. Loginova[1], Diana S. Novikova[1], Evelina S. Mach[1], Lev N. Denisov[1], Nadezhda V. Klimova[1], Shandor Erdes[1], Evgeniy L. Nasonov[1] and Nikolay N. Firsov[2], [1]Institute of Rheumatology of Russian Academy of Medical Sciences, Moscow, Russia, [2]Russian State Medical University, Moscow, Russia

Systemic inflammation may play an important role in the increased cardiovascular mortality of psoriatic arthritis (PsA). Suppression of inflammation with TNF antagonists may improve vascular function in PsA.

Purpose: We examined the changes of mean/maximum carotid intima-media thickness (m-c-IMT/max-c-IMT), arterial stiffness (AS) and parameters of red blood cell aggregation (RBCA) for Adalimumab (ADA) treatment in psoriatic arthritis (PsA) patients (pts)**.**

Method: 18 active PsA pts, age range 24-56 y.o., were treatment ADA 40mg s/c eow for 12 weeks. DAS_4, parameters of RBCA [T_1, Kt, $I_{2,5}$, β] were evaluated at baseline, 4, 12 weeks in erythroagregometer; c-IMT by ultrasound and AS by Pulce Trace Device (PT2000, Micro Medical, UK), carotid-femoral pulse wave velocity (PWVcf) with a 4MHz Doppler probe, stiffness index (SI) and resistance index (RI) with a digital volume photoplethysmography transducer were measured at baseline and 12 weeks. Statistical analyses were performed with Me (Q25; Q75) and Friedman/Wilcoxon tests (t.). All $p<0.05$ were considered to indicate statistical significance.

Results: At the baseline parameters of RBCA and PsA activity are shown: T_1=5.98 (5.42; 6.99), Kt=0.39 (0.33; 0.53), $I_{2,5}$= -8 (-9; -7), β=58.32 (47.0; 77.3), DAS_4 =4,79 (4.0;5.45). RBCA and DAS_4 improved significantly at week 4 [T_1=8.77 (7.9; 10.1), Kt=0.22 (0.17; 0.28), β=32.46 (20.7; 42.5), $I_{2,5}$= -26 (-29; -20); DAS_4=2.8 (2.1;3.1)]. These results were maintained at week 12 [T_1=9.2 (8.4; 11.4), Kt=0.22 (0.2; 0.27), β=34.0 (26.5; 41.9), $I_{2,5}$= -27.5 (-32; -22); DAS_4=1.6 (1.33;2.03)]. All parameters improved significantly (Fr. t., $p<0.002$). ADA treatment resulted significant reduced of m-c-IMT/max-c-IMT [from 0.78 (0.74; 0.84) to 0.73 (0.61; 0.74), W. t., $p<0.001$ and from 0.95 (0.95; 1.03) to 0.80 (0.66; 0.89) W. t., $p<0.002$ respectively], mostly parameters of AS: RI [from 69.5 (58; 74) to 49.5 (44; 64), W. t., $p<0.05$] and PWV cf [from 9.9 (7.7; 17.7) to 9,2 (7.4; 10.6), W. t., $p<0.005$].

Conclusion: ADA significantly improved PsA activity, AS, RBCA and c-IMT as marker of subclinical atherosclerosis.

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EQ-5D and SF-6D Perform Differently in Ankylosing Spondylitis (AS): A Follow-up Study of Patients Receiving Disease Modifying Therapy. Elisabeth Lie[1], Siri Lillegraven[1], Désirée M.F.M. van der Heijde[2], Maria K. Kvamme[3], Till Uhlig[1] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Inst of Health Management and Health Economics, University of Oslo, Norway

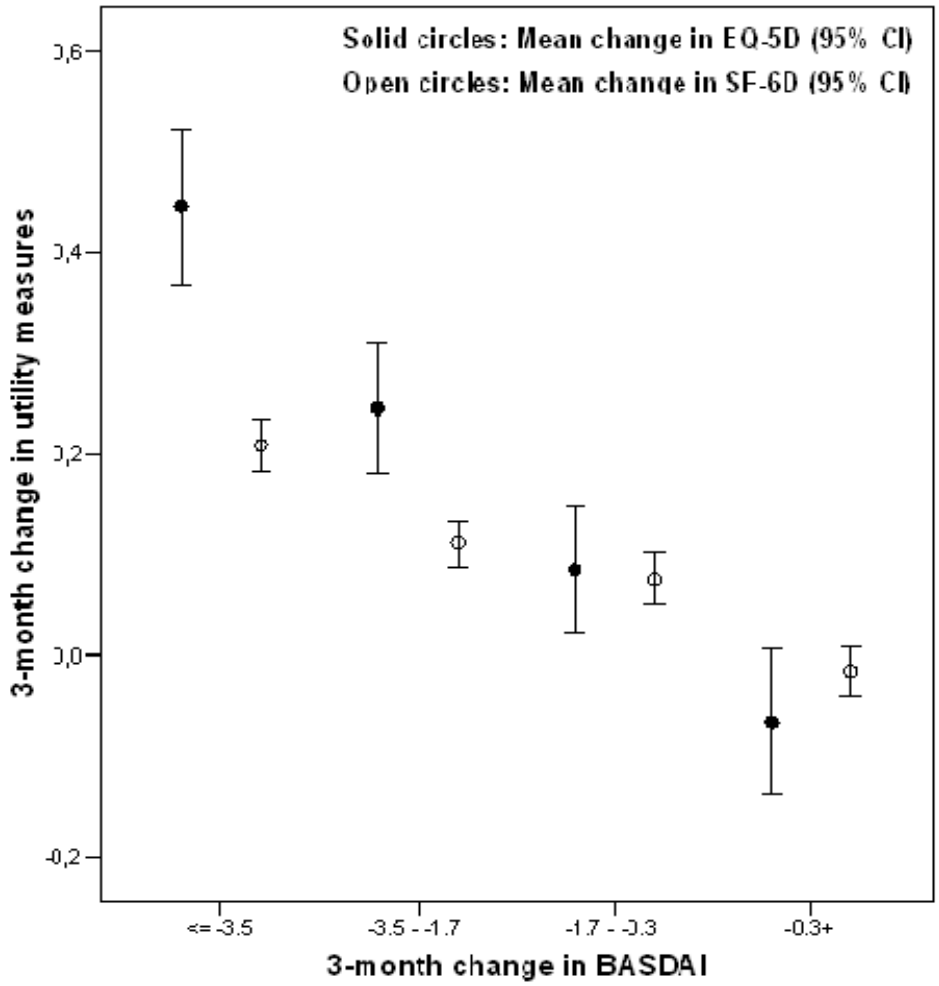
Purpose: Biological therapy has constituted a major advance in the treatment of AS, but therapy is costly and this has raised an interest in the economics of treatment. Preference based instruments like EQ-5D and SF-6D are used to obtain health state utility values which are needed in cost-utility analyses of treatment interventions. In this study we wanted to examine how these measures relate to each other and to BASDAI and BASFI in AS patients (pts) treated with DMARDs or biologicals.

Methods: AS patients were extracted from a multi-center treatment registry where pts with inflammatory arthropathies starting treatment with DMARDs and biologicals are followed longitudinally. 448 pts (67% male, 90% HLA-B27 pos, biologicals n=373, DMARDs n=75) were included for analyses of baseline data. 309 pts had available 3-month data. Baseline and 3-month changes for BASDAI, BASFI, EQ-5D and SF-6D were analysed descriptively and by Spearman correlation coefficients. Baseline BASDAI and BASFI and the 3-month changes of these measures were divided into quartiles, and EQ-5D/SF-6D values/changes were plotted against these quartiles.

Results: At baseline pts had mean/median BASDAI 5.6/5.8, BASFI 4.5/4.5, SF-6D 0.59/0.58 and EQ-5D 0.42/0.59. EQ-5D showed a bimodal distribution. Table 1 shows the utility values across quartiles of baseline BASDAI/BASFI. Pts had the following mean(SD) 3-month changes: BASDAI -2.0(-2.3), BASFI -1.3(-2.0), EQ-5D 0.18(0.34), SF-6D 0.09(0.13). We found significant, moderate correlations (rho range -0.59 to -0.66) between 3-month changes in EQ-5D/SF-6D and BASDAI/BASFI, and between changes in the two utility measures. The figure displays mean changes in EQ-5D/SF-6D in relation to quartiles of BASDAI change. Analysis with quartiles of BASFI change (data not shown) yielded a very similar result.

	BASDAI <4.2	**BASDAI 4.2-5.8**	**BASDAI 5.8-7.1**	**BASDAI >7.1**
Mean/median EQ-5D	0.69/0.73	0.52/0.66	0.34/0.26	0.12/0.00
Mean/median SF-6D	0.68/0.67	0.61/0.60	0.57/0.55	0.50/0.51
	BASFI <2.6	**BASFI 2.6-4.5**	**BASFI 4.5-6.3**	**BASFI >6.3**
Mean/median EQ-5D	0.68/0.73	0.52/0.66	0.36/0.52	0.12/0.00
Mean/median SF-6D	0.68/0.68	0.60/0.60	0.56/0.56	0.50/0.51

Conclusion: EQ-5D is better able to discriminate between different levels of disease activity as compared to SF-6D, which shows a much narrower range. In pts with most improvement in BASDAI, EQ-5D gave twice the utility gain of SF-6D. These data demonstrate that changes in EQ-5D and SF-6D can differ considerably during treatment in AS and subsequently may yield quite different cost-utility results.



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Application of a New Composite Measure of Minimal Disease Activity in Patients with Psoriatic Arthritis Treated with Adalimumab: Subanalysis of the ADEPT Trial. Philip Mease[1], Renee Perdok[2], Sonja Kary[3] and Hartmut Kupper[3], [1]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [2]Abbott Laboratories, Abbott Park, IL, [3]Abbott GmbH & Co. KG, Ludwigshafen, Germany

Purpose: TNF antagonists are highly effective in treating patients (pts) with psoriatic arthritis (PsA), usually within 12 weeks.[1] Most recently, a new outcome score measuring a minimal disease activity (MDA) state was developed for that incorporates various clinical manifestations of PsA. We performed a *post-hoc* analysis of MDA achievement in pts with active PsA treated with adalimumab (ADA) or placebo (PBO) in a 24-week randomized controlled trial (ADEPT).[2]

Methods: MDA is defined as achievement of 5 of the 7 following criteria: tender joint count (TJC, 0–78) ≤1, swollen joint count (SJC, 0–76), Psoriasis Activity and Severity Index (PASI) ≤1 or body surface area (BSA) ≤3%, pt pain on a visual analog scale (VAS, 0–100 mm) ≤15, Patient's Global Assessment of disease activity (PaGA; VAS 0–100 mm) ≤20, Health Assessment Questionnaire (HAQ) ≤0.5, and tender entheseal points (no definition of enthesitis scoring methodology, 0–13) ≤1.[3] Adults with active PsA (≥3 TJC and ≥3 SJC) self-administered ADA 40 mg or PBO every other week for 24 weeks. For calculation of MDA at Weeks 12 and 24, we used the PASI and a heel-limited enthesitis score (0–4). We alternatively evaluated MDA by 5 of 6 criteria (omitting the enthesitis score). Only pts with PsA and active psoriasis (Ps) (i.e., BSA ≥3% affected) were included.

Results: Of the 313 pts with active PsA enrolled in ADEPT, 140 pts had Ps with ≥3% BSA affected and data for all other required criteria of the MDA definition (70 pts received PBO and 70 received ADA). Baseline characteristics in ADA/PBO-treated pts were mean age, 50/48 years; female, 41%/44%; median TJC, 21/26; median SJC, 13/12; median PaGA 49/48; median pain, 53/48; median PASI, 5.5/6.4; median HAQ, 1/1.06; and mean enthesitis, 0.8/1. At Week 24, data were available from 61 (87%) PBO- and 65 (93%) ADA-treated pts. At Week 12, 33.3% of ADA- and 3.1% of PBO-treated pts achieved MDA based on 5 of 7 criteria ($p<0.001$). At Week 24, the percentages were 40.0% (ADA) and 6.5% (PBO) ($p<0.001$). When using 5 of 6 criteria for MDA, 24.2% and 1.6 % of ADA- and PBO-treated pts achieved MDA at Week 12 ($p <0.001$) and 32.3% and 1.6% of ADA- and PBO-treated pts achieved MDA (5 out of 6) at Week 24 ($p<0.001$). Fulfillment of individual MDA components are also summarized (table).

Observed Percentages of Pts Who Fulfilled Individual MDA Criteria at Baseline, Week 12, and Week 24

	Baseline		Week 12		Week 24	
MDA Criterion Fulfilled	**ADA (n=70)**	**PBO (n=70)**	**ADA (n=66)**	**PBO (n=64)**	**ADA (n=65)**	**PBO (n=61)**
TJC≤1, %	0	0	33.3	7.8	40.0	9.8
SJC≤1, %	4.3	1.4	28.8	12.5	35.4	14.8
PaGA≤20, %	20.0	14.5	55.4	10.9	50.8	18.0
Pain≤15, %	7.1	8.7	47.4	6.3	49.2	11.5
PASI≤1, %	1.4	4.3	45.5	3.2	58.5	3.3
HAQ≤0.5, %	25.7	27.1	56.9	34.4	52.3	34.4
Enthesitis ≤1, %	75	68.6	83.1	64.1	82.8	67.2

Conclusion: This study demonstrates the application and utility of a new composite measure of MDA in PsA. Approximately one-third of pts with PsA who had both active arthritis and active Ps experienced MDA after 12 and 24 weeks of ADA treatment.

References: [1]Furst DE, et al *Ann Rheum Dis.* 2008;67:iii2–25; [2]Mease PJ, et al. *Arthritis Rheum.* 2005;52:3279–89; [3]Coates LC, et al. *Ann Rheum Dis.* 2009.doi:10.1136/ard.2008.102053.

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Development of a Composite Psoriatic Disease Activity Index. Aizad Mumtaz[1], Phil Gallagher[2], Brian Kirby[1], Laura C. Coates[3], Robin Waxman[4], Tom O'Hara[5], Douglas J. Veale[6], Philip S. Helliwell[3] and Oliver FitzGerald[7], [1]St Vincents University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]University of Leeds, Leeds, United Kingdom, [4]Leeds, United Kingdom, [5]Trinity College, Dublin, Ireland, [6]St.Vincent's University Hospital, Dublin, Ireland, [7]St Vincent's University Hospital, Dublin, Ireland

Purpose: To develop a composite disease activity index for Psoriatic disease and to further test its ability as a responder index in patients undergoing treatment.

Method: All patients included were recruited from our rheumatology out- patients and satisfied the CASPAR criteria for diagnosis of Psoriatic Arthritis . Five domains were assessed including joint, skin, dactylitis, enthesitis and back involvement to formulate the Composite Psoriatic Disease Activity Index (CPDAI). Specific instruments were employed to determine the extent of domain involvement and their effect on quality of life/function: joint (68 tender, 66 swollen joint counts, HAQ), enthesitis (Leeds enthesitis index, HAQ), spine (BASDAI, ASQOL), skin (PASI, DLQI) and dactylitis (Digit count and HAQ). Disease activity was then graded as mild, moderate and severe using these instruments on a severity score of 0 to 3. The maximum attainable score was 15. Patient and physician related global disease activity measures were also recorded and a physician was independently asked to indicate if treatment change was required. Spearman's rank correlation coefficient was applied to check for correlation between the CPDAI, patient and physician global assessments. A tree analysis to depict the cut off values of the CPDAI predicting a treatment change was also derived.To explain maximum variability in the data,factor analysis with component extraction was done. To overcome the problem of patients without involvement of a particular domain, weighted linear scale regression analysis was performed. Finally binary logistic regression analysis was used to evaluate which factors most predict the treatment change.

Results: In total 92 patients were analysed; median age was 46 years with a range of 52 (20-72); mean duration of arthritis before the first assessment was 10 months.In total treatment change was thought indicated in 33 patients. The median CPDAI score consistent with change of treatment required was 9 (n=92) ($p<0.05$);in patients not requiring treatment change the median of CPDAI values was 3. The tree analysis revealed that 96.3 percent of patients had their treatment changed if their CPDAI values were greater than 6;none of the patients had their treatment changed when CPDAI values were <5. The CPDAI showed significant correlation with the patient($r=0.834$) and physician($r=0.825$) derived global assessments($p=0.01$).The linear regression model demonstrated that the HAQ, LEI, PASI, swollen joint count and dactylitis are the factors contributing most to the CPDAI . Binary logistic regression analysis revealed the HAQ, tender joint count and dactylitis as most closely predicting a need for treatment change.

Conclusion: The CPDAI is an effective tool which correlates with patient and physician global health assessments and which clearly distinguishes those who require a treatment change from those who do not. Further testing of the CPDAI in patients undergoing treatment change is underway.

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High-Field MRI in Patients with Ankylosing Spondylitis Under Etanercept Treatment. Maria Hoehle, Rheumatology, Hamburg, Germany

Purpose: Data on efficacy were collected in axial AS patients who received etanercept (ETA) monotherapy for up to 7 ys. High-field MRI was used to measure disease activity.

Method: A retrospective investigation was undertaken in 20 patients with axial AS who had received ETA monotherapy continuously since 2001. Diagnosis was based on clinical parameters according to the modified New York and/or European Spondylarthropathy Study Group preliminary criteria. BASFI, BASDAI, CRP, ESR and AS DAS were measured as clinical and paraclinical parameters of disease activity. For reasons of radiological protection, high-field MRI was used as the imaging technique for the cervical, thoracic and lumbar spine with imaging of the iliosacral joint in native T1, T1 fat saturation/fat saturated T2-weighting (STIR), as well as a fat-saturated T1-weighting before and after i.v. application of contrast medium (gadolinum). If clinical symptoms were present, MRI of hip joints was also carried out. MRI scans were interpreted analogous to the known m-SASSS and supplementary to the additional possibilities of MRI in terms of the early detection of inflammatory activity with contrast medium enhancement. The axial AS patients were divided into 3 groups. First group early axial AS: at the start of treatment, high AS criteria and/or AS DAS, in CM high-field MRI: Grade 1 sacroiliitis with/without spinal

activity (possible hip joints) without bony remodelling processes and/or erosions. Second group active established axial AS: at the start of treatment, high AS DAS criteria, Grade 2 sacroiliitis with/without spinal involvement and bony remodelling processes and/or erosions less than 50%. Third group chronic established axial AS: at the start of treatment, high AS DAS criteria, Grade 3 and upwards sacroiliitis with inflammatory activity and bony remodelling processes with syndesmophyte formation more than 50%.

MRI examination took place according to the scheme: baseline, 6 months, annually after the start of therapy and individually after clinical and radiological complete remission.

Results: 20% of patients were assigned to Group 1, 60% of patients to Group 2 and 20% of patients to Group 3.

In all patients in Group 1 a clinical and MRI-recorded complete remission occurred after a period of at least 2 but not more than 3 ys, so that the ETA therapy could be ended. 4 further annual controls continued to show a remission. In Groups 2 and 3, a reduction in MRI-measured disease activity criteria (m-SASSS) from 3 to 0, and a score as low as Grade 1 in the ASspiMRI-a, as well as bony remodelling processes and an improvement in functional parameters, were recorded. Attempts to discontinue ETA led, however, to reactivation of the inflammatory disease.

Conclusion: Continuous monotherapy with ETA led to a clinical and MRI-recorded complete remission within 3 ys in the patients with high clinical activity and Grade 1 sacroiliitis in high-field MRI (with CM) with and without spinal activity without bony reaction, remodelling processes and erosions (corresponds to the group with early AS). In this group of patients, ETA could be stopped. A further 4 years of follow-up showed no return of symptoms. Due to its sensitivity, high-field MRI with CM enhancement should be used as a diagnostic tool for the early detection of axial AS.

Disclosure: M. Hoehle, None.

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Rheumatologist Training to Recognize Lesions On T1-Weighted MRI Enhances Diagnostic Utility of MRI in Patients with Ankylosing Spondylitis. Walter P. Maksymowych[1], Ulrich Weber[2], Juerg Hodler[2], Mikkel Ostergaard[3], Susanne J. Pedersen[3] and Robert GW Lambert[1], [1]University of Alberta, Edmonton, AB, [2]University Clinic Balgrist, Zurich, Switzerland, [3]Copenhagen University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark

Purpose: In using MRI to diagnose AS, we have shown that rheumatologists rely primarily on diagnostic information from fat-suppressed sequences where inflammation is readily discernable and de-emphasize the contribution of abnormalities on T1-weighted sequences (T1W) which may reflect difficulty in interpreting complex structural abnormalities such as erosions and sclerosis and the uncertain diagnostic significance of fat infiltration. We aimed to test the hypothesis that systematic calibration of readers directed at recognition of abnormalities on T1W MRI would enhance the diagnostic utility of MRI in early AS.

Method: Six experienced readers (4 rheumatologists, 2 radiologists) from 3 international centres, blinded to patient and diagnosis, independently assessed MRI scans (T1W and STIR) from the following subjects all aged < 45 years: 77 patients with AS; 85 controls (26 with mechanical low back pain (mLBP) and 59 healthy individuals). MRI scans of the SIJ were read systematically as described in a standardized online training module. We recorded bone edema, fat infiltration, erosions, and ankylosis according to standardized definitions using an online data entry system. In addition to deciding on the presence/absence of SpA, readers were asked to record the following: 1. Whether their diagnostic conclusion was primarily based on abnormalities observed on the STIR, T1W, or both. 2. Which type of lesion was the primary basis for the diagnostic conclusion. The exercise was repeated 6 months later on a random selection of 30 AS patients (symptom duration ≤ 5 years) and 34 controls (26 with mLBP and 8 healthy) from the original cohort after 2 training exercises directed at abnormalities on T1W MRI and development of a reference image set developed by group consensus.

Results: Diagnostic utility of MRI improved for both concordant as well as individual readers following calibration. Rheumatologist readers also based their diagnostic conclusion on the T1W MRI and recorded erosions as the principal diagnostic feature significantly more frequently after calibration ($p = 0.013$ and <0.0001, respectively). However, this was not accompanied by significant improvement in the inter-reader agreement of detection of erosions as recorded in individual SIJ quadrants.

	Pre-Calibration				**Post-calibration**			
	Sensitivity	**Specificity**	**LR+**	**LR-**	**Sensitivity**	**Specificity**	**LR+**	**LR-**

Individual reader (mean (range))	92.2% (76.7-100)	93.6% (79.4-100)	14.4	0.08	97.9% (96.7-100)	95.6% (88.2-100)	18.1	0.02
All Rheumatologists (mean (range)	91.7% (76.7-100)	91.2% (79.4-100)	10.4	0.09	97.8% (96.7-100)	94.1% (88.2-97.1)	16.6	0.02
Concordant data (all 6 readers)	66.7%	76.5%	2.8	0.44	90.0%	82.4%	5.1	0.12

Conclusion: Rheumatologist training directed specifically at detection of MRI abnormalities on T1W scans enhances diagnostic utility by increasing overall interpretation of the T1W scan.

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Does Fat Infiltration in the Sacroiliac Joint Contribute to the Diagnostic Utility of MRI in Ankylosing Spondylitis? Ulrich Weber[1], Susanne J. Pedersen[2], Juerg Hodler[1], Mikkel Ostergaard[2], Robert GW Lambert[3] and Walter P. Maksymowych[3], [1]University Clinic Balgrist, Zurich, Switzerland, [2]Copenhagen University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB

Purpose: Fat infiltration in bone marrow of the sacroiliac joint (SIJ) and spine is frequently detected on T1-weighted (T1W) MRI in patients with AS but also in healthy individuals and those with other causes of back pain. There have been no systematic studies to address its diagnostic utility in AS. We aimed to evaluate the diagnostic utility of fat infiltration in the SIJ per se and to determine whether any morphological features characterize pathological infiltration.

Method: Six experienced readers (4 rheumatologists, 2 radiologists) from 3 international centres, blinded to patient and diagnosis, independently assessed MRI scans (T1W and STIR) from the following subjects all aged < 45 years: 30 patients with AS and symptom duration 5 years or less; 34 controls (26 with mechanical low back pain (mLBP)). MRI scans of the SIJ were read systematically as described in a standardized online training module using an online data entry system. In addition to deciding on the presence/absence of AS readers were asked to record the following: the primary MRI feature on which the diagnosis of AS was based, the presence/absence of fat infiltration, the degree to which fat infiltration was considered due to AS (0-10 scale), its location (sacral, iliac, both), and associated morphological features (bone edema, erosion, sclerosis, ankylosis, distinct border, infiltration adjacent to iliac/sacral joint surface, homogeneity of infiltration). We calculated sensitivity, specificity, and likelihood ratios.

Results: Fat infiltration was considered present in 28/30 (93.3%) of AS patients by a majority (≥4) of readers and in 29/30 (96.7%) by at least 2 readers but stated to be the principal diagnostic feature by only 2 readers in only 3 patients. Only one AS patient was considered to have no infiltration by any reader. It was also present in 6/34 (17.6%) of controls by a majority (≥4) of readers and in 13/34 (38.2%) by at least 2 readers (sensitivity 96.7%, specificity 61.8% for AS as recorded by at least 2 readers). Only 20/34 (58.8%) of controls were considered to have no fat infiltration by any reader. Applying a pre-specified definition of any 2 readers recording fat infiltration and each reader scoring ≥7 for fat infiltration considered due to AS gave a sensitivity of 80% and specificity of 97.1%. At least 1 associated feature was recorded in all patients by all readers. Table values represent concordant data from at least 2 readers.

Morphological Features	**Sensitivity**	**Specificity**	**LR+**	**LR-**
Both sacral and iliac	70%	94.1%	11.9	0.32
Bone edema	60%	100%	nc	0.4
Sclerosis	70%	97.1%	24.1	0.31
Erosion	83.3%	97.1%	28.7	0.17
Ankylosis	6.7%	100%	nc	0.93

Distinct margin	60%	97.1%	20.7	0.41
Homogeneity	43.3%	94.1%	7.3	0.60
Adjacent to sacral/iliac endplate	90%	88.2%	7.6	0.11

Conclusion: . Fat infiltration in the SIJ per se has high sensitivity but low specificity for AS. Its diagnostic utility primarily reflects the presence of associated abnormalities, especially erosions, characteristic of AS.

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Efficacy of Switching Between Anti-Tnf Agents in Spondylarthropathies. Julien Paccou Sr. Hôpital Roger Salengro, CHRU de Lille, Lille cedex, France

Purpose: TNF alpha antagonists are remarkably effective in the treatment of spondylarthropathies. However, 20% of patients will have to interrupt their treatment prematurely due to primary non-response, and 10 to 20% due to loss of efficacy. The objective of this study was to assess, in a large cohort of patients, the response to a 2nd and a 3rd TNFα antagonist in the event of failure, and to determine whether or not the cause of failure influenced the response.

Method: Retrospectively, we included all patients with spondylarthropathies who had received at least 2 TNFα antagonists or more. In patients in whom the treatment failed, the initial therapeutic response and the reason for the withdrawal of the TNFα antagonists were analyzed with respect to reason for failure and disease subtype. Patients were evaluated for response to the change in anti-TNF alpha therapy after 6 to 12 weeks. The reasons for withdrawal were (i) primary non-responder, (ii) loss of efficacy and (iii) occurrence of side effects over the follow-up period. An attempt was made to identify response-predictor factors using univariate and multivariate analysis.

Results: 103 patients with spondylarthropathies were included in this study (41 women and 62 men; mean age was 46 years and average duration of disease was 13 years). One switch was made in 73 patients and 2 switches in 30 patients. Following the failure of a first TNF alpha antagonist, the response to a 2nd agent was satisfactory (81% of the patients responded 6 to 12 weeks after starting treatment). The response to the second agent was not conditioned by the reason for withdrawal of the first TNF alpha antagonist. Patients who had received a 3rd TNF alpha antagonist following failure of the first 2 also showed a satisfactory response (79% of the patients responded 6 to 12 weeks after starting treatment). The reason for withdrawal of the 1st or 2nd agent did not conditioned response. Logistic regression analysis failed to distinguish response predictors.

Conclusion: In the event of failure or intolerance to TNF alpha antagonists in the treatment of spondylarthropathies, performing a first or a second switch produces a satisfactory therapeutic response, regardless of the reason for discontinuing previously prescribed TNF alpha antagonists.

Disclosure: J. Paccou, None.

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Does Clinical Examination Overestimate the Amount of Active Enthesitis in Early Psoriatic Arthritis? - A Comparison with Power Doppler Ultrasound. Jane E. Freeston[1], Laura C. Coates[1], Philip S. Helliwell[1], Elizabeth M. A. Hensor[2], Richard J. Wakefield[1], Paul Emery[1] and P. Conaghan[3], [1]University of Leeds, Leeds, United Kingdom, [2]LIMM, University of Leeds, Leeds, United Kingdom, [3]U of Leeds, Leeds, United Kingdom

Purpose: Enthesitis is thought to be important in the spondyloarthropathy (SpA) group of diseases, including psoriatic arthritis (PsA). Some groups have proposed enthesitis as the primary pathological abnormality in PsA, therefore enthesitis should be a prevalent finding in early PsA. The accuracy of clinical examination (CE) for enthesitis has been shown to be inferior to imaging assessment in established SpA cohorts, and a significant proportion of patients have been found to have sub-clinical enthesitis using ultrasound (US) imaging. However there is no data on the use of US in early PsA. The aim of this study was to compare CE and US findings in an early PsA cohort.

Method: 40 patients with new onset PsA, according to the CASPAR criteria, were recruited. They were all DMARD naïve and had a median disease duration of 10 months. All patients underwent CE of 66/68 joints and an entheseal assessment for tenderness and swelling as well as grey scale (GS) and power doppler (PD) US of the corresponding entheses. Bilateral lateral epicondyles of the elbow, Achilles tendons and plantar fascia were examined. GS and PD were scored separately on a 0-3 semi-quantitative scale for each enthesis imaged. A GS score of ≥2 and/or a PD score >0 were used to identify active US enthesitis.

Results: On CE, 34/202 entheses were tender, but none were clinically swollen. Using combined GS and PD, 14/202 had active enthesitis on US. Of all entheses examined, 85% had imaging findings consistent with CE. A substantial correlation (prevalence and bias-adjusted Kappa = 0.70) was identified between clinical assessment of activity (tender and/or swollen) and imaging assessment of activity.

In this early cohort, there was little evidence of sub-clinical disease with only 2% (5/202) of non-tender entheses showing significant US changes. Interestingly, all of the 5 non-tender, US active entheses were in the lower limb, and there was no sub-clinical disease seen at the lateral epicondyles. However, CE over-estimated activity in 12% of entheses. Of the 25 tender but US inactive entheses, 7 were adjacent to clinically tender joints. Bony erosion was only present in 8 of 202 entheses.

Table – Comparison of clinical and ultrasound assessment of disease activity by individual enthesis.

Type of assessment	US active	US inactive	Total
Tender	9	25	34
Non-tender	5	163	168
Total	14	188	202

Conclusion: These data have shown that the prevalence of enthesitis in early PsA is relatively low compared with previous studies of established disease. CE over-estimated the amount of enthesitis in this study, possibly due to pain from adjacent joint disease. There is no significant burden of sub-clinical enthesitis seen in this cohort of early PsA, and the few sub-clinically inflamed entheses were in the lower limb, where mechanical stress through entheses is likely to be more significant. These preliminary data have implications for research into pathogenesis, particularly as studies attempt to elucidate the primary pathology in PsA.

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To Verify the Clinical Value of the New Ankylosing Spondylitis Disease Activity Scores (ASDAS) in Chinese as and USpA Patients.

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Background and Purpose: Nowadays, the most widely used measure for assessing the disease activity of AS is Bath Ankylosing spondylitis Disease Activity Index (BASDAI). However, it is a self-administered instrument and does not include any objective index. In July 2008, the Assessment of SpondyloArthritis international Society (ASAS) developed a new assessment tool of disease activity in AS: ankylosing spondylitis disease activity score (ASDAS). This study is to assess the clinical value of ASDAS in Chinese AS and USpA patients, in comparison to BASDAI, the individual components of it as well as patient global and the acute inflammation score of MRI.

Method: All the AS and USpA patients in the study included two cohorts: 1) patients participated in double-blind placebo-controlled randomized clinical trials with Etanercept (n=117), 2) the out-patients who were receiving the treatment of Infiximab (n=90). The data about every patient at baseline and a following up visit at 6 weeks later as well as the data including the results of MRI of the lumbar and sacroiliac joints about some patients at a following up visit at 12 weeks later were collected. The disease activity and treatment effect were assessed by ASDAS and BASDAI. Discrimination between patients in low versus high disease activity according to various definitions, and between various levels of changes was analyzed as standardized mean difference (difference of the group means divided by the pooled SD of the group means).

Results: 1. On the disease activity assessment: (1)All the four ASDAS and BASDAI correlated significantly with patient global. The results of them were similar. However, the four ASDAS performed much better than BADAI in correlating with ESR and CRP in both AS and

USpA groups. (2) The four ASDAS outperforms BASDAI in discriminating the different status of disease activity, in the settings of ESR based. The SMDs of the four ASDAS were: 1.52, 1.55, 1.24 and 1.51 in AS group respectively and 1.41, 1.48, 1.38 and 0.43 in USpA grouprespectively. The SMDs of BASDAI were0.62 in AS group and 0.43 in USpA group. 2. On assessing the different levels of change of disease activity according to the treatment of TNF-α blockers, the SMDs of ASDAS in discriminating the changes of disease activity between baseline and 6 weeks after treatment were 1.16, 1.09, 1.09 and 1.15 in AS group respectively and 1.38, 1.48, 1.32 and 1.37. in USpA group respectively. While the SMDs of BASDAI were 0.88 in AS group and 1.06 in USpA group. Obviously, the discriminatory power of the ASDAS proved to be better than the BASDAI. 3. The four ASDAS outperforms the total acute inflammation score of the MRI of lumbar and sacroiliac joint in correlating with patient global assessment , ESR and CRP.

Conclusion: In comparison to the BASDAI and the other conventional indices, the four new ASDAS are more sensitive in discriminating the disease activity and the efficacy of TNF-αblocker treatment at 6 weeks in AS patients. Furthermore, ASDAS will be value to be used for assessing disease activity and the treatment effect of TNF-αblocker in USpA patients.

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Evaluation of the ASAS Classification Criteria for Axial Spondyloarthritis, A Diagnostic Algorithm and the Probability Approach (likelihood ratio product) in Diagnosing Axial Spondyloarthritis. M. Rudwaleit, J. Vahldiek, H. Brandt, H. Appel, H. Haibel, I.-H. Song, S. Zinke, K. Karberg, I. Spiller and J. Sieper, Charité - Campus Benjamin Franklin, Berlin, Germany

Purpose: The diagnosis of non-radiographic axial spondyloarthritis (i.e. axial SpA in the absence of definite radiographic sacroiliitis as required for ankylosing spondylitis (AS)) has been and still is a challenge. The objective of this study was to evaluate the diagnostic accuracy of a recently proposed diagnostic algorithm (1), the likelihood ratio (LR) product approach (2), and the new ASAS classification criteria for axial SpA (3) in patients with chronic back pain presented to a single rheumatology center.

Method: Patients were referred to our rheumatology department because of chronic back pain of unknown origin and already some suspicion of SpA such as inflammatory back pain (IBP), or positivity for HLA-B27, or any other SpA feature. Upon routine diagnostic work up, the diagnosis was made by the treating rheumatologist (n=9 in total), often after consultation of the team. The clinical diagnosis (SpA vs no SpA) served as gold standard in this study.

Results: In total, 374 patients were analysed. Of these 200 were diagnosed as axial SpA (53.5%) and 174 as no SpA (mechanical low back pain: median age 43 yrs, median symptom duration 6 yrs). Definite radiographic sacroiliitis was present in 101 of the 200 axial SpA patients (median age 39 yrs, median symptom duration 7.5 yrs), and 99 patients had non-radiographic axial SpA (median age 34 yrs, median symptom duration 3.0 yrs). IBP was present in 91.5% vs 49%, HLA-B27 positivity in 86% vs 39%, and elevated CRP in 55% vs 30% of SpA vs no SpA patients, respectively. MRI investigation of the sacroiliac joints was performed in 76% of patients diagnosed as non-radiographic axial SpA, and 86% of these patients had active sacroiliitis on MRI. In the 374 back pain patients the new ASAS classification criteria for axial SpA had a sensitivity/ specificity of 97.0%/ 74.7%, the diagnostic algorithm of 82.8%/ 74.7%, and the LR product approach (with a threshold of 90% for definite diagnosis) of 83.8%/ 85.1%, respectively. In patients diagnosed as non-radiographic axial SpA the imaging arm of the ASAS classification criteria (i.e. sacroiliitis on radiographs or MRI plus at least 1 SpA parameter) was fulfilled by 64.6% but only 1.1% of no SpA (specificity 98.9%).

Conclusion: All three diagnostic approaches seem suitable for establishing a diagnosis. The new ASAS classification criteria for axial SpA revealed an excellent sensitivity and a reasonable specificity, the latter was also excellent if the imaging arm only of the criteria was applied. In comparison to the LR product approach the ASAS criteria are easy to use in daily rheumatology practice.

1. Ann Rheum Dis 2004; 63:535-43
2. Arthritis Rheum 2005; 52:1000-8
3. Ann Rheum Dis 2009; 68:777-83

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Comparison Between Inspire and Domjan Method for Measuring Lumbar Lateral Flexion in Patients of Psoriatic Arthritis (PsA) and Correlation with Radiographic Damage. Anupam Wakhlu[1], Veerapong Phumethum[1], Vinod Chandran[1], Catherine T. Schentag[1], Hua Shen[2], Richard J. Cook[2] and Dafna Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON

Purpose: Assessment of spinal lateral flexion is important in the assessment of spondyloarthritis (SpA). The INSPIRE method of measuring spinal lateral flexion requires one set of measurements, is faster, feasible and correlated with the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) in patients with ankylosing spondylitis. The purpose of the present study is to compare the INSPIRE method of measuring lumbar lateral flexion to Domjan method in PsA patients and correlate it with radiographic changes.

Method: Patients were selected from a longitudinal cohort followed in a PsA clinic since 1978. Detailed demographic and clinical data are obtained every 6-12 months and are tracked on a computerized database. Patients satisfying CASPAR criteria for PsA and axial disease were identified using radiological criteria, which included the presence of at least grade 2 sacroiliitis. Clinical features recorded systematically included the following: age, gender, ethnicity, age at symptom onset, age at diagnosis, arthritis pattern, family history, extra-articular manifestations and medications. The physical examination includes general physical examination, musculoskeletal examination and full spinal clinimetrics including measurement of INSPIRE and Domjan methods of spinal lateral flexion by trained rheumatologists. Spine radiographs, obtained every 2 years included AP pelvis, lateral view of cervical spine, AP and Lateral views of lumbar spine. These were scored by consensus for mSASSS by 2 assessors. Pearson correlation was used to correlate the values of spinal mobility measures and radiographic scores.

Results: 229 patients were included in the study of whom 43% were female. The mean age at study entry was 51 years (16-83) and mean age at onset of PsA was 37 years. The mean disease duration was 15 years (0.5-49). 54% of patients had radiological evidence of sacroiliitis and 45% had evidence of degenerative spinal disease. The spinal mobility and radiographic scores were as follows [mean (minimum, maximum)]: Occiput-to-wall distance (cm)=1.0 (0-17), Tragus-to-wall distance (cm)=12 (7-25), Cervical rotation (degrees)=71 (5-90) , Chest expansion (cm)=6 (2-12), Modified Schoeber (cm)=4.5 (1-8), Lateral spinal flexion-Domjan (cm)=16.5 (3.5-40), Lateral spinal flexion-INSPIRE (cm)=32 (8-60), mSASSS score=2 (0-48). Correlation (95% confidence interval) between INSPIRE and Domjan method was 0.86 (0.82,0.89), between INSPIRE, Domjan methods and mSASSS were -0.28 (-0.40,-0.16) and -0.27 (-0.39,-0.14) respectively. All correlations had a p value of <0.0001. Comparable correlations were obtained when comparisons were made in patients of PsA with axial disease only.

Conclusion: The study demonstrates that both INSPIRE and Domjam methods correlate well as measures of spinal lateral flexion in PsA and correlate well with radiographic damage**.** If the two show a similar sensitivity to change, they may be used interchangeably.

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A Comparison of Cardiovascular Risk in Patients with Spondyloarthropathies and Rheumatoid Arthritis. Laura Grant[1], Kimberley A. Bailey[1] and Namita Kumar[2], [1]Medical School, University of Newcastle, Newcastle upon Tyne, United Kingdom, [2]University Hospital of North Durham, Durham, United Kingdom

Purpose: The management of cardiovascular disease (CVD) and its risk factors play an important role in the multi-factorial management of patients with inflammatory arthritis (IA). The British Society for Rheumatology and NICE all recommend that patients with IA should be offered annual CVD review.

A suggested multiplier of risk in Rheumatoid Arthritis (RA) is 1.5 greater than the general population and we have shown this significantly increases numbers of patients requiring primary prevention (1). This is also a fair estimate of CVD burden in Seronegative Spondylarthropathies (SpA) also (2). We wished to establish the number of SpA patients who reached primary prevention treatment threshold prior to establishing a CVD screening service .

Method: Consecutive RA patients and SpA patients, both without diabetes or CVD were recruited over a five week period in 2 consecutive years. Ten year CVD risk was calculated using the Joint British Societies risk calculator and comparisons were made between the 2 groups. Both sets of data were multiplied by 1.5. Paired t tests were then used to compare risk scores within each disease group.

Results: 45 RA patients were assessed 26 female, 18 male. Mean age was 57.53 years (range 39-74 years). Mean systolic BP 136.4mmHg (SD 13.6), diastolic 86.3mmHg (SD 14.0) 51 SpA patients were assessed, 20 male, 31 female. The mean age was 49.5 years (range 30-72 years). Mean systolic BP was 140.4 mmHg (SD 18.3) and mean diastolic BP was 86.1 (SD 10.7). All patients had a diagnosis of one year or longer.

Table 1: Projection of 10 Year Cardiovascular Risk

	RA		**SpA**		**P**
N	**45**		**51**		
	Actual risk greater than 20%	**Risk X1.5**	**Actual risk greater than 20%**	**Risk X1.5**	
	6*	18*	7[#]	15[#]	*[#]0.001

Conclusion: CVD is an important cause of mortality and morbidity in IA. Disease burden is underestimated by standard risk assessment. Multiplying by 1.5 is an acceptable estimation of true risk. This however significantly increases the number of patients requiring primary prevention in this work twofold. This should be recognised when establishing such services and results of studies such as TRACE RA will guide Rheumatologists in whether primary prevention has a significant impact in patients with IA.

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ACR Plenary Sessions

Plenary Session I: Discovery 2009

Sunday, October 18, 2009, 11:00 AM - 12:30 PM

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Genome-Wide Association Study of Systemic Sclerosis in a Large US Cohort of Over 1,500 Cases. Olga Gorlova[1], Shih-Feng Weng[1], Jun Ying[1], Fredrick M. Wigley[2], Laura K. Hummers[2], Peter K. Gregersen[3], AnnetteT Lee[3], Christopher Amos[1], Frank C. Arnett[4], Shervin Assassi[4], Pravitt R. Gourh[5], Filemon K. Tan[4], John D. Reveille[6], J. Lee Nelson[7], Terry A. McNearney[8], Michael Fischbach[9] and M. Mayes[10], [1]M.D. Anderson Cancer Center of the University of Texas, Houston, TX, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]University of Texas Medical School at Houston, Houston, TX, [5]UTHSC-Houston Medical School, Houston, TX, [6]Univ Texas Health Sci Ctr, Houston, TX, [7]Fred Hutchinson Cancer Rsch, Seattle, WA, [8]Univ of Texas Med Branch, Galveston, TX, [9]Univ Texas Hlth Sci Ctr, San Antonio, TX, [10]U.Texas Houston, Houston, TX

Purpose: Systemic Sclerosis (SSc) is a rare and severe rheumatologic disease. Multiple lines of evidence suggest that genetic factors play a role in SSc susceptibility and disease expression. To analyze the genetic component of SSc risk we performed a genome-wide association study comparing 1,617 Caucasian SSc cases to data from 3,597 Caucasian controls utilizing the Ilumina 550k gene chip.

Methods: Cases were obtained from three U.S. centers Cases (initial n=1,678) were obtained from three U.S. centers: the University of Texas (UT) Health Science Center-Houston, Johns Hopkins University Medical Center in Baltimore and the Fred Hutchinson Cancer Research Center in Seattle. Control data were obtained from 3 publicly available databases: (1) breast cancer controls CGEMS; (2) prostate cancer controls CGEMS; and (3) Illumina controls. After eliminating duplicates, gender discrepancies and call rates <95%, the final case population consisted of 1,534 individuals (182 men and 1,352 women). After similar quality control and gender matching by randomly eliminating male controls to adjust M:F ratio to that in cases, the final control population consisted of 3,597 individuals (464 men; 3,133 women).

Results: Thirty-three SNPs representing 12 genes were significantly associated with SSc with p-values from $9.9 \cdot 10^{-15}$ to $5 \cdot 10^{-8}$. The most significantly associated genes were those in the MHC region (6p21), including, but not limited to, HLA-Class II alleles. Aside from the MHC region, 4 gene regions were identified as significantly associated with SSc. These include TNPO3 ($p= 1.2 \cdot 10^{-9}$ for the most significant SNP) which is in linkage disequilibrium with IRF5 and previously associated with SSc in candidate gene studies, XKR4 on chromosome 8 ($p= 5.15 \cdot 10^{-9}$), TSSC1 on chromosome 2 ($p=2.53 \cdot 10^{-9}$), and TUBA3C (tubulin alpha 3 C) on chromosome 13 ($p= 3.73 \cdot 10^{-8}$). The p-values for T-cell signaling related genes (CD3Z p=2.37E-06), cytokine receptors (IL21R) and other previously studied candidate loci were in the range of 10^{-7} to $10^{-6.}$

Conclusion: We confirm the association with HLA alleles thus firmly establishing that this disease has a strong autoimmune component. In addition, multiple other gene regions have been identified. Our study is the largest GWAS yet reported and one of the few where multiple candidate genes with P-values as low as 10^{-15} were identified.

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dsRNA Drives Type I and Type II Interferon-Mediated Inflammation, Fibroblast Activation and Dermal Fibrosis through TLR3-Dependent and Independent Signaling. Giuseppina Alessandra Farina, Mike Di Marzio, Cindy Collins, Michael R. York and Robert A. Lafyatis, Boston University School of Medicine, Boston, MA

Purpose: The goal of this study was to better understand innate immune regulation and associated IFN responsive gene expression in systemic sclerosis (SSc). We also sought to better understand the role of innate immune activation of dermal fibroblasts and in particular the effect of different Toll-like receptor (TLR) ligands on dermal fibroblast expression of type I and type II IFN responsive genes. Finally we wanted to develop a murine model for chronic innate immune stimulation for studying TLR-regulated dermal inflammation and the effect of type I IFNs on dermal fibrosis.

Method: Skin biopsies from Lesional (L/SSc) (n=36), Non Lesional (N/LSSc) (n=15), and healthy control skin (n=6), and SSc (n=6) and normal (NL) (n=4) dermal fibroblasts were studied for mRNA expression of IFN responsive genes using real-time PCR. Dermal fibroblasts were stimulated with different TLR ligands (TLR2, TLR3, TLR4, TLR7, TLR8, TLR9), IFNa,b,g or TGFb. Groups of C57BI/6, and type I IFN receptor deleted mice (IFNAR1-/-), were implanted with osmotic pumps designed to deliver the TLR3 agonist PolyIC or control (PBS). Skin was taken after a week of treatment and then analyzed for gene expression using real-time PCR, and examined by H&E staining.

Results: Both type I and II IFN responsive genes were found significantly increased in L/SSc compared to control skin (OAS2: average 3.3 fold increase in L/SSc, 2.9 fold in SSc N/L); (CXCL9: average 7.03 fold increase in L/SSc, 5.80 fold in N/LSSc). Moreover, expression of genes known to be related to TLR activation was also overexpressed in SSc skin (IRF7: average 3.71 fold increase in L/SSc; SOCS3: average 3.07 fold increase in L/SSc). Of the TLR ligands tested PolyIC most potently stimulated SSc and NL fibroblasts showing marked induction of IFN responsive genes. Mice treated with PolyIC developed striking skin inflammation and fibrosis. PolyIC treated skin also showed highly upregulated expression of Mx-2, a type I IFN-responsive gene and CXCL9, a type II IFN responsive gene, as well as increased expression of TGFb responsive genes, PAI-1 and Thrombospondin (TSP1).

PolyIC treatment of IFNAR-/- mice did not induce Mx-2 gene expression, and CXCL9 expression was partially reduced compared to WT mice. In contrast deletion of IFNAR showed no effect on TGFb responsive gene expression.

Conclusion: Type I and II responsive gene expression is increased in SSc skin. Chronic immune stimulation by TLR3 agonist stimulates inflammation, fibrosis, and IFN and TGFb responsive gene expression. IFNAR plays a relatively modest role in regulating TGFb activation in skin by the TLR3 agonist, PolyIC.

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Rituximab Versus Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitis: A Randomized Controlled Trial (RAVE). J.H. Stone[1], P.A. Merkel[2], P. Seo[3], R. Spiera[4], C.A. Langford[5], Gary S. Hoffman[5], C.G.M. Kallenberg[6], E. William St. Clair[7], B.J. Fessler[8], N. Tchao[9], L. Ding[10], L.V. Webber[10], D. Ikle[11], D. Weitzenkamp[11], W. Wu[12], P. Brunetta[13], L. Seismundo[3], F.C. Fervenza[14], K.A. Keogh[14], E. Y. Kissin[2], K.S. Mieras[14], P.A. Monach[2], T. Peikert[14], C. Stegeman[15], S.R. Ytterberg[14], U. Specks[14] and The RAVE-ITN Research Group[9], [1]MGH, Boston, MA, [2]BU, Boston, MA, [3]Johns Hopkins, Baltimore, MD, [4]HSS, New York, NY, [5]Cleveland Clinic, Cleveland, OH, [6]University Medical Center Groningen, Groningen, Netherlands, [7]Duke University Medical Center, Durham, NC, [8]UAB, Birmingham, AL, [9]ITN, San Francisco, CA, [10]NIH, Bethesda, MD, [11]Rho, Chapel Hill, NC, [12]PPD, Wilmington, NC, [13]Genentech, Inc., S. San Francisco, CA, [14]Mayo Clinic, Rochester, MN, [15]Med.Univ., Groningen, Netherlands

Purpose: Combined use of cyclophosphamide (CYC) and glucocorticoids (GCS) has been the standard of care for remission induction for ANCA-associated vasculitis (AAV) for decades. Uncontrolled studies suggest rituximab (RTX) may be effective for AAV, and its use may avoid some of the toxicities associated with CYC therapy. This trial compares the efficacy of RTX to that of CYC for AAV.

Method: A multicenter, randomized, double-blind, placebo-controlled trial was conducted to determine if treatment with RTX (375 mg/m^2 i.v. weekly x 4) was not inferior to CYC (2 mg/kg/d p.o.) for inducing remission in severe AAV. Once remission was achieved, CYC was replaced by azathioprine between months 3-6. All patients received the same GCS treatment protocol: 1-3 g i.v. methylprednisolone followed by prednisone 1 mg/kg/d p.o. reduced to 40 mg/d by month 1, and then tapered and discontinued completely by month 6. The primary endpoint was disease remission in the absence of prednisone therapy at month 6. Remission was defined as a Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0.

Results: Nine centers enrolled a total of 197 patients with severe Wegener's granulomatosis or microscopic polyangiitis (3:1), all positive for PR3-ANCA or MPO-ANCA (2:1). The mean BVAS/WG at enrollment was 8.4 (range 3-19). Disease severity, organ involvement, proportion of newly diagnosed disease (49%), AAV type, and ANCA type were similar in both treatment arms. All results reported refer to the initial 6 months of study participation for each patient. Eighty-four (85%) of the 99 patients in the RTX arm and 81 (83%) of the 98 in the CYC arm completed 6 months of follow-up. Sixty-three (64%) of the patients assigned to RTX achieved the primary outcome, compared with 52 (55%) in the CYC arm (P=0.21). Seventy patients (71%) in the RTX arm achieved a BVAS/WG of 0 and a prednisone dose < 10 mg/day at six months, compared with 61 patients (62%) in the CYC arm (P=0.22). No differences were observed between the groups in the rates of disease flares. The rates of protocol-defined selected adverse events were similar between the RTX and CYC groups (0.06 versus 0.08; P=0.29), but fewer patients in the RTX group experienced one or more of these events (19 vs 32 patients; P=0.03). There was no difference in treatment response within the subgroups with major renal involvement (n=99) or alveolar hemorrhage (n=50).

Conclusion: RTX is not inferior to CYC for the induction of remission in severe AAV. These results provide strong support for the use of RTX as an alternative to CYC in AAV.

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Towards a Risk-Adapted Therapy to Maintain Clinical Remission in Juvenile Idiopathic Arthritis: Results of a Randomized Trial of 6 Versus 12 Months Withdrawal of Methotrexate. Dirk Foell[1], Nico Wulffraat[2], L. R. Wedderburn[3], Nicola Ruperto[4], Helmut Wittkowski[1], Michael Frosch[1], A. Martini[5], Johannes Roth[1] and Printo, [1]University of Muenster, Muenster, Germany, [2]University Medical Centre Utrecht, Utrecht, Netherlands, [3]UCL Institute of Child Health, London, United Kingdom, [4]IRCCS Istituto G. Gaslini, Universita' di Genova, Genova, Italy, [5]Pediatria-II PRINTO, IRCCS G. Gaslini, Genova, Italy

Purpose: Methotrexate (MTX) is effective in juvenile idiopathic arthritis (JIA), but about half of the patients experience a relapse after withdrawal. Thus prolonged treatment for at least another year in remission was recommended. We analyzed 1) whether the duration of treatment after reaching inactive disease status influences the risk of flares and 2) whether patients at risk for flares may be identified by molecular biomarkers.

Methods: A total of 364 JIA Patients with inactive disease for at least 3 months were randomized to discontinue MTX either 6 months (Group 1, n=183) or 12 months (Group 2, n=181) thereafter. At baseline, demographic and clinical characteristics were well balanced. At the time of withdrawal, Myeloid-Related Proteins 8 and 14 (MRP8/14) were analyzed.

Results: Six patients were lost to follow-up, and in 61 (16.8%) flare occurred before MTX stop (19 within 6 months in group 1 and 42 within 12 months in group 2). In the remaining 297 patients, there were 88/162 [54.3%] flares in group 1 and 59/135 [43.7%] in group 2). The flare rates were 28.8 *per* 1000 person-months in group 1 and 27.4 *per* 1000 person-months in group 2 (p=0.83). Clinical (disease subtype, duration or dosage of therapy, time of continuous MTX therapy in inactive disease) or standard laboratory (CRP, ESR) parameters could not differentiate between patients at risk for relapse and those without. In contrast, MRP8/14 levels were significantly higher in those patients who subsequently developed relapses (715±140 ng/ml) compared to patients with stable remission (400±105 ng/ml; p=0.003). MRP8/14 was even higher in patients with relapses occurring within 6 months (955±270 ng/ml; p<0.001). A Log-rank analysis confirmed the prediction of relapse risk at cut-off 690 ng/ml (p<0.001). **Conclusion:** Longer treatment with MTX in inactive disease does not in general improve the stability of remission. Clinical and therapeutic characteristic do not influence the risk of relapse. Subclinical disease activity may result in instable remission, e.g. a status of clinical but not immunologic remission. MRP8/14 as marker of phagocyte activity indicates subclinical inflammation and identifies patients with increased risk of relapse in whom therapy may not be safely stopped.

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Tracking JIA Predisposition Genes From Genome-Wide Association Studies to Next Generation Sequencing to Functional Relevance. Terri H. Finkel[1], Edward M. Behrens[1], Yongwon Choi[2], Robert A. Eisenberg[2], Johannes Dapprich[3], Dimitrios S. Monos[1] and Hakon Hakonarson[1], [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Generation Biotech, Lawrenceville, NJ

Purpose: Juvenile Idiopathic Arthritis (JIA) is the #1 cause of acquired disability in children. We recently identified TRAF1-C5 as a genetic locus associated with JIA, and have undertaken a comprehensive translational approach to elucidate the genetic contributions to this disease. Here, we identify single nucleotide polymorphisms (SNPs) associated with JIA by a genome-wide (GW) screen of a large well-phenotyped patient cohort; resequence loci with GW significant association; and for one candidate, TRAF1, employ a mouse model of inflammatory arthritis to probe the mechanisms by which the locus and its variants contribute to disease.

Method: We define genes and genomic regions with evidence for association with JIA in a discovery cohort of 1,500 cases (diagnosed by revised ILAR criteria) recruited from greater Philadelphia and internationally (Stage 1). In Stage 2, we selectively genotype an additional 1,000 existing samples from well-phenotyped JIA cases recruited by other collaborating sites. This database is leveraged against matched samples from >8,000 genotyped controls. In parallel studies, we use novel methodology to target and isolate regions of interest, and resequence genomic regions containing or in high linkage disequilibrium (LD) with TRAF1 and other putative disease variant SNPs in cases with polyarticular subtype JIA. To confirm functional relevance of a candidate locus, we assess onset and severity of arthritis after K/BxN serum transfer to TRAF1 mutant mice.

Results: We genotyped a cohort of >400 children with JIA and >80,000 other subjects (adults and children), using the Illumina HumanHap550/610Q BeadChip to track 600,000 polymorphisms. Our candidate gene analysis of JIA identified a predisposition locus in LD with the TRAF1-C5 locus (p=0.031, OR=1.38), and we identified multiple SNPs that tag a novel locus on 3p12.3 and achieve GW

significance ($p=4.94x10^{-8}$; OR=2.32). We utilized 'Region Specific Extraction' (RSE), a simple, automated method of enriching large chromosomal regions of genomic DNA that can be used directly in next generation sequencing platforms. We applied this technology to resequence the TRAF1 and PTPN22 genomic regions in high LD with putative disease variant SNPs in cases with polyarticular JIA. In a single RSE, we used 67 oligos to target 3 separate gene regions over 0.5 Mb total. >95% of all 3 target regions were successfully sequenced, with 100% concordance between sequencing and SNP genotyping data. We developed and characterized TRAF1-KO and –GFP-KI mice.

Conclusion: TRAF1-C5 and a novel locus on 3p12.3 are associated with all forms of JIA and could represent "master switches" predisposing to arthritis. The functional role of TRAF1 is assessed for the first time in a murine model of inflammatory arthritis (K/BxN). RSE can be used to target, sequence, and identify genomic variation in regions defined by significantly associated SNPs, with the goal of identifying genomic variations associated with JIA and elucidating potential pathogenic mechanisms.

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ACR/ARHP Combined Abstract Sessions

Pain and Disability in Rheumatic Disease

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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The Association of Parity with Knee Osteoarthritis (OA) and Total Knee Replacement in the MOST Cohort. B.L. Wise[1], J. Niu[2], Y. Zhang[2], David T. Felson[3], Laurence A. Bradley[4], J. Torner[5], M. Nevitt[6] and N.E. Lane[1], [1]UCDMC, Sacramento, CA, [2]BUSM, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]UAL, Birmingham, Birmingham, AL, [5]UIowa, Iowa City, IA, [6]UCSF, SF, CA

Purpose: A recent study found that risk of total knee replacement (TKR) among women increased on a per-birth basis. The purpose of this study was to further evaluate the association of TKR and knee OA with parity.

Method: The NIH-funded Multicenter Osteoarthritis Study (MOST) is a longitudinal observational study of persons age 50 to 79 years with either symptomatic knee OA or at high risk of disease. Women in the study reported their number of births at the 30 month visit. Baseline and 30 month knee radiographs were collected and read, and radiographic OA (ROA) was defined as Kellgren/Lawrence (K/L) grade>=2. Women were grouped based on their number of children: 0, 1-3 births, and 4 or above. We examined the relation of parity to the prevalence of baseline ROA and TKR, to incident ROA and to incident TKR over the 30 month follow-up as well as to prevalent TKR at 30 months using a Poisson regression model. Generalized estimating equations were used to control for correlation between two knees within a subject. We adjusted for age, BMI, race, education, labor occupation versus non-labor versus “other”, WOMAC pain subscale at baseline, pain medication, and baseline K/L grade (WOMAC, medication, and K/L grade not used in the prevalent TKR analyses; prevalent and incident OA analyses also adjusted for history of knee injury or surgery).

Results: 1820 women reported parity information at the 30 month visit (mean age 62.6, mean BMI 30.7, mean WOMAC pain subscale score 3.7). Women who had 4 or more children were older, were more likely to have a labor occupation, and had lower education levels than women with 0 or 1-3 children. After adjusting for covariates, compared to nulliparous women, those with 1-3 children had a 70% increased risk of incident TKR (RR=1.7, 95% CI 0.8, 4.0), while women with 4-12 children had a 2-fold increased risk for incident TKR (RR=2.0, 95% CI 0.8, 4.9) (p for trend=0.03). At baseline there were only 45 prevalent TKRs, which was not enough to achieve significance. After adjusting for covariates, compared to nulliparous women, those with 1-3 children had a relative risk of 30 month prevalent TKR of 2.4 (95% CI 1.2, 4.8), while women with 4-12 children had a relative risk for prevalent TKR of 2.3 (95% CI 1.1, 4.9). No association was observed between parity and baseline ROA, but incident tibiofemoral ROA was slightly increased in women with 4-12 children (RR 1.5; 95% CI 0.8, 2.8), although this observation did not reach significance.

Conclusion: Parity in women is associated with incident and prevalent TKR, but we did not find an association with prevalent or incident radiographic OA. This suggests that the effect of parity on risk of TKR is not an artifact of an association between parity and ROA, but instead may be mediated by social, neurological, hormonal or other factors.

Disclosure: B. L. Wise, NIH, 2 ; **J. Niu**, None; **Y. Zhang**, None; **D. T. Felson**, None; **L. A. Bradley**, None; **J. Torner**, None; **M. Nevitt**, None; **N. E. Lane**, None.

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Relationship of Weight and Weight Change with Knee Pain and Function in Persons with Symptomatic Radiographic Knee Osteoarthritis: Two-Year Data From the Osteoarthritis Initiative. Danuta I. Bujak, Knachelle Favors, John D. Sorkin and Marc C. Hochberg, University of Maryland School of Medicine, Baltimore, MD

Purpose: Overweight is a major risk factor for the development and progression of knee osteoarthritis (OA) and weight loss is recommended as part of the non-pharmacologic management of patients with knee OA. This analysis examined the relationship between weight and weight change and change in self-reported symptoms and function and physical performance in adults with symptomatic radiographic knee OA over two years.

Method: Data for this analysis were obtained from the Osteoarthritis Initiative (OAI) public access database (http://www.oai.ucsf.edu). Specifically, we examined data from the baseline, 12- and 24-month follow-up visits for subjects with symptomatic radiographic knee OA enrolled in the OAI Progression subcohort. Subjects completed the Western Ontario McMaster Osteoarthritis Index (WOMAC) and the Knee Osteoarthritis Outcome Score (KOOS) at all visits and the Physical Activity Scale for the Elderly (PASE) at the baseline and 24-month follow-up visits. Weight was measured with a balance beam scale and physical performance was measured with a timed 20-meter walk at all visits and a timed 400-meter walk at baseline and 24-month follow-up visits; height was measured with a stadiometer at baseline. Names and dosages of medications and dietary supplements were recorded at all visits by trained personnel. Correlations between weight and weight change and change in outcomes were examined in multiple variable adjusted models using repeated measures analysis and generalized estimating equations to control for the correlation between knees in subjects with both knees involved at baseline.

Results: Of 1388 subjects with symptomatic radiographic knee OA in one or both knees enrolled in the Progression subcohort, 1189 (85.7%) and 1109 (79.9%) completed 12- and 24-month follow-up visits, respectively. The mean (SD) age at baseline was 61.4 (9.1) years; 791 (57.1%) were women and 972 (70.2%) were white. The mean (SD) weight and body mass index (BMI) at baseline were 86.1 (16.2) kg and 30.2 (4.9) kg/m^2, respectively. Mean (SD) weight change from baseline to 12 months and from 12 to 24 months were -0.31 (4.2) and -0.06 (3.8) kg, respectively. In analyses adjusted for age, sex, race and use of analgesic and/or antiinflammatory drugs at each visit, weight change was significantly correlated with WOMAC stiffness, function and total score (but not pain score), PASE score and 20-meter walk speed. In similar multiple variable adjusted analyses, absolute weight was significantly correlated with all clinically relevant outcomes with heavier persons having more pain and worse function.

Conclusion: These data support an association between weight loss and improvement in function assessed by both self-report and performance measures but not pain in persons with symptomatic radiographic knee OA. In addition, greater absolute weight was significantly associated with higher pain scores and worse function at all visits. These data support recommendations for weight loss in persons with symptomatic knee OA.

Disclosure: D. I. Bujak, None; **K. Favors**, None; **J. D. Sorkin**, None; **M. C. Hochberg**, Osteoarthritis Research Society International, 9, Bayer Health Care LLC, 9, Bioiberica S.A., 9, Combinatorx, 9, Endo Pharmaceuticals, 9, Ferring Pharmaceuticals, 9, Genzyme Corporation, 9, Merck & Co., Inc., 9, NiCox, S.A., 9, Novartis Pharmaceutical Corporation, 9, Pozen Inc., 9, NIAMS-NIH, 9 .

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Patterns of Compartment Involvement in Tibiofemoral Osteoarthritis (TFOA) in Men and Women and in Caucasians and African Americans: The MOST Study. B.L. Wise[1], M. Yang[2], J. Niu[2], N.E. Lane[1], W.F. Harvey[3], David T. Felson[4], M. Nevitt[5], J. Hietpas[5] and Y. Zhang[2], [1]UCDMC, Sacramento, CA, [2]BUSM, Boston, MA, [3]NEBH, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]UCSF, SF, CA

Purpose: Previous studies have reported ethnic differences in radiographic OA and malalignment for medial versus lateral compartment TFOA. We conducted a cross-sectional study to describe the compartmental patterns of TFOA between men and women as well as between Caucasians (CC) and African Americans (AA), and assess whether the difference, if present, was related to differences in knee malalignment between comparison groups.

Method: The NIH-funded Multicenter Osteoarthritis Study (MOST) is an observational study of persons age 50 to 79 years with either symptomatic knee OA or at high risk of disease. In knees with radiographic OA (ROA; Kellgren/Lawrence grade>=2), we defined medial compartment involvement as maximum medial joint space narrowing (JSN) on baseline radiograph PA view greater than maximum lateral JSN, and lateral compartment involvement as maximum lateral JSN greater than maximum medial JSN; if a knee had equal maximum JSN, it was considered to have both compartments involved if JSN>0 and neither involved if JSN=0. Using long limb films, valgus malalignment was defined as mechanical axis angle >181 degrees, while varus malalignment was defined as < 179 degrees. We compared the proportion of JSN in lateral and medial compartments among subjects with ROA between men and women as well as CC and AA using a logistic regression model adjusting for age, BMI, education, and prior injury to the knee. We also explored whether knee alignment was related with any difference in prevalence of lateral and medial JSN by adding this variable to the model. We used generalized estimating equations to account for correlation between two knees within a subject.

Results: Of 2014 knees with TF ROA, 1554 knees (77.2%) had medial JSN, and 414 knees (20.6%) had lateral JSN (107 knees had neither). Lateral JSN was more prevalent in women than in men (OR=1.84, 95% CI 1.40-2.42) and was also more prevalent in AA than in CC (OR=2.22, 95% CI: 1.59-3.11). The differences in proportion of lateral JSN between men and women as well as between CC and AA were consistent across K/L grades. Among knees without ROA, women were more likely than men to have valgus alignment, but there was no difference in malalignment between AA and CC. After further adjustment for knee alignment, we found no difference between women and men in proportion of lateral JSN (OR=0.74, 95% CI: 0.51-1.07), but continued to find a difference between AA and CC (OR=3.04, 95% CI: 1.96-4.74).

Conclusion: Women and AA with TF ROA are more likely to have lateral JSN. After adjusting for malalignment this difference disappeared between men and women but remained significant between AA and CC. These findings suggest that factors other than alignment may account for observed compartment specific differences in OA by race.

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A Biomechanical Approach Predicts Hip Fracture Independent of Bone Mineral Density (BMD) in Women: The Framingham Osteoporosis Study. Alyssa B. Dufour[1], Benjamin Roberts[2], Douglas P. Kiel[3], Mary L. Bouxsein[2] and Marian T. Hannan[3], [1]IFAR, Boston, MA, [2]BIDMC, Boston, MA, [3]Hebrew SeniorLife & Harvard Medical School, Boston, MA

Purpose: Hip fractures are disabling events for older persons. Studies have identified low BMD as a major risk factor, yet up to half of those suffering a hip fracture do not have low BMD; thus, alternative methods of assessing fracture risk are needed. One such method is the biomechanical Factor-of-Risk (Φ), defined as the ratio of force applied to the hip from a sideways fall to femoral bone strength. We examined the relation between Φ and risk of hip fracture in men and women of the population-based Framingham Study.

Method: Subjects included 1100 Framingham Original Cohort members who had hip BMD scans (LUNAR DPA) in 1988-89 (baseline). Body weight, height (used to calculate BMI (kg/m^2)) and age were measured at baseline. Incident hip fractures were ascertained and confirmed by interview and review of medical records through 12/31/05. We calculated Φ in two ways: using the ratio of either the estimated peak force or the attenuated (atten) force applied to the hip in a sideways fall from standing height divided by the femoral strength. Peak force (N) was calculated from height (m) and weight (kg). The attenuated force incorporated the cushioning effect of trochanteric soft tissue thickness (mm), as estimated by BMI, using published sex-specific regressions. Femoral strength (N) was estimated from femoral neck BMD, using a relation derived from published cadaveric femoral strength testing. Sex-specific crude, age- and BMD-adjusted Cox Proportional Hazards regressions were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the relation between hip fracture risk and both Φ_{peak} and Φ_{atten}.

Results: In the 425 men and 675 women (mean age 76 yrs) mean BMI was 26.8 kg/m^2. Median follow-up was 11.3 yrs and 155 hip fractures occurred (28 in men). Φ_{peak} and Φ_{atten} were associated with increased risk of hip fracture, adjusting for age (Table). A 1 SD increase in Φ_{peak} was associated with a HR of 1.88 in men and 1.23 in women. Similarly, for Φ_{atten}, the HR for hip fracture was 1.78 in men and 1.41 in women. After adding BMD to the model, Φ_{atten} remained predictive of hip fracture in women. In men, we could not adjust for BMD due to collinearity with Φ.

Conclusion: In summary, both Φ_{peak} and Φ_{atten} predict subsequent hip fracture in men and women. In women, we showed for the first time that Φ_{atten} predicts hip fracture independent of hip BMD. These findings provide strong rationale for additional studies testing the ability of this biomechanical approach to predict hip fracture.

Table: Adjusted hip fracture hazard ratios (95% CI) in men and women for a 1 standard deviation (SD) increase.

Model	**Men**	**Women**
Age-adjusted		
Factor-of-Risk$_{peak}$	1.88 (1.38, 2.55)	1.23 (1.10, 1.37)
Factor-of-Risk$_{attenuated}$	1.78 (1.30, 2.44)	1.41 (1.26,1.58)
Age- and BMD-adjusted		
Factor-of-Risk$_{peak}$	– *	0.80 (0.51, 1.27)
Factor-of-Risk$_{attenuated}$	– *	1.20 (1.01,1.41)

*In men, Factor-of-Risk$_{peak}$ and Factor-of-Risk$_{attenuated}$ were collinear with BMD. Therefore, we were unable to examine this association.

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Predicting Arthritis-Related Work-Transitions within One Year: Which at-Work Disability Measure Is Best? Kenneth Tang[1], Dorcas E. Beaton[1], Monique A. Gignac[2], Diane Lacaille[3], Elizabeth M. Badley[2], Aslam H. Anis[3] and Claire Bombardier[4], [1]St. Michael's Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of British Columbia, Vancouver, BC, [4]University Health Network, Toronto, ON

Purpose: To cope with the effects of arthritis, workers may opt to reduce work hours, take a disability leave of absence, or change jobs. Evidence of such "work-transitioning" is a concern, and may indicate a risk for future work loss. The ability to predict arthritis-related work-transitions would be useful for early identification of workers at-risk. Our aim is to assess and compare the ability of three at-work disability measures to predict arthritis-related work-transitions over a 1 year period.

Method: Workers with arthritis (*n*=250, OA=130, RA=120) recruited from community or clinical settings were followed for 1 year (four timepoints: baseline & 3, 6, 12-month follow-up). Measures tested as predictors include the *Workplace Activity Limitations Scale* (WALS, range=0-33), *Work Instability Scale for Rheumatoid Arthritis* (RA-WIS, range=0-23), and *Work Limitations Questionnaire* (WLQ, index range=0-28.6), all with previous validation in both OA and RA. To compare their predictive ability, 3 parallel multivariate logistic regressions were performed with work-transitioning expressed as a dichotomized outcome (occurrence vs. non-occurrence within 1 year). Each model featured 1 of the 3 measures to be compared, in addition to statistically-relevant covariates (e.g. pain intensity, HAQ) controlled across parallel models. Statistical indictors of model fit and predictive ability (AIC, Cox & Snell's pseudo R^2, standardized coefficient [std β]) were directly compared across models, as well as adjusted odds ratio (OR) associated with the 3 measures. In addition, area under the receiver operating characteristic curve (AUROCC, 95%CI) was also assessed for each measure for further comparisons of discriminative ability.

Results: Within 1 year, 20.4% of the sample had made a work-transition. Although all 3 regression models showed some ability to predict this outcome, the lowest AIC and highest pseudo R^2 were observed when the RA-WIS was the predictor measure. An increase in RA-WIS score (std β=0.24, OR=1.1 [95%CI: 1.0-1.2]) was also shown to have greater predictive ability than any of the covariates assessed (std β=0.05-0.15). Notably, HAQ scores were consistently found to contribute little to the prediction of a work-transition. Between the 3

measures, the RA-WIS also demonstrated the largest AUROCC associated with specific forms of work-transitions assessed (disability leave: 0.74 [0.58-0.89]; reduced work hours: 0.81 [0.72-0.89]; job change: 0.61 [0.45-0.78]), indicating superior discriminative ability.

Conclusion: Overall, all 3 measures were found to contribute to the prediction of arthritis-related work transitions, with the RA-WIS emerging as the slightly better performer. Constancy of the predictive effects of the scales was also found to be independent of the influence of HAQ scores.

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Berg Balance and Risk of Indoor and Outdoor Falls in Elderly Men and Women. Uyen-Sa DT Nguyen[1], Lien Quach[1], Jennifer L. Kelsey[2], Douglas P. Kiel[1], Andrew M. Galica[1], Carol A. Oatis[3] and Marian T. Hannan[1], [1]IFAR HSL, Boston, MA, [2]UMass, Worcester, MA, [3]Arcadia Univ, Glenside, PA

Purpose: Falls occur frequently, 1/3 of older adults have a fall each year. Balance, as measured with the Berg Balance Scale (BBS), has been shown to be a risk factor of falls in nursing home patients but its association with falls in community-dwelling older adults is less clear. Furthermore, little research has examined the association of balance with indoor and outdoor falls. The goal of this study was to examine the association of BBS with risk of falls separately for indoor and outdoor falls in community-dwelling older adults.

Method: We studied the 765 participants from MOBILIZE Boston, a population-based prospective cohort study of elderly men and women living in the Boston area. We assessed balance using the BBS (range: 0 – 56), and followed the cohort for falls using monthly falls calendars (mean follow-up: 1.8 years). We dichotomized BBS using the clinical cut-point for poor balance of 45 (BBS <= 45 vs. BBS > 45), and calculated annualized fall rates (number of falls/year of follow-up) separately for indoor and outdoor falls. We used negative binomial regression to estimate incidence rate ratios (RRs) and 95% confidence intervals (CIs), and controlled for factors related to both falls and balance including age (years), college education (y/n), fall in the past year (y/n), depression symptoms (CESD-R), number of medications, physical activity (PASE), and vision (> 40/100).

Results: Poor balance (BBS <= 45) occurred in 16% of participants. Those with poor balance had an annualized fall rate of 0.83 per person year (ppy) for indoor and 0.24 ppy for outdoor falls. Those with BBS > 45 had an annualized fall rate of 0.35 ppy for indoor and 0.39 ppy for outdoor falls. Baseline characteristics are shown in Table 1. Adjusting for confounders (Table 2), those with BBS <= 45 compared to BBS > 45 had a 70% increased rate of indoor falls (95% CI: 1.2, 2.4) and a 30% decreased rate of outdoor falls (95% CI: 0.4, 1.0).

Conclusion: Poor balance was associated with an increased rate of indoor falls, and was inversely associated with the rate of outdoor falls in our population-based cohort of older adults. Our results indicate that poor balance is related differently to indoor and outdoor falls and that these outcomes should be examined separately.

Table 1. Baseline Characteristics of Study Population

	Mean ± SD or N (%)*	
Characteristics	**BBS <= 45 (n=126)**	**BBS > 45(n=638)**
Age (years)	82 ± 6	77 ± 5
College Education (y/n)	63 (50)	438 (69)
Falls history (y/n)	63 (50)	222 (35)
Depression (CESD-R)	54 ± 11	50 ± 10
Medications (number)	8 ± 3	6 ± 3

Physical Activity (PASE)	61 ± 42	116 ± 72
Vision (> 40/100)	104 (84)	594 (93)

*** p < 0.05 for all baseline variables across BBS groups**

Table 2. Rate Ratios for the Association Between Berg Balance Scale and Rate of Indoor and Outdoor Falls.

BBS<=45 vs. BBS>45 (referent)	Indoor Falls RR (95% CI)	Outdoor Falls RR (95% CI)	All Falls RR (95% CI)
Crude	2.2 (1.6, 3.0)	0.6 (0.4, 0.9)	1.4 (1.1, 1.9)
Adjusted for Age, Falls History, Education, CESDR, Medications, PASE, Vision	1.7 (1.2, 2.4)	0.7 (0.4, 1.0)	1.2 (0.9, 1.6)

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ACR Concurrent Abstract Sessions

Clinical Aspects of Systemic Lupus Erythematosus

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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A Randomised Controlled Trial of Mycophenolate Mofetil Versus Placebo On Surrogate Markers of Atherosclerosis in Systemic Lupus Erythematosus. R. Davies, SR. Sangle, V. Murru, ML. Bertolaccini, Munther A. Khamashta and David P. D'Cruz, Lupus Research Unit, The Rayne Institute, King's College London School of Medicine, St Thomas' Hospital, London, United Kingdom

Purpose: Systemic lupus erythematosus (SLE) is an independent risk factor for atherosclerosis. Endothelial dysfunction is the earliest marker of atherosclerosis and is measured by flow mediated dilation (FMD) of the brachial artery. The purpose of the study was to measure FMD in mild, stable SLE patients and look for change in FMD with the immunosuppressant drug mycophenolate mofetil (MMF).

Method: A prospective, double-blind, randomised, placebo-controlled trial evaluating MMF on surrogate markers of atherosclerosis in mild SLE. 70 females fulfilling ACR criteria were recruited and allocated by minimisation to either placebo or MMF 1gm bd for 8 weeks. The primary end point was change in FMD assessed on an intention to treat basis. Other inclusion criteria were mild and stable disease, 18-60 years, on hydroxychloroquine and/or ≤15mgs prednisolone od. Exclusions were severe active disease, other immunosuppressants, smokers, diabetes mellitus and ischaemic heart, cerebrovascular or end stage renal disease. A minimum of 30 subjects per group were required to detect a change in FMD with a power of 90% at a 5% significance level.

Results: Seventy patients were recruited and 63 completed the study. The FMD for both groups was within the normal range at baseline and failed to change significantly post treatment. There was a significant decrease in BILAG score within the treatment group and this was reflected by a downward trend in Hs-CRP levels, although not reaching statistical significance. The Hs-CRP rose significantly during the study period in the placebo group. Secondary end points looked at change in levels of serum biomarkers previously shown to be associated

with increased cardiovascular risk (ADMA) and endothelial dysfunction (tPA and PAI-1), however levels failed to change in either group and using multiple regression analysis there were no assoiciations with reduced FMD or traditional cardiovascular risk factors.

Table 1

	Placebo visit 1	Placebo visit 2	p values	MMF visit 1	MMF visit 2	p value
FMD%	7.61 (±3.48)	7.29 (±3.21)		8.36 (±4.11)	8.98 (±5.47)	
BILAG	9.8 (±4.2)	9.5 (±4)		10.1 (±4.5)	8.5 (±3.9)	p=0.03
HsCRP	5.1 (±5.8)	7.4 (±9.7)	p=0.05	6.3 (±8.6)	5.8 (±7.4)	
ADMA	0.39 (±0.23)	0.38 (±0.16)		0.36 (±0.22)	0.35 (±0.17)	
tPA	16.03 (±	19.83 (±		29.33 (±	18.39 (±	
PAI-1	23.07 (±20.12)	23.08 (±19.98)		21.35 (±14.56)	23.29 (±12.55)	

Values; mean(±sd), BILAG; British Isles Lupus Assessment Group disease activity score, HsCRP; high sensitivity C-reactive protein (mg/l), ADMA; Asymmetric dimethylarginine (µmol/l), tPA; Tissue plasminogen activator (ng/ml), PAI-1; Plasminogen activator inhibitor 1 (ng/ml).

Conclusion: Endothelial function is well preserved In SLE patients with mild, stable disease on hydroxychloroquine and with few or absent traditional cardiovascular risk factors. It is likely that aggressive immunosuppressive treatment to suppress vascular inflammation may not be warranted in these patients.

Disclosure: R. Davies, Aspreva Pharmaceuticals Ltd, 2 ; **S. Sangle**, None; **V. Murru**, None; **M. Bertolaccini**, None; **M. A. Khamashta**, None; **D. P. D'Cruz**, Aspreva, 2 .

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Low Mycophenolic Acid Area Under the Curve Is a Major Parameter of Systemic Lupus Erythematosus Activity. Laurent Arnaud[1], Noël Zahr[2], Julien Haroche[1], Jean-Sébastien Hulot[2], Pierre Marquet[3], Christian Funck-Brentano[2], Jean-Charles Piette[1] and Zahir Amoura[1], [1]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [2]Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France, [3]INSERM U850, Limoges, France

Purpose: Mycophenolate Mofetil (MMF) is widely used for the treatment of Systemic Lupus Erythematosus (SLE). Mycophenolic Acid (MPA) is the active metabolite of MMF. In transplantation, MPA Area Under the plasma Concentration-time Curve from 0 to 12 hours (MPA AUC_{0-12}) is the most reliable assessment of MPA exposure and is correlated with the clinical outcome. We assessed possible relationships between SLE activity and MPA AUC_{0-12}.

Method: Seventy-one consecutive SLE patients, 61 women and 10 men, mean (± SD) age at sampling 34 ± 10 years, with stable MMF dose, were enrolled in the study. On the same day, SLE activity was assessed with the SLEDAI and the BILAG (SLEDAI-active and BILAG-active SLE were defined, respectively, as SLEDAI ≥ 6 or BILAG A or B). MPA AUC_{0-12} was determined by using a Bayesian estimator developed for SLE.

Results: Two groups were studied: active SLE (n=26; mean SLEDAI: 11.6 ± 4.4) and inactive SLE (n=45; mean SLEDAI: 1.9 ± 1.6), that were similar for sex-ratio, mean age at sampling, mean weight, mean Body Mass Index, mean daily doses of MMF, of steroids, and mean hydroxychloroquine blood levels. MPA AUC_{0-12} correlated weakly with the daily dose of MMF (r=0.33, p=0.005). Mean (±SD) MPA AUC_{0-12} of the active SLE group was significantly lower than that of the inactive SLE group (26.8 ± 13.6 µg.h/ml vs 46.5 ± 16.3 µg.h/ml, respectively; p<0.0001). MPA AUC_{0-12} negatively correlated with the SLEDAI (r=-0.64, p<0.0001), with anti-dsDNA levels (r =-0.25,

p=0.04), and correlated positively with C3 levels (r=0.38, p=0.001). Similar results were obtained when comparing BILAG-active and BILAG-inactive patients. In multivariate analysis, MPA AUC_{0-12} was the sole independent parameter associated with SLE activity (odds ratio = 0.893; 95% CI = 0.834-0.956; p = 0.001). By ROC curve analysis, we determined that the MPA AUC_{0-12} value of 35 µg.h/ml provided the best trade-off between sensitivity and specificity associated with the lowest risk of SLEDAI- or BILAG-active SLE on the day of sampling.

Conclusion: SLE activity is strongly correlated with MPA AUC_{0-12} in SLE. Individualized dosing regimen of MMF, with a recommended target AUC threshold of 35 µg.h/ml has to be considered to improve the efficacy of MMF in SLE. Because there is a high inter-individual variability of MMF pharmacokinetics, it is now mandatory to include MPA AUC_{0-12} in future clinical trials evaluating MMF in SLE.

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Validation of Interferon-Regulated Chemokines as Predictors of Lupus Flare. Jason W. Bauer[1], Michelle Petri[2], Franak Batliwalla[3], Joseph C. Wilson[1], Thearith Koeuth[1], Marlene Hyer Kern[3], Sukhminder Singh[2], Hanna Tesfasyone[2], Peter K. Gregersen[3], Timothy W. Behrens[4] and Emily C. Baechler[1], [1]University of Minnesota, Minneapolis, MN, [2]JHU, Baltimore, MD, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]Genentech, South San Francisco, CA

Purpose: We previously showed that serum levels of interferon (IFN)-regulated chemokines are biomarkers of systemic lupus erythematosus (SLE) disease activity. In a cohort of 267 SLE patients, high baseline chemokine levels were predictive of flare. Here we have measured serum levels of IP-10, MCP-1, and MIP-3b in an independent group of 373 SLE patients in a replication study.

Method: We studied 373 SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Clinical and laboratory data were available for 1 year of follow-up (1815 visits). Multiplex sandwich-based immunoassays were used to measure serum levels of IP-10, MCP-1, and MIP-3b. A normalized chemokine score was used to reflect the combined levels of all 3 chemokines. For flare prediction, we selected baseline visits from 257 patients with mild or inactive disease (SLEDAI≤4) and tabulated flares within 1 year (increase in SLEDAI≥3). ROC curves were used to identify the chemokine concentration with optimal sensitivity and specificity for flare prediction. These concentrations were used to stratify patients into chemokine-high and –low groups, and flare rates were compared by Kaplan-Meier (KM) analysis. Univariate Cox regression was performed with chemokines and laboratory tests with flare-free survival as the dependent variable. Significant variables were subjected to stepwise multivariate Cox regression.

Results: As expected, patients with active SLE (SLEDAI≥6; n=50) had elevated chemokine levels vs. inactive SLE (SLEDAI≤2, PGA=0; n=94) ($p<2x10^{-10}$). In KM analysis, flare rates were significantly higher in patients who had high baseline levels of IP-10, with 41% of IP-10 high patients and 23% of IP-10 low patients having a flare (p=0.002). Similar results were obtained with MIP-3b (46% of MIP-3b high vs. 27% of MIP-3b low patients; p=0.006), but not MCP-1 (29% of MCP-1 high vs. 32% of MCP-1 low; p=0.49). The composite chemokine score reached greater significance than any single chemokine (42% of chemokine-high vs. 23% of chemokine-low; p=0.001). Significant flare predictors from univariate Cox regression were IP-10 (p=0.001), chemokine score (p=0.002), MIP-3b (p=0.01), anti dsDNA Abs (p=0.02), ESR (p=0.04) and C3 (p=0.04). These variables was subjected to a multivariate analysis in which only IP-10 levels were significant (p=0.002)

Conclusion: This is the first validation, in an independent group of 257 SLE patients, of our previous report that chemokine levels are predictive of flare. Our data suggest that IP-10 may have the greatest predictive power, and further studies are needed to determine whether models containing both chemokines and laboratory results will prove optimal.

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Urine Cyto/Chemokines Correlate with Renal Histopathology in Systemic Lupus Erythematosus. C. Landolt-Marticorena[1], H. Reich[2], S. Morrison[3], E. Aghdassi[3], C. A. Pineau[4], J. Scholey[5], D. Gladman[3], M.B. Urowitz[1], A. Herzenberg[5], P. R. Fortin[6], J. E. Wither[1] and CaNIOS LuNNET Investigators, [1]U of Toronto, Toronto Western Hospital, Toronto, ON, [2]University Heath Network, Toronto, ON, [3]Toronto Western Hospital, Toronto, ON, [4]MUHC, Montreal, QC, [5]University Health Network, Toronto, ON, [6]U. Toronto, Toronto, ON

Purpose: Renal biopsies are the gold standard for the assessment of renal activity and chronicity in SLE patients. Urinary biomarkers may serve as a less invasive alternative in the management of lupus nephritis (LN). In an initial screen of 20 cyto/chemokines urine concentrations of IP-10, MCP-1, adiponectin, IL-15 and sVCAM were found to be elevated in patients with active LN. We therefore examined the relationship between renal histopathology and the urine concentration of these 5 analytes at the time of biopsy.

Methods: Patients (n = 22) satisfying 4 or more ACR criteria undergoing renal biopsy were recruited from a longitudinal clinical cohort. Plasma and urine were obtained coincident with biopsy. 19 healthy controls were also recruited. The plasma and urine concentrations of 5 analytes was determined by a Luminex assay with urine concentrations corrected for creatinine excretion. Patients were segregated into active (ISN/ASN; III to V; n = 19) and inactive (chronic, n = 3) based on renal histopathology. Elevated urine analyte concentration was defined as values ≥ 2 standard deviations above the mean in controls. Mann Whitney non-parametric test was used for comparisons between groups. The statistical significance of correlations was determined by linear regression analysis.

Results: The urine concentration of IP-10 ($p < 0.0001$), MCP-1 ($p < 0.0001$), adiponectin ($p = 0.0004$), IL-15 ($p = 0.0006$) and sVCAM ($p = 0.007$) were significantly elevated in SLE patients versus controls. There was a moderate positive correlation between the urine and plasma concentration of IP-10 ($r = 0.54$, $p = 0.009$) but none of the other analytes. Elevated urine concentrations of MCP-1, IP-10, adiponectin and IL-15 were seen in 82.3%, 68.1%, 54.5% and 40.9% respectively. As only 22.7 % of patients had elevated urine sVCAM this analyte was excluded from further analysis. To assess if increased urinary analyte concentrations discriminate between active and inactive LN, the absolute number of elevated values for all 4 analytes were summed to create a global score (maximum = 4). Patients with active renal lesions had a statistically significant increase ($p = 0.03$) in the global score versus patients with established fibrosis. All 3 patients with fibrosis had scores ≤ 1 whereas the majority (73.8 %) of patients with active renal lesions had scores ≥ 2. In patients with proliferative lesions (ISN III or IV) 85.7% patients (n = 14) had scores of 2 or greater whilst 75 % (n = 4) patients with membranous LN (ISN V) had scores of 1 with a single patient having a score of 4.

Conclusion: Urinary elevation in selected cyto/chemokines effectively discriminate between active and chronic renal lesions. The elevation of 2 or more analytes was sufficient to identify proliferative renal lesions. These results suggest that urinary cyto/chemokines reflect underlying renal pathology and may serve as alternatives to renal biopsy.

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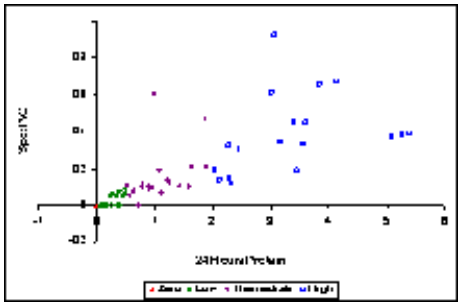
Expressing Urinary Protein Excretion in Lupus Nephritis. Debra Dye-Torrington[1], Emily Siu[2], Dominique Ibañez[1], Murray B. Urowitz[1] and Dafna D. Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON

Purpose: Lupus nephritis is seen in more than 50% of patients with SLE and is one of the most serious manifestations of this disease. Kidney involvement in these patients is monitored by the amount of proteinuria. This is ordinarily done by measuring total protein in a 24hr urine collection. A more convenient way of measuring proteinuria is the protein-to-creatinine ratio in an untimed urine (spot p/c ratio).Whether this is an accurate measure of high proteinuria is still not clear. The objective of this study was to determine the correlation between p/c ratio and 24 hr urine protein among patients with SLE over a range of proteinuria.

Method: SLE patients recruited from a single centre were asked to collect a spot urine within 24 hrs after the end of the 24 hr urine collection. 24 hr protein excretion was categorized into three groups: Low <0.5g/24h, intermediate 0.5-2g/24h, high >2.0g/24h. Comparison of P/C ratio with levels of proteinuria was done through correlation coefficients.

Results: 76 samples of 24hr urine and spot urines were collected. (86%) of the patients were female, 50% Caucasian, 19% Black, 18% Chinese and 12% Other. Age (± std) at SLE diagnosis was 28.8 ± 12.4 years and disease duration at the time of sampling was 11.8 ± 6.9 years. 84% of the samples were positive for protein. 25(33%) were in the low range, 21(28%) were intermediate and 18(24%) were high. The mean Spot P/C (± std) by protein levels was; for no protein, Spot P/c 0 ± 0; for low protein, Spot P/C 0.02 ± 0.03; for intermediate

protein, spot P/C 0.15 ± 0.14; for high protein, spot P/C 0.39 ± 0.21 Overall, the correlation coefficient between all 24 hours protein and spot P/C was 0.79 (p<0.0001). For each of the protein level, the correlation coefficient with spot P/C was; for low protein, r=0.69 (p=0.0001); for intermediate protein, r=0.44 (p=0.05); for high protein, r = 0.34 (p=0.16). *Plot of 24 hours protein with Spot P/C by protein levels.*



Conclusion: There is a poor correlation between spot P/C ratios and 24 hour urine protein excretion at levels of proteinuria of 2 grams or more. P/C ratios should not be used to monitor protein excretion in patients with lupus nephritis.

Disclosure: D. Dye-Torrington, None; **E. Siu**, None; **D. Ibañez**, None; **M. B. Urowitz**, None; **D. D. Gladman**, None.

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Impact of Clinical and Demographic Features On Influenza Vaccination Responses in Human Systemic Lupus Erythematosus.

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Purpose: Infectious diseases are a serious cause of morbidity and mortality in immunocompromised individuals, such as those with systemic lupus erythematosus (SLE). Vaccination against common infections, such as influenza, is recommended for SLE patients to decrease infections and improve health. However, few reports detail how SLE patients respond to this common vaccination. The goal of this study is to understand the clinical, serological, therapeutic, and demographic factors which influence the immune response to influenza vaccination in SLE patients.

Method: Over three influenza seasons (October 2005 to February 2008), 72 SLE patients and matched controls were enrolled. Each individual provided detailed clinical (medication usage, previous vaccinations, etc) and demographic (age, race, etc) information. Blood was collected from each individual on the day of influenza vaccination, as well as two, six, and twelve weeks post vaccination. Influenza-specific antibody responses were evaluated by standard ELISAs, relative antibody affinities, and hemagglutination inhibition levels. Based upon these data, individuals were grouped into high and low responders. Autoantibody levels were evaluated at each time-point by immunoflourescence and standard ELISAs.

Results: Poor responders to influenza vaccination were more likely to have hematologic criteria (p = 0.009), exhibit more ACR criteria (p = 0.05), and be receiving prednisone treatment (p = 0.037). No significant differences in the initial autoantibodies between the high and low responders were found, although low responders were more likely to have serum anti-cardiolipin antibodies. Interestingly, the high influenza responder group was enriched for African Americans (p = 0.03) and in fact low responders were 3 times more likely to be Caucasian than African American. All measures of disease activity significantly increased following vaccination: SLEDAI (p = 0.012), PGA (p = 0.007), and SLAM (p = 0.001), but disease activity changes were not enriched in either the high or low responders. Finally, low responders were more likely to increase ANA titers following vaccination (p = 0.045).

Conclusion: In summary, influenza vaccination impacts a significant fraction of SLE patients by increasing autoantibody production and/or disease activity. Poor responders have more ACR criteria, use prednisone and have hematological criteria, suggesting that studies of split doses or withholding prednisone on day of vaccination in some patients may be warranted.

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ACR Concurrent Abstract Sessions

Fibromyalgia and Soft Tissue Disorders I: Diagnosis and Management

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Clinical Diagnostic and Severity Criteria for Fibromyalgia. F. Wolfe[1], Daniel Clauw[2], MA Fitzcharles[3], Don L. Goldenberg[4], KA Harp[1], RS Katz[5], PJ Mease[6], KD Michaud[7], Anthony S. Russell[8], IJ Russell[9], JB Winfield[10] and MB Yunus[11], [1]National Data Bank, Wichita, KS, [2]University of Michigan, Ann Arbor, MI, [3]MGH, Montreal, QC, [4]Newton-Wellesley Hosp, Newton, MA, [5]Rheumatology Associates, Chicago, IL, [6]Seattle Rheumatology, Seattle, WA, [7]U Neb Med Cntr and NDB, Omaha, NE, [8]U Alberta, Edmonton, AB, [9]U TX Hlth Sci Ctr, San Antonio, TX, [10]UNC, Chapel Hill, NC, [11]U IL Coll of Med, Peoria, IL

Purpose: Among the criticisms of current ACR fibromyalgia criteria is their reliance on the tender point (TP) examination, which is largely ignored in primary care, and the absence of criteria items, beyond pain, that relate to key fibromyalgia symptoms by which patients are identified and diagnosed clinically. However, ACR criteria represent the gold standard, and any modified criteria must move away from the ACR definition to some extent. We performed a multicenter study to develop clinical diagnostic criteria while remaining generally true to the ACR classification criteria.

Methods: We performed a two-stage 55-site multicenter study of 1,002 FM patients and pain controls to develop simple clinical criteria for fibromyalgia. Physicians and patients were evaluated separately. Patients underwent a detailed interview and examination, including TP examination and assessment of the extent of widespread pain using a 0-19 widespread pain index (WPI), and also completed a detailed questionnaire. We used Random Forest data mining methods in a series of analyses that included a maximum of 134 variables to identify best variables for FM criteria, not including tender points. Some variables (e.g., fatigue) were included in continuous and categorical forms.

Results: The WPI was the best predictor of FM. Analyses excluding WPI identified unrefreshed sleep, fatigue, cognitive difficulties, and the extent of somatic symptom reporting as the key FM predictors. We combined the 4 categorical symptom variables into a 0-12 Symptom Severity (SS) scale. The SS scale correlated with the TP count (r=0.688) and the WPI (0.733). We propose that FM may be diagnosed when (WPI >6 AND SS >4) OR SS >=9. These criteria correctly identified 80.9% of ACR (+) cases while physician diagnosis agreed with ACR criteria in 84.1% of cases. New diagnostic criteria agreed with an SS scale >=7 in 93% of cases. The SS scale correlated with a wide series of FM severity measures and was effective in describing FM severity and severity status of persons previously diagnosed with FM, but now not satisfying ACR criteria. In the 2nd phase of the study, a simple categorical form, suitable for use in the clinic, was used and performed as well as Phase 1 variables.

Conclusion: We have proposed simple clinical criteria for FM that do not require the use of tender points. These criteria expand the definition of fibromyalgia to include symptoms other than pain, and provide a measure to assess FM symptom related severity. The agreement with ACR criteria of 80.9% reflects disagreement related to the expanded definition and removal of the tender point criterion. We propose that the 1990 ACR classification criteria continue to be used for their intended purpose (to identify individuals for research studies), but that these new criteria may be more applicable in clinical settings, or research settings (e.g. epidemiological studies) where a TP count is not feasible.

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Chronic Widespread Pain Predicts Higher Levels of Fatigue: Results From a Population Based Prospective Survey. John McBeth and Barbara I. Nicholl, University of Manchester, Manchester, United Kingdom

Purpose: Chronic widespread pain (CWP) is associated with numerous co-morbidities including high levels of fatigue. It is unclear whether this relationship is explained by other factors associated with pain, which may act to increase the likelihood of becoming fatigued or whether there is a direct relationship between pain and fatigue. The aim of this study was to test the hypothesis that individuals with CWP would have an increased risk of becoming fatigued, independently of putative confounders.

Method: We conducted a population based prospective cohort study. 1953 adult subjects, selected from a population register, completed a detailed questionnaire which included a pain drawing. Based upon their reports subjects were classified into one of three groups: those reporting no pain, those with some pain but not CWP, and those satisfying the ACR criteria for CWP. Baseline levels of fatigue were assessed using the 11 item Fatigue Questionnaire. Subjects also completed measures of psychological distress (General Health Questionnaire), somatisation (Somatic Symptom Checklist), and Illness Behaviour and Health Anxiety scales. All subjects who participated at baseline were followed up 12 months later at which time they completed another questionnaire that assessed levels of fatigue using identical instruments. The relationship between pain status at baseline and levels of fatigue (in tertiles) at follow up was assessed using multinomial regression and the results are expressed as relative risk ratios (RRR) with 95% confidence intervals (CI). All analyses were adjusted for age and gender.

Results: A total of 1910 subjects provided pain data at baseline and were eligible for follow up. Of those 1681 (88.0%) returned the follow up questionnaire, 1482 (77.6%) completed the fatigue questionnaire and 1384 (72.5%) provided full data and were included in the current analysis. Compared to those reporting no pain at baseline, those reporting some pain were more likely to have fatigue levels at follow up in the highest third of the scale (12.2% v 19.8% respectively) and those with CWP were most likely (36.0%). After adjusting for age and gender, subjects with some pain (OR = 2.3, 95% CI (1.6, 3.2)) and CWP (5.8 (3.8, 8.9)) had a higher risk of being in the top third of fatigue score. These relationships were attenuated when adjusted for baseline psychosocial factors (some pain: 1.6 (1.1, 2.3) and CWP: 3.0 (1.9, 4.8)). Only the relationship with CWP persisted after adjusting for baseline levels of fatigue (1.9 (1.1, 3.2)).

Conclusion: CWP is strongly associated with higher levels of fatigue. Future studies should explore potential mechanisms including behavioral factors such as physical inactivity and diet.

Disclosure: J. McBeth, None; **B. I. Nicholl**, None.

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Genetic Polymorphisms of the Beta 2-Adrenergic Receptor Relate to Gs Protein Dysfunction in Fibromyalgia Syndrome. Yangming Xiao, I. Jon Russell, Wanda L. Haynes and Joel E. Michalek, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Purpose: The beta 2-adrenergic receptor (β_2AR) is a G protein-coupled receptor (GPCR) that mediates the actions of catecholamines in multiple tissues. We previously documented a GPCR stimulatory (Gs) dysfunction in patients with fibromyalgia syndrome (FMS). The aims of the present study were to determine the frequencies of β_2AR gene polymorphisms in FMS compared with healthy normal controls (HNC) and to determine whether polymorphisms in the β_2AR gene might contribute to the Gs dysfunction in FMS.

Method: The study was conducted with ethics committee approval and study subjects signed informed consent to participate. Morning blood samples were obtained from primary FMS (1990 ACR criteria) and demographically-matched HNC in what was intended to be a ratio of 2:1. Peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation. The Gs functions of PBMC were tested using isoproterenol (ISO) as the adrenergic Gs ligand and measuring intracellular cAMP levels (second message) by enzyme linked immunosorbent assay (ELISA). The β_2AR genotypes at amino acid position 16 and 27 were determined for each subject using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Differences between the genotype frequencies of FMS and HNC were evaluated using a chi-square test.

Results: Study subjects included 97 FMS patients and 59 HNC. The frequency of the β_2AR gene polymorphism Arg16Gly (45.1%) in FMS was significantly lower ($p = 0.035$) than in HNC (62.7%). Conversely, the Gly16Gly genotype in FMS (37.1%) was marginally more frequent than in HNC (25.4%, $p = 0.06$). The frequencies of other tested β_2AR genotypes, such as Arg16Arg, Gln27Gln, Glu27Glu, and Gln27Glu did not differ between FMS and HNC. FMS patients carrying the β_2AR polymorphism Arg16Arg exhibited significantly lower PBMC basal cAMP levels ($p<0.025$) and lower ISO-stimulated cAMP levels ($p<0.025$) than FMS carrying Gly16Gly or Arg16Gly.

Conclusion: These data show that *in vitro* testing of GPCR function of PBMC can be fruitful in FMS. Several associations were found between FMS and β_2AR genetic polymorphisms at codon 16. Indeed, this is the first study to demonstrate β_2AR polymorphism-related differences in intracellular cAMP levels within FMS PBMC before and after beta adrenergic stimulation. These findings imply that β_2AR polymorphism in FMS may influence responses to a variety of beta adrenergic ligands. This concept may help to explain some of the differences in responsiveness of FMS subgroups to the adrenergic agonist medications currently approved for FMS treatment. Finally, one could speculate that these findings may directly relate to the adrenergic autonomic nervous system dysfunction documented in FMS.

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Chronic Widespread Pain Is Associated with Reduced Psychomotor Processing Speed in Middle-Aged and Older Men: Results From the European Male Ageing Study (EMAS). David M. Lee[1], Abdelouahid Tajar[1], Neil Pendleton[1], Gyorgy Bartfai[2], Gianni Forti[3], Aleksander Giwercman[4], Dirk Vanderschueren[5], Frederick CW Wu[1] and John McBeth[1], [1]The University of Manchester, Manchester, United Kingdom, [2]Albert Szent-Gyorgy University, Szeged, Hungary, [3]University of Florence, Florence, Italy, [4]Malmö University Hospital, Malmö, Sweden, [5]Katholieke Universiteit Leuven, Leuven, Belgium

Purpose: There is evidence from clinic based studies that fibromyalgia is associated with impairment in cognitive function though the mechanism is unclear. The aim of this analysis was to determine whether there is an association between chronic widespread pain (CWP), a cardinal feature of fibromyalgia, and impaired cognition in a community setting.

Method: 3,369 men aged 40 to 79 years were recruited from population registers in eight centres for participation in the European Male Ageing Study (EMAS). Subjects completed a postal questionnaire which included questions about the occurrence of pain experienced in the past month and were asked to draw on a body manikin the site of any pain. Based on the pain questionnaire and body manikin the presence of CWP was defined using the ACR criteria. Self-report data on age on leaving education, smoking, physical function and a range of co-morbidities were also collected. Subjects were then invited to attend a clinic visit which included assessments of depressive symptomology and physical function in addition to several cognitive function tests: the Rey-Osterrieth Complex Figure test (ROCF) to assess visuospatial construction (copy score) and memory (recall score), the Camden Topographical Recognition Memory test (CTRM) to assess non-verbal recall and the Digit Symbol Substitution test (DSST) to measure psychomotor processing speed. For all these tests higher scores reflect better cognitive performance. The relationship between the occurrence of CWP and the various cognitive tests was assessed using linear regression with the cognitive test as the outcome and the results expressed as β coefficients and 95% confidence intervals (CI).

Results: We restricted our analysis to those subjects reporting no pain, those reporting pain that satisfied the ACR criteria for CWP and in whom complete data on cognition was available. Of these 1,540 men [mean (SD) age 60 (11) years], 266 (17.3%) had CWP. The mean (SD) for the ROCF copy was 33.5 (4.3), ROCF recall 17.7 (6.6), CTRM 22.9 (4.7), and DSST 27.9 (8.7). All test scores were negatively associated with age ($p<0.05$). In age-adjusted linear regressions, compared to those without CWP, those with CWP had a lower DSST score (β coefficient = -2.4; 95%CI -3.4 to -1.5). After additional adjustment for other putative confounders (age leaving education, depression, physical function, smoking, alcohol, presence of morbidities, and centre), the association between pain status and the DSST score was attenuated but remained significant (β coefficient = -1.4; 95%CI -2.7 to 0.00). There was no association between CWP and the ROCF copy, ROCF recall or CTRM scores.

Conclusion: CWP is associated with reduced psychomotor processing speed among middle-aged and older European men. Prospective studies are required to confirm this observation and to explore possible mechanisms for the association.

Disclosure: D. M. Lee, None; **A. Tajar**, None; **N. Pendleton**, None; **G. Bartfai**, None; **G. Forti**, None; **A. Giwercman**, None; **D. Vanderschueren**, None; **F. C. Wu**, None; **J. McBeth**, None.

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Typology of Patients with Fibromyalgia: Cluster Analysis of Duloxetine Study Patients. Laurence A. Bradley[1], Ernest H. Choy[2], Peter Van Wembeke[3], Ilya A. Lipkovich[4] and Walter Deberdt[5], [1]UAL, Birmingham, Birmingham, AL, [2]Kings College London, London, United Kingdom, [3]Univerity Hospitals Leuven, Leuven, Belgium, [4]Eli Lilly and Company, Indianapolis, IN, [5]S.A. Eli Lilly Benelux N.V., Brussels, Belgium

Purpose: To identify distinct groups of subjects with fibromyalgia across multiple outcome measures and to evaluate their predictors.

Method: Eighteen variables from 7 scales covering areas of pain, mental and physical impairment, global impression, and overall functioning from 631 duloxetine-treated females collected post-treatment (endpoint within >2-12 weeks; last observation carried forward [LOCF]) in 4 randomized placebo-controlled duloxetine trials were included in a cluster analysis (k-means method) to identify distinct

patient groups. Classification rules were derived using a classification tree algorithm to define categories that mimic the clusters. Probabilities for transitioning from baseline to endpoint category were evaluated using logistic regression.

Result: Five clusters were identified, ranging from "worst" with high pain levels and severe mental/physical impairment to "best" with low pain levels and nearly normal mental/physical function:

Cluster characteristics (selection) and classification rules

		Endpoint mean score					
Cluster	**N**	**BDI total**	**BPI pain intensity**	**BPI pain interference (BPIAI)**	**FIQ interference with work (FIQ14)**	**FIQ depression (FIQ20)**	**Classification rule**
1 (worst)	78	25.08	7.58	7.89	8.26	6.91	BPIAI ≥7.14
2 (physically poor)	135	7.93	5.93	4.77	6.29	1.45	3.29 ≤BPIAI <7.14, FIQ20 <5
3 (mentally poor)	104	15.81	4.12	4.21	4.82	5.09	3.29 ≤BPIAI <7.14, FIQ20 ≥5
4 (moderate)	185	5.99	3.55	2.23	3.16	1.12	BPIAI <3.29, FIQ14 ≥2
5 (best)	129	3.46	1.43	0.60	0.77	0.57	BPIAI <3.29, FIQ14 <2
BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; FIQ=Fibromyalgia Impact Questionnaire							

Classification rules for categories that mimic the clusters were derived (see table) and used to classify duloxetine- and placebo-treated females at baseline and endpoint (N=1199). Patient characteristics and category frequencies at baseline were similar between treatments; >80% of patients were in the 3 worst categories ("worst": 30.6% overall; "physically poor": 32.8%; "mentally poor": 21.2%). Frequencies for the 2 best categories combined changed from 15.7% at baseline to 51.6% at endpoint with duloxetine and from 14.8% to 35.6% with placebo. The analysis of probabilities for transitioning from baseline to endpoint category showed that duloxetine patients were significantly more likely to improve the outcome category than placebo patients. Baseline category and treatment were the best predictors for endpoint outcome category.

Conclusion: Fibromyalgia patients are heterogeneous and can be classified into distinct subgroups based on overall severity and by differentiating between mental and physical impairment. Such classification facilitates outcome prediction and thus may have implications for individual patient management.

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Gonadotrophins Are Associated with Chronic Widespread Pain in Middle-Aged and Older Men. Abdelouahid Tajar[1], John McBeth[1], Gyorgy Bartfai[2], Felipe F. Casanueva[3], Gianni Forti[4], Krzysztof Kula[5], Margus Punab[6], Alan J. Silman[7], Dirk Vanderschueren[8], Frederick CW Wu[1] and Terence W. O'Neill[1], [1]The University of Manchester, Manchester, United Kingdom, [2]Albert Szent-Gyorgy Medical University, Szeged, Hungary, [3]Santiago de Compostela University, Santiago, Spain, [4]University of Florence, Florence, Italy, [5]University of Lodz, Lodz, Poland, [6]United Laboratories of Tartu University Clinics, Tartu, Estonia, [7]Arthritis Research Campaign, Chesterfield, [8]Katholieke Universiteit Leuven, Leuven, Belgium

Purpose: The role of sex hormones in the aetiology of chronic musculoskeletal pain is unclear. The aim of this study was to determine the influence of hypothalamic pituitary testicular axis (HPT) hormones on the occurrence of chronic widespread pain (CWP).

Methods: Men aged 40-79 years were recruited from population registers in eight centres for participation in the European Male Aging Study (EMAS). Subjects were asked to complete a postal questionnaire which included questions about lifestyle, co-morbid illnesses and musculoskeletal pain experienced in the past month. They were asked to highlight on a body manikin the sites of any pain they had

experienced. Subjects subsequently attended for assessment which included an interviewer assisted questionnaire and fasting blood sample from which total testosterone (TT), sex hormone binding globulin (SHBG), luteinising hormone (LH), and follicle-stimulating hormone (FSH) were assayed. Free testosterone (FT) was calculated from TT and SHBG using an established formula. Subjects were classified into one of three groups according to their pain reports: those reporting no pain, those with CWP, as classified using the ACR criteria, and those reporting some pain (non CWP). The association between pain status and sex hormone levels was assessed using multinomial logistic regression with results expressed as relative risk ratios (RRR) and 95% confidence intervals (CI). In all analyses the "no pain" group was the referent category.

Results: A total of 3,184 men [mean (SD) age 60 (11) years] had complete data on sex hormones and pain status. Of these 1,304 (41.0%) reported no pain, 1,605 (50.4 %) had some pain and 275 (8.6%) had CWP. The mean (SD) for TT was 16.5 (5.9) nmol/L, FT 292.0 (93.2) pmol/L, LH 6.2 (4.5) U/L , FSH 8.7 (9.2) U/L and SHBG 42.9 (19.8) nmol/L.After adjustment for age and other putative confounders including body mass index, smoking, alcohol intake, number of co-morbidities, depression and centre, the association between higher levels of LH and FSH and pain persisted. Being in the highest tertile of LH was associated with an increased risk of having some pain (RRR = 1.3; 95% CI, 1.1, 1.5) and CWP (RRR = 1.6; 95% CI, 1.1, 2.2). Similarly, being in the highest tertile of FSH was associated with an increased risk of having some pain (RRR = 1.3; 95% CI 1.01,1.5) and CWP (RRR = 1.5; 95% CI 1.2, 2.0).

Conclusion: Testosterone levels were similar among the pain groups with high levels of gonadotrophins (LH and FSH) among those with pain (some pain and CWP). This relationship may indicate that deficits in testicular function can be adequately compensated for in the presence of musculoskeletal pain. Further studies appear warranted to investigate these findings.

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ACR Concurrent Abstract Sessions

Genomics of Rheumatoid Arthritis

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Genome-Wide Association Study of Genetic Predictors of Anti-Tumour Necrosis Factor (TNF) Treatment in Rheumatoid Arthritis (RA) Identifies Associations with Polymorphisms at Five Loci. Laura J. Gibbons[1], Catherine Potter[2], K. L. Hyrich[1], Ann W. Morgan[3], Anthony G. Wilson[4], John D. Isaacs[2], Braggss and A. Barton[1], [1]arc Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Musculoskeletal Research Group, Newcastle University, Newcastle Upon Tyne, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Sheffield Uni /Medical School, Sheffield, United Kingdom

Purpose: Anti-tumour necrosis factor (TNF) agents are successful therapies in rheumatoid arthritis (RA); however, inadequate response occurs in 30-40% of patients treated. Knowledge of genetic factors influencing response may facilitate personalised therapy. The aim of this study was to identify genetic predictors of response to anti-TNF therapy in RA and to validate our findings in independent cohorts.

Method: Genome-wide association (GWA) data from the WTCCC[1] was analysed in terms of treatment response for 595 anti-TNF-treated RA patients. Multivariate linear regression analysis of change in 28 joint count disease activity score (DAS28) at 6 months was conducted at each single nucleotide polymorphism (SNP) using an additive model. Associated markers ($P < 10^{-3}$) were genotyped in two independent validation cohorts (n = 403 and n = 332) and a combined analysis was performed.

Results: Of 193 markers associated with treatment response in the GWA data, 5 were replicated in both validation cohorts. In the combined analysis, the strongest effect was at rs9292156, an intergenic SNP on chromosome 5q11.2: the minor allele conferred improved response (Table 1), with a clinically relevant improvement of 0.61 units between the minor and major allele homozygotes. Association was also replicated at intronic SNPs in *PDZD2* and *EYA4*, and at intergenic SNPs at chromosomal regions 1q23.3 and 12p12.3.

Table 1: Treatment response data in the combined cohort

		All cohorts combined (n = 1,330)						
SNP	**Locus**	**Genotype**	**Count**	**Mean baseline DAS28 (SD)**	**Mean change in DAS28 (SD)**	**Genotypic global *P***	**Additive model**	
							Global *P*	**Coefficient (95% CI)**
		11	399	6.61 (0.95)	-2.70 (1.47)			
rs12081765	Chr1q23.3	12	661	6.68 (1.01)	-2.44 (1.47)	5.12×10^{-4}	2.26×10^{-4}	0.20 (0.10, 0.31)
		22	267	6.64 (0.95)	-2.33 (1.54)			
		11	540	6.61 (1.03)	-2.57 (1.49)			
rs1532269	*PDZD2*	12	635	6.70 (0.94)	-2.52 (1.47)	6.54×10^{-4}	4.04×10^{-4}	0.21 (0.09, 0.32)
		22	153	6.59 (0.98)	-2.16 (1.54)			
		11	917	6.67 (0.97)	-2.42 (1.50)			
rs9292156	Chr5q11.2	12	367	6.60 (0.99)	-2.62 (1.43)	9.76×10^{-5}	1.97×10^{-5}	-0.31 (-0.45, -0.17)
		22	44	6.66 (1.18)	-3.03 (1.50)			
		11	875	6.64 (0.97)	-2.39 (1.46)			
rs17301249	*EYA4*	12	400	6.64 (1.01)	-2.69 (1.57)	9.93×10^{-5}	5.87×10^{-5}	-0.27 (-0.41, -0.14)
		22	54	6.86 (0.95)	-2.85 (1.25)			
		11	346	6.76 (0.99)	-2.36 (1.46)			
rs7305646	Chr12p12.3	12	665	6.65 (0.98)	-2.49 (1.49)	4.18×10^{-4}	8.41×10^{-5}	-0.22 (-0.33, -0.11)
		22	309	6.55 (0.98)	-2.68 (1.52)			

Conclusion: Using a genome-wide strategy, we have identified and replicated association at 5 genetic loci with response to anti-TNF treatment in RA patients. Adding these loci to known clinical variables improves the predictive model by ~25%, but additional predictors have yet to be identified.

[1]Wellcome Trust Case Control Consortium: Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet. 2007 Nov;39(11):1329-37.

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Gene Function Relationships to Discover Novel Rheumatoid Arthritis Risk Loci. S. Raychaudhuri[1], E.F. Remmers[2], S. Eyre[3], G. Xie[4], L. Alfredsson[5], J. Coblyn[1], Lindsey A. Criswell[6], T.W.J. Huizinga[7], F.A.S. Kurreeman[1], A.T. Lee[8], L. Padyukov[9], M.F. Seldin[10], Paul P. Tak[11], UKRAG Consortium, I.E. van der Horst-Bruinsma[12], Elizabeth W. Karlson[13], R.E.M. Toes[14], N. de Vries[12], A.B. Begovich[15], K.A. Siminovitch[16], J. Worthington[17], L. Klareskog[9], P.K. Gregersen[8], M.J. Daly[18] and R.M. Plenge[1], [1]Brigham & Women's Hospital, Boston, MA, [2]NIH-NIAMS, Bethesda, [3]The University of Manchester, Manchester, United Kingdom, [4]University of Toronto, Toronto, [5]Karolinska Institute, Stockholm, Sweden, [6]University of California San Francisco, San Francisco, CA, [7]Leiden University Medical Center, Leiden, Netherlands, [8]Feinstein Insititute Med Rsch, Manhasset, NY, [9]Karolinska Institutet, Stockholm, Sweden, [10]Davis, [11]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [12]GENRA Consortium, Amsterdam, Netherlands, [13]Brigham and Women's Hospital, Boston, MA, [14]Leiden University Medical Centre, Leiden, Netherlands, [15]Roche Diagnostics, Pleasanton, CA, [16]University of Toronto, [17]arc Epidemiology Unit, Manchester, United Kingdom, [18]Broad Institute, Cambridge, MA

Purpose: Genetic studies in RA have identified 16 loci containing genes involved in key immunologic processes. We hypothesized that undiscovered RA risk loci likely contain genes functionally related to previously validated gene loci, and that a systematic approach to establishing those functional relationships will effectively help identify novel RA loci from genome-wide association studies (GWAS).

Method: To test this hypothesis, we examined 370 SNPs from 179 independent loci with $p<0.001$ in a published meta-analysis of three RA GWAS (Raychaudhuri et al, Nat Genet 2008), most of which likely represent spurious associations. We developed and applied *GRAIL* (Gene Relationships Across Implicated Loci, Raychaudhuri et al PLOS Genet), a computational method that automatically assesses functional relationships between genes by applying statistical text mining to PubMed abstracts. We scored these 179 loci for functional relationships to genes in 16 known RA disease loci. We genotyped representative SNPs from loci with the highest scores in an independent set of 8,096 autoantibody positive RA cases and 11,822 matched controls.

Results: We identified 22 loci with a high degree of functional connectivity as determined by high GRAIL scores. Three of these validate convincingly: *CD2/CD58*, *PRDM1*, and *CD28* (see Table 1). In addition, four loci replicate at $p<0.0023$ (=0.05/22), indicating that these almost certainly represent true RA risk loci: *PTPRC*, *TAGAP*, *TRAF6/RAG1* and *FCGR2A*. Many of these loci are already associated to other immunologic diseases.

Conclusion: We present novel RA risk loci, discovered by utilizing pathway-based approaches; these loci could indicate key immunologic processes in pathogenesis.

Table 1. 7 of 22 SNPs tested replicate in independent samples (p<0.0023).

SNP			Meta-Analysis (3,393 Cases; 12,460 Controls)		Replication (8,096 Cases; 11,822 Controls)				Joint	
ID	Chr	Gene(s)	*p*	OR	*p*	*OR*	Minor Allele Control	Minor Allele Case	*p*	*OR*
rs11586238	*1p13.1*	*CD2, IGSF2, CD58*	2.0E-04	1.14	3.0E-06	1.11	0.228	0.253	2.3E-09	1.12
rs548234	*6q21*	*PRDM1*	3.4E-04	1.12	2.5E-05	1.09	0.322	0.342	4.5E-08	1.10
rs1980422	*2q33.2*	*CD28*	4.2E-05	1.16	4.8E-05	1.10	0.238	0.251	1.8E-08	1.12
rs10919563	*1q31.3*	*PTPRC*	3.8E-04	0.84	1.6E-04	0.90	0.132	0.117	4.0E-07	0.88
rs394581	*6q25.3*	*TAGAP*	5.6E-04	0.89	4.9E-04	0.92	0.286	0.272	1.5E-06	0.91
rs540386	*11p12*	*RAG1, TRAF6*	6.1E-04	0.86	2.1E-03	0.91	0.144	0.130	1.2E-05	0.90
rs12746613	*1q23.3*	*FCGR2A*	9.1E-04	1.16	2.3E-03	1.10	0.124	0.130	1.6E-05	1.12

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Cumulative Association of Twenty-Two Genetic Variants with Seropositive Rheumatoid Arthritis Risk. Elizabeth W. Karlson[1], Lori B. Chibnik[1], Peter Kraft[2], Jing Cui[1], Brendan T. Keenan[1], Bo Ding[3], Soumya Raychaudhuri[1], Lars Klareskog[4], Lars Alfredsson[5] and Robert M. Plenge[1], [1]Brigham and Women's Hospital, Boston, MA, [2]Channing Laboratory, Brigham & Women's Hospital and Harvard Medical School, [3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska University Hospital, Stockholm, [5]Karolinska Institutet, Stockholm, Sweden

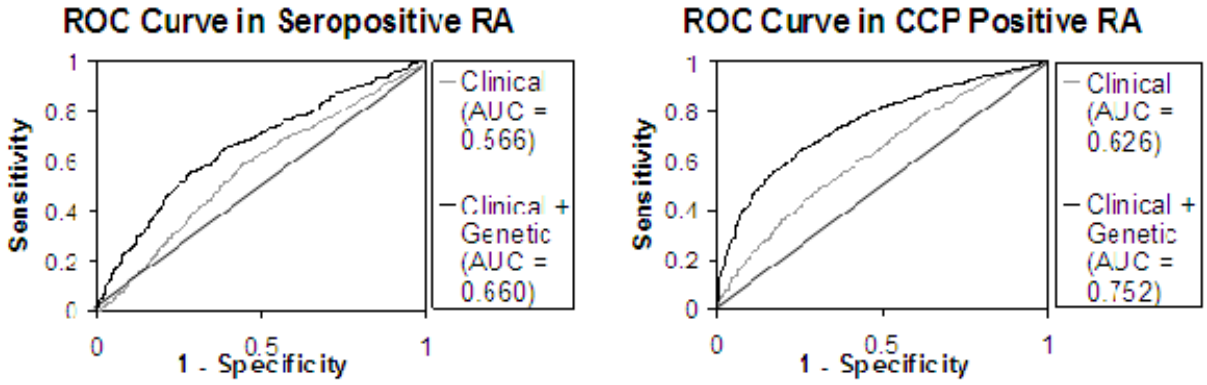
Purpose: Recent discoveries of risk alleles have made it possible to define genetic risk profiles for RA. We examined whether a cumulative score based on 22 validated genetic risk alleles for seropositive RA would identify high-risk individuals who might benefit from preventive interventions.

Methods: We genotyped 14 single nucleotide polymorphisms (SNPs) at 13 validated RA risk loci based on published GWAS, or meta-analysis and 8 HLA alleles among (1) 289 Caucasian seropositive (CCP+ and/or RF+) cases and 481 controls from the U.S. Nurses' Health Studies (NHS), and (2) 630 Caucasian CCP antibody positive cases and 623 controls from the Swedish Epidemiologic Investigation of RA (EIRA). We created a weighted genetic risk score (GRS), where the weight for each risk allele is the log of the published odds ratio (OR). We used logistic regression to study associations between incident RA and GRS grouped in 7 categories based on the GRS distribution among the controls, using the median (group 4) as the referent group. We compared area under the ROC curve (AUC) from a clinical-only model and clinical + genetic model in each cohort. Clinical models included year of birth and pack-years of smoking for NHS and age, pack-years of smoking, sex, and residential area in EIRA. To determine the clinical utility of our GRS in individual patients, we calculated risk-score specific absolute risks within each cohort.

Results: Subjects in group 7 with the highest GRS (> 1.25 standard deviations from the mean) had a significantly higher OR for seropositive RA in both NHS (OR=2.9, 95% CI 1.8-4.6) and EIRA (OR=3.4, 95% CI 2.3-5.0) referent to the population average. After removing HLA alleles from the GRS, subjects in group 7 with the highest GRS had a significantly higher OR for seropositive RA in both NHS (OR=2.5, 95% CI 1.5-4.3) and EIRA (OR=2.8, 95% CI 1.7-4.7) referent to the population average. The AUC for a clinical model was 0.566 and for a clinical + genetic model was 0.660 in NHS (p=0.0001), and 0.626, 0.752 in EIRA (p=0.0001), respectively. In the NHS cohort, the absolute risk of sero+ RA was 0.3%. Having a GRS in group 7 increases the absolute risk to 0.7%. In EIRA, the absolute risk of CCP+ RA was 0.4% for women and 0.2% for men. Having a GRS score in group 7 increases these absolute risks to 1.3% for women and 0.7% for men, respectively.

Conclusion: The combination of 22 risk alleles into a weighted genetic risk score significantly improves prediction for RA risk beyond clinical risk factors alone. However, given the low absolute risk of RA, the clinical utility of a weighted genetic risk score is still to be determined.

Receiver Operator-Characteristic (ROC) Curves for Cumulative Genetic Risk Score Predicting Seropositive RA in NHS and CCP Positive RA in EIRA



AUC comparisons: NHS: p=0.0001; EIRA: p=0.0001

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Association and Linkage Proof for IRF5 as a Rheumatoid Arthritis Susceptibility Gene. Karen Dawidowicz[1], Yannick Allanore[2], Céline Pierlot[3], Vitor-Hugo Teixeira[3], Elisabeth Petit-Teixeira[3], Francois Cornelis[3], P. Dieudé[1] and the ECRAF, [1]Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [2]Paris Descartes Univ, Paris, France, [3]Evry University, Evry-Genopole, France

Background: Type 1 IFNs play a key role in autoimmunity when tolerance is lost and autoreactivity appears. Increased expression of type 1 IFN genes, also referred as an IFN signature, has been detected in various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis (RA), Sjögren's syndrome and in a subgroup of systemic sclerosis patients. Interferon regulatory factors, such as IRF5, coordinate type I IFNs expression. To date, multiple *IRF5* variants were suggested as susceptibility genetic factors of various autoimmune diseases, including RA.

Purpose: As the linkage proof remains important to fully establish *IRF5* as genetic RA susceptibility factor, we aimed at providing it, tacking advantage of the largest reported European family resource dedicated to RA linkage studies.

Method: Overall, 1014 European Caucasian individuals from 338 RA trio families were genotyped for *IRF5* rs3757385, rs2004640 and rs10954213 single nucleotide polymorphisms (SNPs).

Results: Single marker analysis provided linkage evidence for each *IRF5* SNP investigated. *IRF5* linked to RA with two significant haplotypes out of 8. The IRF5 C-T-A susceptible haplotype "S" (T = 62.2%, $P = 2.9 \times 10^{-4}$) and the A-G-G protective haplotype "P" (T = 38.7%, $P = 1.86 \times 10^{-3}$). Linkage was significantly stronger in non-erosive disease for both *IRF5* S and P haplotypes: T = 82.2%, $P = 1.34 \times 10^{-5}$ and T = 19.4%, $P = 2.46 \times 10^{-4}$, respectively. No other significant independent clinical, including ACPA status, nor genetic factor influencing linkage was detected. *IRF5* homozygous haplotypic genotypes SS and PP were strongly associated with RA: P = 0.0026, OR1.88, 95%CI [1.24-2.84], P = 0.006, OR 0.71 95%CI [0.55-0.91], respectively. leading us to purpose a practical approach according to the *IRF5* SS, PP and XX haplotypic genotype individual status (X being non-S and non-P haplotypes).

Conclusion: This study provides the final piece of the "association and linkage proof" for *IRF5* as a RA susceptibility gene and led to the identification of a potential factor which could influence the rheumatoid erosive phenotype. Further studies in inception cohorts are required to clarify the role played by *IRF5* in the rheumatoid arthritis erosive phenotype.

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RA Susceptibility Is Associated with An Epistatic Interaction Between Shared Epitope Alleles and MMEL1-TNFRSF14. Hani S. El-Gabalawy[1], Nina A. Daha[2], David B. Robinson[1], Kiem G. Oen[1], Irene Smolik[1], Donna Hart[1], Annemiek Willemze[2], Wendimagegn Ghidey[2], Jeanine J. Houwing-Duistermaat[2], René E.M. Toes[2], Tom W.J. Huizinga[2] and K.A. Siminovitch[3], [1]University of Manitoba, Winnipeg, MB, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of Toronto, Toronto

Purpose: North American Native (NAN) populations have a high prevalence rates for RA. We have studied a Cree/Ojibway population in Central Canada for disease risk, and our previously published data indicate an early age of onset, high rates of multi-case families, high prevalence and titers of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), and prevalent shared epitope (SE) alleles in the background control population. We therefore asked the question of whether additional genetic factors may interact with SE alleles in predisposing this population to the development of RA

Method: RA patients (n=317), their first degree relatives (FDR, n=295), and unrelated controls (C, n=300) were tested for 21 single nucleotide polymorphisms (SNP) that have been shown to be associated with RA in whole genome scans, including PTPN22, TRAF1-C5, CTLA4, PADI4, STAT4, FCRL3, CCL21, MMEL1-TNFRSF14, CDK6, PRKCQ, KIF5A-PIP4K2C, IL2RB, TNFAIP3, IL10 -1082G/A, REL. HLA-DRB1 alleles were tested by sequencing. Significant SNP associations detected in the NAN population were tested for replication in a Dutch RA population (n= 880) and controls (n= 546)

Results: The prevalence of SE alleles in the NAN population was RA = 85%, FDR = 79%, and C = 66%. The most common SE alleles were *0404 (38%) and *1402 (28%). With the exception of rs3890745 (MMEL1-TNFRSF14), there were no significant associations with any of the RA SNP tested, including the 1858T allele of PTPN22, which was present at a frequency of 9% in all groups. The data indicate that homozygosity for the major allele of MMEL1-TNFRSF14 was significantly higher in RA compared to both the C and FDR groups (OR 1.31, CI 1.05 -1.63, p=0.02). Further analysis indicated that this association was present only in SE+ individuals (OR 1.46 CI 1.15 -1.89, p=0.004),

with no association detectable in SE- individuals. Binary logistic regression indicated that SE and MMEL1-TNFRSF14 were both independently associated with an RA diagnosis. Using a recessive model for the major allele of MMEL1-TNFRSF14 (AA vs AG or GG), there was clear evidence of an interaction between MMEL1-TNFRSF14 and SE (OR 1.84 p<0.0001 in SE+, and OR 0.75, p=NS in SE- individuals). Analysis in the Dutch population using the rs6684865 SNP (MMEL1), which is in complete linkage disequilibrium with rs3890745, demonstrated a similar trend in RA association (OR 1.16 CI 0.89-1.52), but there was no statistical evidence for interaction with SE.

Conclusion: The MMEL1-TNFRSF14 SNP has recently been shown to be associated with RA in a large genome wide analysis of primarily Caucasian populations. Here we demonstrate a novel interaction between SE and MMEL1-TNFRSF14 that is highly associated with RA susceptibility in the NAN population. This epistatic interaction is particularly important since SE alleles are prevalent in this population yet most individuals remain disease free.

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Effect of Glutathione S-Transferase T1, M1, P1 and Heme Oxygenase-1 Gene Promoter Polymorphisms Interactions with Heavy Smoking On the Risk of Rheumatoid Arthritis. Brendan T. Keenan, Lori B. Chibnik, Jing Cui and Elizabeth W. Karlson, Brigham and Women's Hospital, Boston, MA

Purpose: Glutathione S-transferase (GST) and heme oxygenase-1 (HMOX1) genes encode enzymes that detoxify carcinogens and protect against oxidative stress. Variations in these genes may be associated with increased susceptibility to carcinogens in tobacco smoke. We studied the effect of interactions between these genetic variations and smoking (a risk factor for RA) on the risk of RA using a nested case-control sample from 2 large prospective female cohorts.

Method: Blood was obtained from 32,826 women in the Nurses' Health Study (NHS) and 29,611 women in the Nurses' Health Study 2. Buccal cell samples were provided by 33,040 additional women in NHS. Cases and controls with available DNA were selected. Incident RA was confirmed by record review for ACR criteria. Controls were matched on age, menopausal status, and postmenopausal hormone use. Genotyping by Taqman was performed for GSTM1, GSTT1 homozygous deletions (null) and GSTP1 (rs1695), HMOX1 (rs2071746) alleles. Heavy smoking was defined as >10 pack-years (packs per day X years smoked). We studied gene-environment (GxE) interactions between genetic variations of GST genes or HMOX1 and heavy smoking for the risk of all RA and seropositive (sero+) RA (CCP+ and/or RF+) in separate logistic models adjusted for matching factors. We calculated multiplicative interactions by including a GxE product term in the logistic model and additive interactions using the attributable proportion due to interaction (AP).

Results: 549 matched Caucasian pairs were included. Mean age at diagnosis was 56.9 ± 10.3 years and 325 (59%) were sero+ cases. For all RA risk, we observed a significant multiplicative interaction (p=0.03) between HMOX1 and heavy smoking; we observed significant multiplicative (p=0.05) and strong additive (AP=0.51, p=0.0008) interactions between GSTT1-null and heavy smoking. For sero+ RA risk, we found a significant additive interaction (AP=0.41, p=0.03) but not multiplicative interaction between HMOX1 and heavy smoking; we observed significant multiplicative (p=0.01) and strong additive (AP=0.63, p<0.0001) interactions between GSTT1-null and heavy smoking. GSTM1-null and GSTP1 did not show significant interactions with heavy smoking for all RA or sero+ RA risk.

Conclusion: We observed significant gene-environment interactions between HMOX1 and heavy smoking and strong interactions between GSTT1-null and heavy smoking for the risk of all RA and seropositive RA. Future studies are needed to assess the impact of these interactions on RA prediction.

Gene	**OR (95% CI)**				**AP (95% CI)**	**p-add[1]**	**p-mult[2]**
	G- E-	**G- E+**	**G+ E-**	**G+ E+**			
All RA (N = 549 Cases, 549 Controls)							
HMOX1	1.00 (ref)	1.4 (0.9-2.1)	0.9 (0.7-1.2)	1.9 (1.3-2.7)	0.32 (-0.01-0.65)	0.06	0.03
GSTT1-null	1.00 (ref)	1.4 (1.1-1.8)	0.8 (0.5-1.2)	2.4 (1.5-4.0)	0.51 (0.21-0.81)	0.0008	0.05

Sero+ RA (N = 325 Cases, 549 Controls)							
HMOX1	1.00 (ref)	1.3 (0.8-2.1)	0.8 (0.6-1.2)	1.8 (1.2-2.7)	0.41 (0.04-0.78)	0.03	0.06
GSTT1-null	1.00 (ref)	1.4 (1.0-1.9)	0.7 (0.4-1.2)	2.7 (1.6-4.6)	0.63 (0.36-0.89)	<0.0001	0.01

[1]p-value for additive interaction; [2]p-value for multiplicative interaction

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ACR Concurrent Abstract Sessions

Human Etiology and Pathogenesis

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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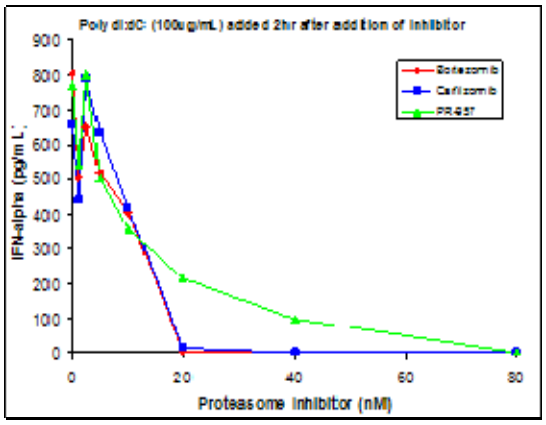
Proteasome Inhibitors Block Production of Alpha Interferon and B Cell Activation. R. J. Looney, Thomas Conley, James Kobie and Jennifer H. Anolik, University of Rochester, Rochester, NY

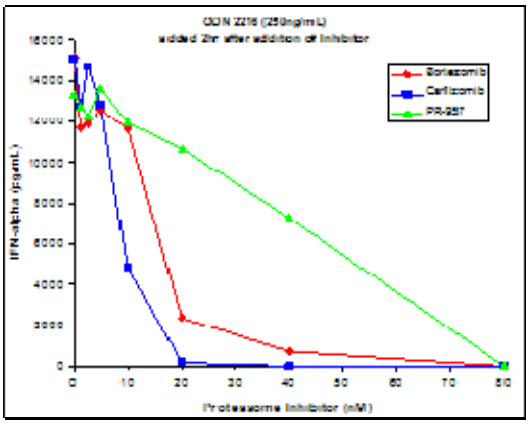
Purpose: Proteasome inhibitors have been proposed as a new therapy for SLE because of their effects on plasma cells. Animal studies have shown that bortezomib, a dipeptide boronate that targets the constitutive and immunoproteasome, induces apoptosis of short-lived and long-lived plasma cells via induction of the unfolded protein response, and is also able to decrease autoantibody production and prolong survival. Since proteasome inhibitors block activation of NFkappaB by preventing degradation of IkappaB, they should also have effects on cellular activation such as alpha interferon production after stimulation of toll-like receptors. Bortezomib is approved for the treatment of multiple myeloma but its use in non-malignant conditions may be limited due to unacceptable toxicities such as painful peripheral neuropathy. Because of this problem, new proteasome inhibitors are being developed. Carfilzomib is a peptide epoxyketone proteasome inhibitor that has greater selectivity for the proteasome than bortezomib and is currently in phase 2 clinical studies in myeloma. PR-957 is a novel, immunoproteasome selective inhibitor of the same chemical class as carfilzomib.

Methods: The effects of carfilzomib and PR-957, were compared to bortezomib in PBMCs and B-cells. Alpha interferon was assayed by ELISA, immunoglobulin production by ELISPOTS, and proliferation by CFSE/flow cytometry.

Results: Induction of alpha interferon production by PBMCs treated with polyIC or with ODN2216 activating respectively TLR-3 or TLR-9 was dramatically inhibited by all three proteasome inhibitors. (See below.) The effects of these proteasome inhibitors on B cell activation by IL-2 and CpG were also examined. B cell proliferation and IgM or IgG antibody secreting cells were inhibited by all three proteasome inhibitors. (Data not shown.).

Conclusion: These results demonstrate for the first time that proteasome inhibitors are able to block production of alpha interferon induced by stimulation of toll-like receptors, and also show that proteasome inhibitors can block B cell proliferation and differentiation. Furthermore, activity with PR-957 suggests that the effects of carfilzomib and bortezomib are mediated through immunoproteasome inhibition. Thus, the potential beneficial effects of proteasome inhibitors in SLE may work through multiple mechanisms.





Disclosure: R. J. Looney, Proteolix, 2 ; **T. Conley**, None; **J. Kobie**, None; **J. H. Anolik**, Proteolix, 2 .

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Vitamin D Deficiency Is Associated with B Cell Hyperreactivity in Systemic Lupus Erythematosus. Lauren R. Cole[1], Susan Macwana[2], Rufei Lu[2], Wendy Klein[2], Virginia Roberts[2], Amy Dedeke[1], Sherry R. Crowe[2], Gillian M. Air[1], Linda F. Thompson[3], Joel M. Guthridge[2] and Judith A. James[3], [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]OMRF & OUHSC, Oklahoma City, OK

Purpose: Autoimmune diseases have complex etiologies, likely including variable interactions between genetic predispositions and environmental risks. Vitamin D (Vit D) deficiency has recently been linked with many autoimmune disorders, including systemic lupus erythematosus (SLE). Vit D inhibits antibody secretion and autoantibody production in B cells of animal models; however, the influence of Vit D deficiency on autoantibody production and antigen specific immune responses in SLE patients is unknown. Our study tests whether Vit D deficiency is associated with SLE B cell hyperreactivity or improved antigen-specific antibody responses.

Method: This study enrolled 92 SLE patients who met ACR criteria and matched controls. 25-hydroxyvitamin D (25D) levels, lupus-associated autoantibodies (Ro, La, Sm, nRNP, ribosomal P, dsDNA, ANAs and phospholipid antibodies) and influenza humoral immune response parameters including Bmax (relative amounts of anti-influenza antibodies against native or denatured antigen, measured separately), Ka (relative affinity), and hemagglutination inhibition (relative protective antibody response) were measured. Isolated PBMCs were used for multiparameter PhosFlow analysis of downstream B cell activation markers such as phospho-LYN (pY_{397} and pY_{508}) and phospho-ERK1/2 (pERK1/2).

Results: SLE patients and autoantibody-positive controls were significantly more likely to be Vit D deficient than autoantibody-negative controls, 75% vs 65% vs 25%, respectively (p=0.0003 and p=0.0124). Additionally, anti-Ro positive SLE patients had significantly lower 25D levels than anti-Ro negative SLE patients (p=0.0311). In SLE patients, we saw a significant negative correlation between 25D levels and their humoral immune response to influenza vaccination (p=0.004, r^2=0.189). Furthermore, decreased vitamin D levels in SLE patients were correlated with hyperreactive B cells as measured by pY_{508}LYN and pERK1/2. This correlation with 25D was seen in anti-IgM F(ab)'2 and PMA stimulated B cells ([PMA: pY_{508}LYN p=0.002, pERK1/2 p=0.014] [anti-IgM F(ab)'2: pY_{508}LYN, p=0.018]), as well as in unstimulated B cells (pY_{508}LYN p=0.019, pERK1/2 p=0.029).

Conclusion: Our evidence suggests a role for Vit D deficiency in human B cell hyperreactivity and autoantibody production. We saw an increase in Vit D deficiency in autoantibody-positive controls that is similar to what is seen in SLE patients. Supporting the idea that Vit D deficiency leads to increased B cell activity, we saw a negative correlation between Vit D levels and the ability to mount a humoral immune response to the flu vaccine. The increase in B cell activity was corroborated by flowcytometric data indicating increased phosphorylation of LYN and ERK1/2 in Vit D deficient patients.

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Gadd45a Overexpression Contributes to Autoimmunity by Demethylating DNA in Lupus T Cells. Yaping Li[1], Ming Zhao[1], Yongqi Luo[1], Sha Zhao[1], Xiujuan Zhang[1], Heng Yin[1], Hai Long[1], Yuwen Su[1], Bruce C. Richardson[2] and Qianjin Lu[1], [1]The Second Xiangya Hospital, Central South University, Changsha, China, [2]University of Michigan, Ann Arbor, MI

Purpose: Demethylation of CD11a (ITGAL) and CD70 (TNFSF7) regulatory regions in $CD4^+$ T cells contributes to the development of autoreactivity and the overstimulation of autoantibodies. Gadd45a reduces epigenetic silencing of genes by removing methylation marks. Ultraviolet (UV) irradiation upregulates Gadd45a expression and also aggravates systemic lupus erythematosus (SLE). In this study, we explored whether Gadd45a may contribute to the development of autoimmunity by promoting DNA demethylation in $CD4^+$ T cells from SLE patients.

Methods: $CD4^+$ T cells from 17 SLE patients and 10 healthy controls were isolated using Miltenyi beads. Expression of Gadd45a mRNA and protein were detected by real-time RT-PCR and Western blotting. Global methylation was evaluated by Methylamp™ global DNA methylation quantification kits. Gadd45a-expressing plasmids and Gadd45a siRNA constructs were transfected into $CD4^+$ T cells by transient electroporation. CD11a and CD70 expression were detected by real-time RT-PCR and flow cytometry. $CD4^+$T cell proliferation and autologous B cell IgG antibody detection were performed using commercially available kits. Methylation of CpG pairs in CD11a promoter regulatory elements was detected by sodium bisulfite sequencing.

Results: Compared to controls, $CD4^+$ T cells from SLE patients exhibited elevated levels of Gadd45a mRNA (p=0.006) and protein (p=0.026), and reduced global DNA methylation (p=0.024). Gadd45a mRNA expression correlated negatively with global methylation levels (R=-0.676, p=0.002), and positively with disease activity in our SLE patient cohort (R= 0.568, p=0.015). Gadd45a expression in $CD4^+$T cells was significantly upregulated 6, 24 hours and 48 hours after UVB irradiation, with concomitant increases in CD11a and CD70 mRNA expression at each time point. Global methylation was significantly decreased 48 hours after irradiation. Transfecting $CD4^+$ T cells with Gadd45a led to significant increases in CD11a and CD70 expression, as well as autoreactivity and B cell stimulation. Furthermore, methylation of CpG pairs in the CD11a promoter region was reduced in Gadd45a-transfected cells. In contrast, siRNA-mediated knockdown of Gadd45a in SLE $CD4^+$ T cells significantly reduced autoreactivity and B cell stimulation, and increased CD11a promoter methylation.

Conclusion: Our findings indicate that Gadd45a expression is increased in $CD4^+$ T cells of SLE patients, promoting DNA demethylation and thereby leading to autoimmune responses.

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Type I Interferon Gene Signatures Are Associated with Vascular Risk and Atherosclerosis in Systemic Lupus Erythematosus. Wenpu Zhao, Emily C. Somers, W. Joseph McCune and Mariana J. Kaplan, University of Michigan, Ann Arbor, MI

Purpose: Patients with SLE have a striking increase in cardiovascular (CV) risk due to accelerated atherosclerosis, which can not be fully explained by traditional risk factors. We and others have proposed that type I Interferons (IFN) induce premature vascular damage in lupus at least in part by promoting an imbalance between vascular damage and repair. We have now assessed if the induction of type I IFN signatures by SLE serum is associated with functional and anatomical evidence of vascular damage, atherosclerosis and with biomarkers of CV risk in a well characterized Lupus Cohort.

Method: Serum samples from 75 SLE and 20 control females without previous CV events were analyzed to assess their capacity to induce type I IFN signatures on an epithelial cell line using a validated bioassay. IFN scores were calculated. The quantified IFN-inducible genes were *MX-1, PRKR, IFI44L* and *IFIT1*. Flow mediated- and nitroglycerin mediated- dilatation of the brachial artery (FMD and NMD) were quantified by ultrasound to measure endothelial dependent and independent function, respectively. Carotid intima media thickness (CIMT) and plaque were determined by ultrasound and coronary calcification was measured with electron beam CT. Circulating apoptotic

endothelial cells (CAECs) and endothelial progenitor cells (EPCs) were quantified by FACS and serum ICAM-1, VCAM-1, tissue factor (TF), PAI-1, TPA, MCP-1, VEGF and CRP were quantified by ELISA.

Results: IFN scores were higher in SLE patients than in controls and correlated with SLEDAI ($p=0.04$). In SLE, IFN scores significantly correlated with CIMT and with carotid plaque ($p=0.0009$ and $p=0.033$, respectively). In addition, levels of ICAM-1, tissue factor, MCP-1 and CAECs correlated with IFN scores and individual type I IFN scores ($p<0.05$). In multivariable analysis accounting for SLEDAI, Framingham score and CAECs, type I IFNs showed significant association with CIMT and carotid plaque. In addition, levels of CAECs at baseline predicted progression of coronary artery calcification ($r=0.33$, $p<0.05$).

Conclusion: Type I IFNs are associated with atherosclerosis development in a cohort of SLE patients with low Framingham risk factors. This study further supports the hypothesis that type I IFNs promote premature vascular damage in SLE.

Disclosure: W. Zhao, None; **E. C. Somers**, None; **W. J. McCune**, Genentech and Biogen IDEC Inc., 5, Johnson and Johnson , 5, Human Genome Sciences, 2 ; **M. J. Kaplan**, Takeda, 2 .

583

Antiribosomal P Protein Antibody Induces Th1 Responses by Enhancing the Production of IL-12 in Activated Monocytes. Tatsuo Nagai[1], Tamiko Yanagida[2] and Shunsei Hirohata[1], [1]Kitasato University School of Medicine, Kanagawa, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan

Purpose: Autoantibodies to ribosomal P proteins (anti-P) are detected in 12-16% of patients with SLE, and have been found to be associated with a variety of manifestations of the disease, including lupus psychosis, nephritis and hepatitis. We have recently disclosed that anti-P react with activated human peripheral blood monocytes, and enhance their production of TNFα and IL-6. It is also possible that anti-P might regulate other monocyte functions, including regulation of helper T cell (Th) responses. It has been recently shown that serum levels of IL-12 and IFNγ are higher in patients with lupus nephritis (LN) and peripheral cells from LN patients show a Th1 phenotype. The current study was therefore undertaken to explore the effects of anti-P on the induction of Th1 responses.

Method: IgG anti-P were affinity-purified from sera of anti-P positive lupus patients. Peripheral blood mononuclear cells (PBMCs) from healthy donors were cultured with anti-P or control IgG in round-bottomed polystyrene tubes for 120 hours. Highly purified peripheral blood monocytes were cultured in a 96-well microtiter plate with IFNγ in the presence of anti-P or control IgG for 120 hours. The concentrations of IFNγ and IL-12 in the culture supernatants were measured using ELISA.

Results: Anti-P significantly enhanced the production of IFNγ by PBMCs, compared with normal IgG or IgG from SLE patients devoid of anti-P. Of note, the up-regulation of IFNγ production by anti-P was abrogated by anti-IL-12 monoclonal antibodies. Accordingly, anti-P significantly enhanced the production of IL-12 by peripheral blood monocytes activated with IFNγ.

Conclusion: These results indicate that anti-P induce Th1 responses by up-regulating the production of IL-12 by activated monocytes. The data therefore suggest that anti-P play an important role in the pathogenesis of SLE through promotion of Th1 responses.

Disclosure: T. Nagai, None; **T. Yanagida**, None; **S. Hirohata**, None.

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IgG Anti-NR2 Glutamate Receptor Antibodies From Patients with SLE as Causative Auto-Antibodies of Damage to the Blood-Brain Barrier. Taku Yoshio[1], Shoji Yamazaki[2], Hiroshi Okamoto[3], Sachiko Onishi[1], Shunsei Hirohata[4] and Seiji Minota[1], [1]Jichi Medical University, Shimotsuke, Japan, [2]Jichi Medical University Hospital, Shimotsuke, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Kitasato University School of Medicine, Sagamihara, Japan

Purpose: To determine whether IgG anti-NR2 glutamate receptor antibodies derived from patients with systemic lupus erythematosus (SLE) bind to endothelial cells (EC) causing up-regulation of adhesion molecule expression on and cytokine production.

Methods: EC were established from human umbilical veins. Purified IgG anti-NR2 glutamate receptor antibodies from 14 patients with SLE were tested for to the following: 1) binding to EC, 2) modulation of endothelial adhesion molecule expression, 3) cytokine production from

EC and 4) stimulation of nuclear translocation of NF-kappaB through the degradation of cytoplasmic IkappaB. Purified IgG from 5 healthy individuals were used as negative controls.

Results: Purified IgG anti-NR2 glutamate receptor antibodies bound to EC, and up-regulated the expression of endothelial leukocyte adhesion molecules-1, vascular cell adhesion molecules-1, and intercellular adhesion molecules-1 on EC surface. In addition, these antibodies also increased IL-6 and IL-8 production from EC when compared to IgG from normal controls. However, the anti-NR2 glutamate receptor antibodies failed to induce tumor necrosis factor-alpha or IL-1beta secretion from EC. These auto-antibodies stimulated nuclear translocation of NF-kappaB through the degradation of cytoplasmic IkappaB.

Conclusion: These results suggest that circulating anti-NR2 glutamate receptor antibodies may lead to vascular inflammation and damage to the blood-brain barrier (BBB) thereby resulting in the penetration of these antibodies through BBB and resulting in neuronal damage. This neuronal damage might cause the cognitive disturbance and memory loss, commonly observed in patients with SLE.

Disclosure: T. Yoshio, None; **S. Yamazaki**, None; **H. Okamoto**, None; **S. Onishi**, None; **S. Hirohata**, None; **S. Minota**, None.

ACR Concurrent Abstract Sessions

Inflammatory Myopathies: Bench Discoveries, Clinical Insights and Novel Therapies

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Expanded Proinflammatory T Cells in Inclusion Body Myositis. Jayesh Pandya, Andreas Fasth, Snjolaug Arnardottir, Eva Lindroos, Vivianne Malmström and Ingrid E. Lundberg, Karolinska Institute, Stockholm, Sweden

Purpose: Inclusion body Myositis (IBM) is a chronic, inflammatory myopathy of unknown cause, which is characterized clinically by muscle weakness and muscle atrophy, particularly of the quadriceps and finger flexor muscles, and by being resistant to conventional immunosuppressive drugs. Muscle tissue of IBM patients is characterized histopathologically by leukocyte infiltrates, preferentially T cells and macrophages. We have previously demonstrated the accumulation of a specific phenotype of T cells, so called $CD28^{null}$ T cells in muscles of patients with dermatomyositis and polymyositis. The $CD28^{null}$ T cells are apoptosis resistant, pro-inflammatory and cytolytic cells that hypothetically also may have a role in disease mechanisms of IBM. The aim of present study is to investigate the frequency and effector functions of $CD28^{null}$ T cells in IBM and whether this subset of T cells is clonally expanded. Functional characterization of proinflammatory T cells will provide important clues for designing new T cell-targeted therapeutics for inflammatory myopathies.

Patients and Methods: A cohort of 20 patients with IBM were analyzed for the frequency of circulating $CD4^{+}CD28^{null}$ and $CD8^{+}CD28^{null}$ T cells in peripheral blood and muscle biopsies were taken at different time points during disease course. The TCR-Vβ usage was determined by the flow cytometry based IOTest1 B Mark kit (n=6). For functional analysis, peripheral blood mononuclear cells (PBMC) were polyclonally stimulated with plate bound anti-CD3 for 6 and 72 hrs (n=5) and the frequencies of intracellular IFNγ and CD107a (a marker of degranulation and cytotoxicity) containing T cells were recorded by multicolour flow cytometry.

Results: $CD28^{null}$ T cell populations were clearly expanded in peripheral blood of IBM patients and both the $CD4^{+}$ $CD28^{null}$ and $CD8^{+}$ $CD28^{null}$ T cell populations were highly TCR Vβ restricted compared to the $CD28^{+}$ subsets from the same patient. Different patients displayed different TCR Vβ restrictions, and the expansions were consistent over time. Anti-CD3 stimulation of PBMC resulted in a fast and high frequency of $CD28^{null}$ T cells of both the $CD4^{+}$ and $CD8^{+}$ subsets significantly more positive for IFNγ and CD107a compared to $CD28^{+}$ subsets. Both the TCR Vβ dominant and non dominant $CD28^{null}$ subsets were equally activated under these conditions.

Conclusion: The TCR Vβ restriction of $CD28^{null}$ T cells in IBM patients suggest that a limited numbers of antigens are involved in driving the expansion and high TCR Vβ restriction of $CD28^{null}$ T cells in IBM patients. Functional evaluation experiments revealed that $CD28^{null}$ T cells in both the $CD4^{+}$ and $CD8^{+}$ compartment are devoted proinflammatory and cytotoxic effector cells. Interestingly, the TCR Vβ dominant and non-dominant $CD28^{null}$ T cell subsets displayed equal quality and quantity of effector function. Further analysis is ongoing to evaluate antigen specificity of these $CD28^{null}$ T cells and their presence in skeletal muscle infiltrate of IBM patients.

Disclosure: J. Pandya, None; **A. Fasth**, None; **S. Arnardottir**, None; **E. Lindroos**, None; **V. Malmström**, None; **I. E. Lundberg**, None.

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Evidence for the Implication of Th-1 and Treg Cells but Not Th-17 in Inclusion Body Myositis. Yves Allenbach Jr.[1], Julia Wanschitz Sr.[2], Michelle Rosenzwajg Sr.[1], Coralie Bloch-Queyrat Sr.[3], Serge Herson[4], David Klatzmann Sr.[1] and Olivier Benveniste[4], [1]UMR 7211, CNRS,Université Pierre et Marie Curie, University of Paris 06, Paris, France, [2]UMR 974, CNRS, Université Pierre et Marie Curie, University of Paris 06, Paris, France, [3]Hôpital Pitié-Salpêtrière, [4]Hôpital Pitié-Salpêtrière, Paris, France

Purpose: Inclusion Body Myositis (IBM) is the most common acquired myopathy in patients above the age of 50 years. This disabling disease is an inflammatory myopathy characterized by CD8+ cytotoxic infiltrates and amyloid deposits. IBM remains resistant to conventional treatment. To date, only severe T cell depletion by Anti-thymocyte Globulin or Alemtuzumab can slow down the course of the disease underlining the role of adaptative immune system. Regulatory T cells (Treg) are key regulators of this system. We described Treg in 22 IBM patients, but also Th1/Th2/Th17 and inflammatorys responses, in attempt to develop new therapeutic approaches.

Method: We included 22 IBM patients (mean age; 70.1) and 22 sex and age matched controls. All were not treated with immunosuppressive drugs, nor presented active infection or other autoimmune diseases. Peripheral blood mononuclear cells (PBMC) were analyzed using flow cytometry. PBMC were tested in vitro for their ability to produce IFNg and IL-17 upon stimulation with PMA and Ionomycin. Using a multiplex assay, the concentrations of 25 cytokines and chemokines was determined in the supernatant of stimulated PBMC and in the sera. Muscle biopsies of 7 among the 22 IBM patients were tested by immunohistochemistry for presence of CD4+, CD8+ T cells and Treg.

Results: In blood, mean percentage of activated CD4+ T cells (CD3+CD4+DR+) was higher in IBM patients than in controls (16.2±13.7% vs 8.7±4.2%; p=0.04). Moreover, terminally differentiated CD8+CD28- T cells was increased in IBM patients compare to controls (61±23.9% vs 44±20%, p=0.023). The mean percentage of CD3+CD4+IFNg+, CD3+CD8+IFNg+ and CD3+CD4+IL-17+ was not statically different in both groups. The supernatant concentration of IFNg and IL-17 was not statically different in the two groups. Whereas, we observed an increase of IL-12 concentration in the sera of IBM patients (301.36±142.08 pg/ml vs 154.25±-28.41 pg/ml p=0.0002) and of the chemokine IP-10 (377.73±296.72 pg/ml vs 61.147±44.64 pg/ml; p<0.0001).

The percentage of Treg (CD3+CD4+CD25+CD127-FOX3+) among CD4+ T cells was lower in IBM group compare to controls (5.5 ± 0.3% vs 6.6 ± 0.4% p= 0.043). Treg cells (FOXP3+) were detected in 6/7 muscle biopsies at a low frequency among CD4+ T cell infiltrates.

Conclusion: Together these results suggest that CD4+ and CD8+ T cells are more activated and engaged in a Th1 lineage (and not a Th17 one). Effector Th1 and activated CD8 cells may home the muscle attracted by IP-10. Treg cells are decreased in blood whereas they are present in the muscle, where they seem unable to control effector cells.

Disclosure: Y. Allenbach, None; **J. Wanschitz**, None; **M. Rosenzwajg**, None; **C. Bloch-Queyrat**, None; **S. Herson**, None; **D. Klatzmann**, None; **O. Benveniste**, None.

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Relationship Between Disease Activity and Type 1 Interferon- and Other Cytokine-Inducible Gene Expression in Blood in Dermatomyositis and Polymyositis. Steven A. Greenberg[1], Brandon W. Higgs[2], Christopher Morehouse[2], Philip Brohawn[2], Wei Zhu[2], Ronan J. Walsh[1], Sek Won Kong[1], Jiaqi Huang[2], Anthony Amato[3], Barbara White[2], Peter A. Kiener[2], Bahija Jallal[2] and Yihong Yao[2], [1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]MedImmune, Gaithersburg, MD, [3]Harvard University

Purpose: A longitudinal study evaluated a group of cytokines including type 1 interferon (IFN) that are potentially involved in the pathogenesis of dermatomyositis (DM) and polymyositis (PM) pathogenesis before and during treatment. Peripheral blood of 42 patients with DM or PM was subjected to gene expression profiling using Affymetrix human genome U133 plus 2.0 GeneChips® in an initial study to identify the prevalence of patients exhibiting periphery overexpression of type 1 IFN-inducible genes. To gain further scientific insight on type 1 IFN as a potential therapeutic target for DM and PM, 24 patients with DM or PM were then prospectively enrolled and followed for up to 6 years (mean of 1.9 years) while receiving standard clinical care.

Methods: Clinical courses including MITAX scoring of disease activity were assessed across 150 patient visits. Peripheral blood samples collected at 80 patient visits were used for microarray analysis of , GM-CSF,β, IL-1αcytokine-induced gene expression for type 1 IFN, TNF-IL-10, and IL-13 signaling pathways.

Results: 35 of 42 (87%) DM and PM patients had moderate/strong overexpression of type 1 IFN-inducible genes in the periphery blood. In the longitudinal study during the course of treatment, 21 of 24 patients showed overexpression of a type 1 IFN-inducible gene signature in peripheral blood. Overexpression of type 1 IFN-inducible genes IFI27, IFI44, IFI44L, and RSAD2 and a type 1 IFN-inducible 13-gene composite signature correlated highly with disease activity during treatment. For 3 patients, type 1 IFN-inducible gene overexpression during treatment preceded disease , GM-CSF, IL-10, andβ, IL-1αrelapse within approximately 1 month. TNF- IL-13 inducible gene signatures were also overexpressed in DM and PM patients but were not correlated with disease activity.

Conclusion: Targeting type 1 IFN is likely to provide clinical benefit in DM and PM patient populations with overexpression of type 1 IFN-inducible genes in the periphery. Type 1 IFN-inducible gene overexpression in the periphery blood merits further study for use as a pharmacodynamic and predictive biomarker for developing anti-type 1 IFN therapy for these patients.

Disclosure: S. A. Greenberg, MedImmune Inc., 9 ; **B. W. Higgs**, Astra Zeneca, 3 ; **C. Morehouse**, Astra Zeneca, 3 ; **P. Brohawn**, Medimmune, 3 ; **W. Zhu**, Astra Zeneca, 3 ; **R. J. Walsh**, None; **S. W. Kong**, None; **J. Huang**, Astra Zeneca, 3 ; **A. Amato**, None; **B. White**, Astra Zeneca, 3 ; **P. A. Kiener**, Astra Zeneca, 3 ; **B. Jallal**, MedImmune, 3 ; **Y. Yao**, None.

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Discordance Between Cardiac Troponin T Elevation in Patients with Inflammatory Myopathies Vs. Other Muscle Disease. John P. Case[1], Augustine M. Manadan[2] and Rohit Aggarwal[3], [1]Stroger Hospital of Cook County, Chicago, IL, [2]Rush Univ Med Ctr, Chicago, IL, [3]John H. Stroger, Jr. Hospital of Cook County and Rush University Medical Center, Chicago, IL

Purpose: Patients commonly present with malaise and fatigue associated with elevated creatine kinase (CK), or a CK is determined early in the course of evaluation for musculoskeletal disease. Some are ultimately diagnosed with inflammatory myopathies (IM). In many however, the CK elevation is unrelated to IM but rather to non-IM causes (non-IM). We have previously determined (ACR 2007 and J. Rheum, in press) that cardiac troponin T (cTnT), but not cardiac troponin I (cTnI) is frequently elevated in patients with IM and that cTnT and CK are correlated. We undertook the present study to determine whether cardiac troponins are elevated in non-IM and their relationship to CK.

Methods: We performed a retrospective study using a computerized database to identify patients who were evaluated for non-IM CK elevation, myopathy, or rhabdomyolysis between January 2004 and December 2008 by the Rheumatology service of Cook County Hospital. We compared these patients to those with IM described earlier. In each group, we excluded patients who had chronic kidney disease (CKD) or acute coronary syndrome (ACS). Statistical comparisons were done with Pearson's chi-square test.

Results: The records of 56 patients with a non-IM diagnosis were retrieved. The CK was assayed in 54 (96%) and was elevated in 47 (89%). The etiology of the CK elevation was statin myopathy (16); neuromyopathy (6), metabolic myopathy (2), HIV (2), and viral syndrome (2). Non-statin medication toxicity, muscular dystrophy, alcohol, cardiomyopathy, and hyperthyroidism accounted for one case each. In one case the cause was multifactorial. In 13 cases the diagnosis was not determined. In the 9 patients with normal CKs (17%), the final diagnoses were steroid myopathy (3); and in one case each, alcohol, statin myopathy, cardiomyopathy, and myopathy from a non-statin medication. In two cases (4%) the CK was not assayed. One had cardiomyopathy, another had steroid myopathy. In the 47 patients who had elevated CK and had cTnT or cTnI assayed, cTnT was elevated in 3 of 19 (16%) and cTnI in 0 of 18 (0%). Inclusion body myositis was suspected in two of the patients with elevated cTnT, but biopsy was not done and formal diagnosis not made. In the third patient, elevated cTnT was attributed to the combination of cyclosporine and ezetimibe. cTnT was assayed in four patients with rhabdomyolysis. It was elevated in only one patient (cyclosporine/ezetimibe combination). Overall, cTnT elevation was not associated with CK elevation ($p=0.445$). By comparison (and as previously reported), in patients with IM who had elevated CK the cTnT was elevated in 18 of 23 (78%) and was highly associated with the CK ($p=0.005$). The percent frequency of cTnT positivity in IM patients with elevated CK is significantly higher, almost 5 fold, than in patients with non-IM ($p<0.001$).

Conclusion: An elevated cTnT is not associated with non-IM CK elevation. In evaluating a patient with possible IM in the non-ACS, non-CKD setting, obtaining the cTnT level may help in the diagnosis, since it is usually elevated in IM but rarely elevated in non-IM. The reason is unclear.The cTnI is not elevated in IM or in non-IM.

Disclosure: J. P. Case, None; **A. M. Manadan**, None; **R. Aggarwal**, None.

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Anakinra in Patients with Refractory Idiopathic Inflammatory Myopathies. Christina Dorph[1], Maryam Dastmalchi[1], Helene Alexanderson[2], Christina Ottosson[3], Eva Lindroos[3], Inger Nennesmo[4] and Ingrid E. Lundberg[1], [1]Rheumatology Unit, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine and Department of Physical Therapy, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Division of Pathology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

Purpose: Earlier studies have shown an increased interleukin-1 (IL-1) expression in muscle tissue from patients with polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). The objective of this study was to investigate the efficacy and tolerability of treatment with the IL-1 blocking agent, anakinra, in patients with treatment-resistant inflammatory myopathies.

Method: 15 patients with refractory PM (6), DM (4) or IBM (5) were included in a 12-month open-label study and treated with 100 mg anakinra subcutaneously per day. All patients had stable concomitant immunosuppressive treatment such as prednisolone and methotrexate or azathioprine. Outcome measures included myositis disease activity score with improvement defined according to The International Myositis Assessment and Clinical Studies Group (IMACS) and for muscle performance, the functional index of myositis (FI) at 3, 6 and 12 months. Repeated muscle biopsies (months 0 and 6) were investigated for cellular infiltrates, major histocompatibility complex (MHC) class I, IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra).

Results: 8 women and 7 men who had definitive diagnosis of PM, DM or IBM with disease duration of 2-18 years were included. 9 patients completed the 12 month study. 11 patients completed 6 months, and 13 patients concluded 3 months. 7 patients fulfilled improvement criteria for disease activity (responders) according to IMACS definition (3 DM, 3 PM, 1 IBM). 5 had improved by 3 months (1 sustained until 6 months), 1 by 6 months (sustained until 12 months) and 1 by 12 months. Five were unchanged and three worsened (non-responders). FI improved ≥20 % in 4 of the 7 responders (1 DM, 2 PM, 1 IBM). Two patients withdrew due to a local skin rash at the injection site. Other reasons for premature ending of the study were increased muscle symptoms in 2, headache in 1 and lack of efficacy in 1. Repeated biopsies were available in 14 patients. There were no statistically significant changes in mononuclear inflammatory cells, T cells, IL-1α, IL-1β and MHC class I between pre-treatment and post-treatment biopsies. All responders had IL-1Ra expression in the post-treatment biopsy but only 3 of 8 non-responders.

Conclusion: Treatment with anakinra had beneficial effects on clinical outcome measures including disease activity and muscle performance in some patients in this pilot study of previously treatment-resistant myositis. The clinical positive effects together with the observation of IL-1Ra expression in muscle tissue in more post-treatment biopsies of responders than non-responders need to be confirmed in a larger placebo-controlled trial.

Disclosure: C. Dorph, None; **M. Dastmalchi**, None; **H. Alexanderson**, None; **C. Ottosson**, None; **E. Lindroos**, None; **I. Nennesmo**, None; **I. E. Lundberg**, None.

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Effectiveness of Mycophenolate Mofetil (MMF) as Secondary Therapy for Idiopathic Inflammatory Myopathy (IIM) & Interstitial Lung Disease (ILD): Case Series of 11 Patients. Richard CJ Campbell[1] and Patrick A. Gordon[2], [1]King's College London, London, United Kingdom, [2]Kings College Hospital, London, United Kingdom

Purpose: Controlled trials for treating IIM (and IIM associated with ILD) are limited although corticosteroids and imunosuppressants are standard therapies. A few small case series are beginning to emerge to suggest that MMF may be efficacious and well tolerated in these patients. We present a case series of 11 patients with IIM (5 with ILD) with long-term follow up.

Methods: In this retrospective observational study we examined case notes for 11 patients with IIM treated with MMF. We recorded outcomes before introduction of MMF and at 6 months, 1 and 2 years. We measured muscle strength (IMACS MMT 260 score), change in CK and change in mean steroid dose to assess for successful steroid taper. For the patients with associated ILD, percentage change in predicted TLCO/VC were recorded at 6 months and 1 year. Adverse event data thought to be directly attributable to MMF were also recorded.

Results: 11 patients (8 female) were treated for 257 patient-months. 10 had dermatomyositis, 1 had polymyositis and 5 had associated ILD. 10/11 patients had received steroids and at least one other DMARD prior to MMF.

8 patients had muscle weakness (MMT >260) prior to MMF. 7/8 of these patients with weakness (range 229-258/260, mean 249/260) improved by 6 months (range 256-260/260, mean 258.3). All those on MMF for 2 years (n=4) showed improvement from baseline (range 256-260/260, mean 259/260). 3 patients had a CK>300 prior to MMF but all had normalised by 6 months. Mean steroid dose reduced from 23.9mg to 15.8mg over 1 year (dose reduction was possible in 8/11).

Mean percentage predicted TLCO and VC improved by 13% and 12% respectively by 6 months (n=5) and 14.2% and 13.7% at 1 year (n=4). One patient required rituximab before progressive decline in lung function was halted. Out of 3 patients who had severe dysphagia (including one who required PEG feeding), all improved significantly.

Adverse events for the group, thought to be directly related to MMF, were already known to be associated with its use: TB, shingles, campylobacter diarrhoea, migraine, mania and sleep disturbance. There was one case of penile carcinoma but symptoms were already being investigated prior to introduction of MMF.

Conclusion: For this population, MMF is effective as a second or third line treatment in improving muscle power and for tapering steroids in IIM. It is also efficacious for ILD associated with IIM. Some adverse events including opportunistic infection were noted in this group.

Disclosure: R. C. Campbell, None; **P. A. Gordon**, None.

ACR Concurrent Abstract Sessions

Osteoporosis: Clinical Aspects and Treatment
Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Effects of Once-Yearly Zoledronic Acid 5mg in Combination with Teriparatide (PTH) On Postmenopausal Women with Osteoporosis. Cosman Felicia[1], Kenneth Saag[2], Erik Eriksen[3], Chris Recknor[4], Paul Miller[5], Susan L. Greenspan[6], Philemon Papanastasiou[7], Hanumantha Rao[8], Juerg Gasser[7], Christina Bucci-Rechtweg[9] and Steven Boonen[10], [1]Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, [2]University of Alabama, Birmingham, AL, [3]Aker University Hospital, Oslo, Norway, Oslo, Norway, [4]United Osteoporosis Centers, Gainesville, FL, USA, Gainesville, FL, [5]Colorado Center for Bone Research, Lakewood, CO, [6]University of Pittsburgh, Pittsburgh, PA, [7]Novartis Pharma AG, Basel, Switzerland, [8]Novartis Healthcare Pvt. Ltd, Hyderabad, India, [9]Novartis Pharmaceuticals Corp, East Hanover, NJ, [10]University of Leuven, Leuven, Belgium

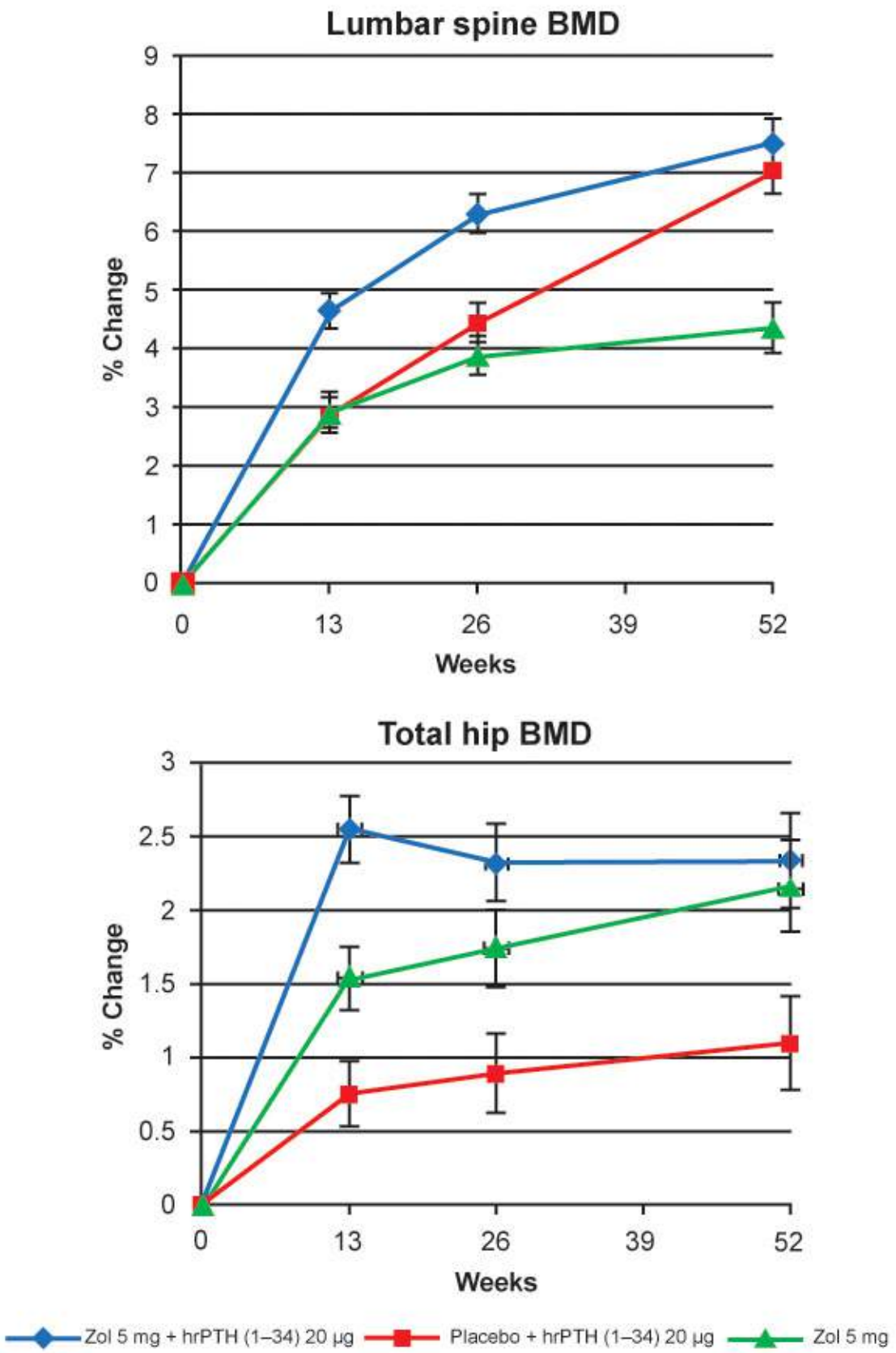
Purpose: The role of combination therapy with hrPTH (1-34) (PTH) and bisphosphonates (BPs) is unclear and although there does not appear to be an additive effect in terms of bone mineral density, certain BPs may blunt the PTH anabolic effect when administered simultaneously. Zoledronic acid (ZOL) does not blunt the PTH effect in rodent models (*Gasser et al. 2006*), and we sought to determine the effects in humans of combination therapy with once-yearly i.v ZOL 5mg and daily sc PTH 20mg *vs.* either agent alone on spine and hip BMD (DXA) and bone turnover markers [serum C-telopeptide, (β-CTx), and N-terminal propeptide of type I collagen, (P1NP)].

Method: This 1-year, partial double-blinded, multicenter study randomized 412 postmenopausal osteoporosis women aged 45–87 yrs, (65±9 yrs) to receive either a combination of ZOL and PTH (n=137), ZOL alone (n=137) or PTH alone (n=138). Between-treatment comparisons for the percent change in lumbar spine (LS) and total hip BMD relative to baseline were performed at weeks 13, 26 and 52 based on the difference of least square means (LSM) from a two-way ANOVA model including all 3 treatments.

Results: 388 women (94.2%) completed the study. At week 52, the LSM estimates of the percent increase in spine BMD were 7.51%, 7.05%, and 4.37% in the combination arm, PTH and ZOL groups, respectively (NS for combination *vs.* PTH , p<0.001 for combination and PTH *vs.* ZOL). The combination therapy significantly increased LS BMD at weeks 13 and 26 and total hip BMD at weeks 13, 26, and 52 *vs.* PTH alone (all p<0.005) (Figure). In the combination arm, β-CTx declined within 4 weeks and rose progressively thereafter, with levels above baseline within 39 weeks; P1NP increased for up to 4 weeks, declined to a nadir at week 8 and then rose progressively with levels above baseline by week 26. Both β-CTx and P1NP levels were lower with combination arm *vs.* PTH alone throughout the trial (all p<0.002). Overall incidence of serious adverse events was 9.5%, 14.6 % and 10.9% in combination, ZOL and PTH arms, respectively. Most frequent adverse events in the combination and ZOL arms *vs.* PTH were transient post-infusion flu-like symptoms.

Conclusion: The concomitant administration of once-yearly i.v ZOL 5mg and daily sc PTH 20mg does not blunt the PTH effect on lumbar spine BMD and results in a significantly greater increment in total hip BMD than PTH alone. Combination therapy could be considered in patients at high risk for hip fracture or those with very low hip BMD.

Figure. Percent change from baseline in lumbar spine BMD (a) and total hip BMD (b) in the treatment groups


Lumbar spine BMD
% Change
0
1
2
3
4
5
6
7
8
9
0
13
26
39
52
Weeks
Total hip BMD
% Change
0
0.5
1
1.5
2
2.5
3
0
13
26
39
52
Weeks
Zol 5 mg + hrPTH (1–34) 20 µg
Placebo + hrPTH (1–34) 20 µg
Zol 5 mg

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The Effects of 6 Years of Continuous Denosumab Treatment On Bone Mineral Density and Biochemical Markers of Bone Turnover.

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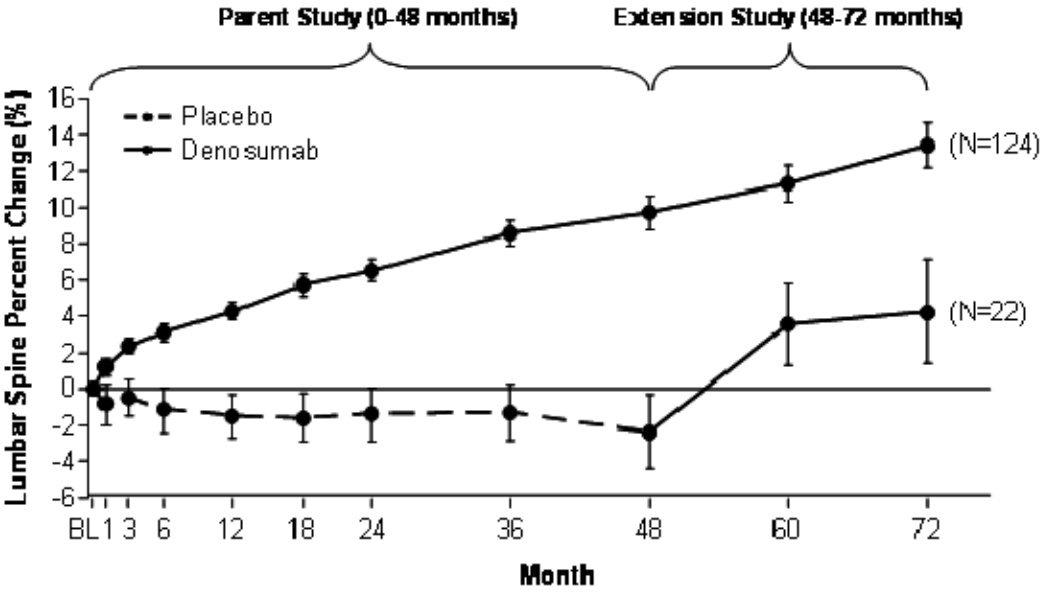
Purpose: Denosumab (DMAb), an investigational fully human monoclonal antibody that inhibits RANKL, significantly reduced the risk of new vertebral, hip, and nonvertebral fractures in a Phase 3 trial at 3 years (Cummings et al., OI 2009;20:S16). In a Phase 2 study, DMAb treatment for 4 years increased bone mineral density (BMD) and reduced bone turnover markers (BTM) (Miller et al., Bone 2008;43:222). Here we present the effects of 6 years of DMAb treatment on BMD and BTM.

Methods: In the Phase 2 parent study, postmenopausal women with a T-score between –1.8 and –4.0 (lumbar spine), or –1.8 and –3.5 (total hip or femoral neck), were randomized to receive placebo (Pbo), alendronate (ALN), or 1 of 7 different doses of DMAb. After 2 years, subjects were reallocated to maintain, discontinue, or discontinue and reinitiate DMAb; discontinue ALN; or maintain Pbo for 2 more years (Miller et al., Bone 2008;43:222). In the extension phase of this study, all subjects received open-label DMAb 60 mg subcutaneously every 6 months (Q6M). Our results focus on subjects who received DMAb treatment for 6 years and those who received Pbo for 4 years followed by DMAb for 2 years.

Results: Of 262 subjects who completed the parent study, 200 enrolled in the extension study and of these, 164 (82%) have completed the first 2 years at the time of this submission. For the 93 subjects who received 6 years of DMAb treatment, BMD at the lumbar spine increased 13.4% compared with their parent study baseline and 2.7% compared with their extension study baseline (Figure). For the 16 subjects in the previous Pbo cohort, 2 years of DMAb treatment resulted in gains in BMD comparable to those observed during the first 2 years of DMAb in the parent study (Figure). Reductions in serum CTX were sustained over the course of continuous DMAb treatment and observed values were comparable to the premenopausal reference range. Reductions in these BTMs also were observed when the Pbo group transitioned to DMAb treatment. The types and rates of adverse events during the extension study were balanced and similar to those observed during the parent study.

Conclusion: Data collected from the 4-year parent study and the 2-year extension study demonstrated that DMAb was safe and effective for 6 continuous years of treatment. There was an increase in BMD in the previous Pbo and continued treatment groups along with reduction of bone turnover markers.

Figure: Percent Change in Lumbar Spine BMD From Parent Study Baseline



Least squares mean (95% CI). N=subjects with at least one parent study baseline and at least one post-baseline measurement. 1 subject who had new vertebra deletion during the extension study was excluded from this analysis.

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The Effects of Denosumab On Fracture Risk Reduction Related to Baseline Bone Resorption. M. McClung[1], D. Bauer[2], C. Christiansen[3], P. Ebeling[4], A. Grauer[5], P. Lakatos[6], W. Lems[7], C. Libanati[5], I. Reid[8], C. Roux[9], P. Sambrook[10], A. Wang[5], S. Cummings[11] and R. Eastell[12], [1]Oregon Osteoporosis Center, Portland, OR, [2]UCSF, San Francisco, CA, [3]CCBR, Ballerup, Denmark, [4]University of Melbourne, Melbourne, Australia, [5]Amgen Inc., Thousand Oaks, CA, [6]Semmelweis University, Budapest, Hungary, [7]Vrije Universiteit medical Centre, Amsterdam, Netherlands, [8]University of Auckland, Auckland, New Zealand, [9]Paris Descartes University, Paris, France, [10]University of Sydney, Sydney, Australia, [11]SFCC, CPMC Research Institute & UCSF, San Francisco, CA, [12]University of Sheffield, Sheffield, United Kingdom

Purpose: Denosumab, an investigational human monoclonal antibody to RANKL, significantly reduced the risk of new vertebral, nonvertebral, and hip fractures in the FREEDOM trial. However, it is not known whether the reduction in fracture risk with denosumab is related to the level of bone resorption at baseline.

Methods: FREEDOM was a 3-year, randomized, placebo-controlled trial in women 60-90 yrs old with postmenopausal osteoporosis defined as a T-score <-2.5 at the spine or hip but not <-4 at either site. Treatment was sc injection of denosumab (60 mg) or placebo every 6 months, along with daily calcium (1000 mg) and vitamin D supplement (400 to 800 IU). We measured 2 bone resorption markers, CTX (ELISA,

Osteometer) and TRACP 5b (immunocapture activity assay, Suomen Bioanalytiikka Oy) in baseline fasting serum samples (n=3906 placebo, n=3902 denosumab).

Results: New vertebral fractures were identified as an increase of ≥1 semiquantitative grade from a baseline grade of 0 on spinal radiographs taken annually, and nonvertebral fractures were confirmed radiologically. Overall, denosumab decreased new vertebral fracture risk by 68% (RR=0.32, *P*<0.0001) and nonvertebral fracture risk by 20% (HR=0.80, *P*=0.01). We divided the study population by quartiles of baseline bone turnover marker levels and examined the denosumab vs placebo risk/hazard ratios for each fracture type and tested for a trend across quartiles in the denosumab group (Table). Denosumab reduced new vertebral fracture risk in all quartiles for CTX and TRACP 5b (*P*<0.001). A greater effect of denosumab on risk of new vertebral fractures was seen in patients with higher baseline serum levels of CTX (*P*=0.01). For nonvertebral fractures, there was a similar trend that did not reach statistical significance (*P*=0.09).

Conclusion: Denosumab reduced the risk of new vertebral fractures regardless of the level of baseline bone resorption. Denosumab-treated patients with higher levels of CTX had a greater reduction in new vertebral fracture risk. The effect of denosumab to reduce nonvertebral fracture risk was not statistically associated with baseline bone turnover.

	CTX, New Vert, RR	CTX, Nonvert, HR	TRACP 5b, New Vert, RR	TRACP 5b, Nonvert, HR
Quartile 1	0.40***	0.09	0.39***	0.80
Quartile 2	0.46***	0.74	0.41***	1.09
Quartile 3	0.14***	0.05	0.30***	0.76
Quartile 4	0.38***	0.70	0.24***	0.65*
Cochran-Armitage trend test	*P*=0.01	*P*=0.09	*P*=0.16	*P*=0.43

Risk ratio (RR) and hazard ratio (HR) <1 favor denosumab, *P<0.05, ***P<0.001. The quartiles for CTX were <0.391 (Quartile 1), 0.391-0.536, 0.537-0.717, and ≥0.718 ng/ml (Quartile 4); the quartiles for TRACP 5b were <3.424 (Quartile 1), 3.424-4.352, 4.353-5.478, and ≥5.479 U/L (Quartile 4).

Disclosure: M. McClung, Amgen, Lilly, Merck, Novartis, Takeda, 5, Lilly, Novartis, sanofi-aventis, 8, Amgen, Lilly, Merck, Procter and Gamble, Takeda, 2 ; **D. Bauer**, Roche Pharmaceuticals, 5, Amgen, 2 ; **C. Christiansen**, Amgen, 5 ; **P. Ebeling**, Merck, Sharpe, Dohme, 5, Merck, Sharpe, Dohme, Amgen, Novartis, GSK-Roche, Servier, 2, Sanofi-Aventis Pharmaceutical, Eli Lilly, 8 ; **A. Grauer**, Amgen, 1, Amgen, 3 ; **P. Lakatos**, Amgen, Novartis, Roche, 5, Amgen, Merck, Roche, 8 ; **W. Lems**, Merck, Procter and Gamble, Eli Lilly, Amgen, Servier, Roche, 5, Merck, Procter and Gamble, Eli Lilly, Amgen, Servier, Roche, 8 ; **C. Libanati**, Amgen, 1, Amgen, 3 ; **I. Reid**, Amgen, Merck, Novartis, 5, Novartis, Merck, 8, Amgen, Novartis, Merck, Procter and Gamble , 2 ; **C. Roux**, Alliance, Amgen, Lilly, MSD, Novartis, Roche, Servier, Wyeth, 2 ; **P. Sambrook**, Merck, Sanofi-aventis, Novartis, Amgen, Servier,, 5, Merck, Sanofi-aventis, Novartis, 8 ; **A. Wang**, Amgen, 1, Amgen, 3 ; **S. Cummings**, Amgen, Eli Lilly, GSK, Organon, Pfizer, 5, Novartis, Eli Lilly , 8 ; **R. Eastell**, Amgen, Procter and Gamble, Novartis, Servier, Ono, GSK , 5, Eli Lilly, 8, Medical Research Council, National Institutes of Health Research UK Dept of Health, AstraZeneca, Procter and Gamble, Novartis , 2 .

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Active Shape Modeling of the Hip and Incident Osteoporotic Hip Fractures. K.R. Luker[1], John A. Lynch[2], R.K Chaganti[3], N. Parimi[4], M. Nevitt[2], J.S. Gregory[5], T. Hillier[6] and N.E. Lane[7], [1]UCSD, San Diego, CA, [2]UCSF, San Francisco, CA, [3]UCSF, SF, SF, CA, [4]CPMC, SF, CA, [5]Aberdeen, United Kingdom, [6]KPMG, Portland, OR, [7]UCDMC, Sacramento, CA

Purpose: Variations in femoral head shape have been reported to predict incident hip fractures. This study evaluated the proximal femur shape as a risk factor for incident hip fractures in a cohort of elderly women through the method of active shape modeling (ASM).

Methods: This analysis was performed using prospectively collected data from a cohort of white women ≥65 years of age at baseline enrolled in the Study of Osteoporotic Fractures (SOF). Supine pelvic radiographs were obtained at the baseline SOF visit. A nested case-

control study was performed. Hips were eligible for inclusion if they had no prevalent radiographic osteoarthritis (RHOA) or fracture in either hip at baseline. Case subjects had no RHOA baseline and had an incident hip fracture after the baseline visit (n=168). Control subjects were a random selection of subjects (n= 231) without RHOA in either hip at baseline or incident hip fractures during the follow-up period. The shape of the right proximal femur was outlined on a digitized baseline radiograph by two readers (KL, KC) using a statistical image analysis technique. Active shape modeling (ASM) was performed to generate 10 unique and independent modes of variations in the proximal femur shape, accounting for 95% of the variance in the shape of the proximal femurs (Gregory et al, Osteo. Inter, 2004). Three other measures of hip geometry associated with hip fracture, namely femoral neck width and length and femoral head diameter, were also measured. The association of proximal femur shape by ASM and other geometric measures were analyzed by logistic regression as independent predictors of incident hip fracture adjusting for covariates.

Results: The incident hip fracture cases were older, weighed less and had lower hip bone mineral density than the control subjects ($p<0.05$). Point-to-point correlations between each film and the composite average shape were computed for the entire set of 399 images and were used to describe 10 modes of variation. Modes 1 (OR 1.62,95% CI: 1.26-2.07 $p<0.001$, per SD change in mode score) and 4 (OR 2.13, CI: 1.63-2.77, $p<0.001$) were found to carry a significantly increased risk for future hip fractures while modes 6 (0.49 95% CI: 0.38-0.65 , $p<0.001$) and 10 (0.60, 95% CI: 0.47-0.78), $P<0.001$) were shown to have a significantly lower risk for incident hip. Femoral neck length was also associated with incident hip fracture, while femoral head diameter and femoral neck diameter were not significantly correlated.

Conclusion: These results suggest that variation in the relative size of the femoral head and neck are moderate determinants of incident hip fractures. The combination of hip shape, femoral neck length, and BMD may improve our ability to identify patients who may be at increased risk for osteoporotic hip fractures and implement appropriate therapy.

Disclosure: K. R. Luker, None; **J. A. Lynch**, None; **R. K. Chaganti**, None; **N. Parimi**, None; **M. Nevitt**, None; **J. S. Gregory**, None; **T. Hillier**, None; **N. E. Lane**, None.

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Fracture Risk Among a Very Large Cohort of RA: Age and Gender-Specific Results. Daniel H. Solomon[1], Gregory Daniel[2], Gina Chang[2], Jun Liu[3] and Sebastian Schneeweiss[3], [1]Brigham & Women's Hospital, Boston, MA, [2]HealthCore, Wilmington, DE, [3]Pharmacoepidemiology, Boston, MA

Purpose: While osteoporosis is known to be more common in persons with RA, little is known about the incidence rates (IRs) for fractures by anatomic site and stratified by age and gender. We compared fracture rates for RA versus age and gender-matched controls.

Methods: Adult beneficiaries of Blue Cross Blue Shield health plans served as the source population. Persons with at least 2 diagnoses of RA with 12+ months of plan eligibility before and after cohort entry date were included. A group of non-RA controls with similar eligibility criteria who were matched on state, plan type and year of cohort entry were also included. Fractures were defined from health care utilization data based on established algorithms. In addition, potential confounders were defined based on data from the 12 months prior to cohort entry. These include age, gender, use of relevant medications (steroids, bisphosphosphonates, benzodiazepines, SSRIs, beta blockers, anti-convulsants, thiazides), co-existence of conditions associated with falls and fractures, and prior diagnoses of a fracture or osteoporosis. IRs and incidence rate ratios (IRRs) were calculated. As well, adjusted Cox proportional hazards models were constructed to estimate the hazard ratio of fracture in subjects with RA compared with controls, adjusting for all of the above confounders.

Results: 47,034 subjects with RA were included along with 828,606 controls. The median age of subjects with RA was 55 years and 45 years for controls. 73% of those with RA were female compared with 71% for controls. The age- and gender-specific IRs for any fracture and by individual anatomic sites were elevated in RA compared with controls (**see Table** for IRs and IRRs). As expected, the IRs across all age strata were higher for women than men in both cohorts (RA and non-RA) and increased with older age. When comparing RA with non-RA across common anatomic sites for osteoporotic fractures, the IRR was consistently elevated for RA: hip IRR 2.07 (95% CI 1.84 – 2.33), wrist IRR 1.19 (95% CI 1.04 – 1.35), pelvis IRR 2.64 (95% CI2.33 – 2.97), and humerus IRR 1.80 (95% CI 1.52 – 2.15). After multivariable adjustment in a Cox regression model, RA was associated with an increased relative risk for any fracture (HR 1.13, 95% CI 1.04 – 1.22).

Conclusion: These analyses demonstrate an elevated relative risk of typical osteoporotic fractures for RA patients compared with non-RA. This trend held up across age and gender strata, as well as across anatomic sites.

Table: Risk of Fracture Comparing Patients with RA to Controls

	RA	Non-RA	Incidence rate ratio, RA vs non-RA(95% CI)
	Incidence rate per 1,000 person-years, (95% CI)		
WOMEN			
< 50 years	3.14 (2.42 – 3.86)	1.73 (1.62 – 1.84)	1.82 (1.43 – 2.30)
50-64 years	6.29 (5.37 – 7.21)	4.63 (4.36 – 4.90)	1.36 (1.16 – 1.59)
65-74 years	20.74 (17.58 – 23.90)	10.03 (9.49 – 10.57)	2.07 (1.76 – 2.43)
75-84 years	39.59 (34.16 – 45.02)	25.98 (24.75 – 27.21)	1.52 (1.32 – 1.76)
85+ years	67.30 (55.21 – 79.39)	55.38 (52.60 – 58.16)	1.22 (1.01 – 1.46)
MEN			
< 50 years	2.31 (1.27 – 3.35)	2.26 (2.07 – 2.45)	1.02 (0.65 – 1.62)
50-64 years	4.19 (2.97 – 5.41)	2.00 (1.74 – 2.26)	2.10 (1.52 – 2.88)
65-74 years	6.11 (3.43 -8.79)	3.77 (3.30 – 4.24)	1.62 (1.03 -2.56)
75-84 years	16.93 (11.06 – 22.80)	11.10 (9.76 – 12.44)	1.53 (1.06 – 2.20)
85+ years	35.75 (17.02 – 54.48)	24.85 (20.72 – 28.98)	1.44 (0.83 – 2.49)

Disclosure: D. H. Solomon, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 ; **G. Daniel**, None; **G. Chang**, HealthCore, 3 ; **J. Liu**, None; **S. Schneeweiss**, HealthCore, 5, WHISCON, 5, RTI, 5 .

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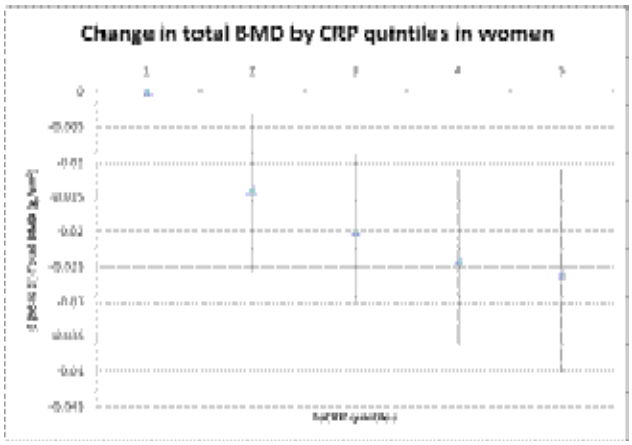
Association Between Bone Mineral Density and High-Sensitivity CRP in a Large Population-Based Sample. Paola de Pablo and Christopher Buckley, University of Birmingham, Birmingham, United Kingdom

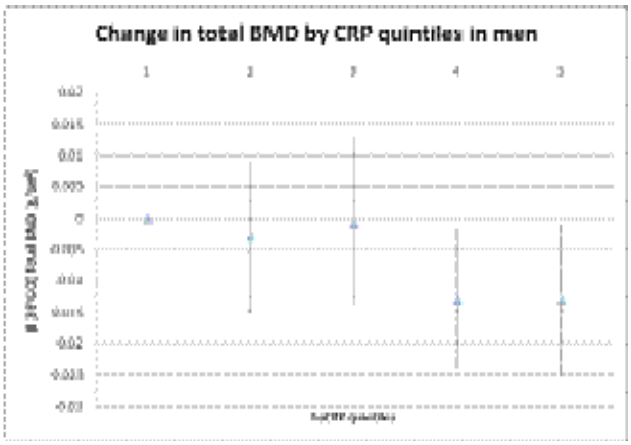
Purpose: Several studies suggest that bone mineral density (BMD) is reduced in chronic inflammatory diseases. Higher serum levels of hs-CRP have been associated with lower BMD in women and older adults. However, whether this association holds in a representative sample of the general population is unclear. The purpose was to examine the relationship between BMD and hsCRP in a large representative US population-based sample from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2004.

Method: We selected subjects over age 20 with BMD (total and subregions) measured by dual-energy x-ray absorptiometry scans from NHANES 1999-2004. The association between CRP concentrations and BMD was evaluated using multivariable linear regression models adjusting for potential confounders. Sensitivity analyses included further adjustment for vitamin D levels, participants taking prescriptions medications, or comorbid diseases, such as arthritis, COPD, CVD, CHF, and stroke.

Results: The study sample included 11,065 participants with a mean age of 50 years (range 20-85). Of those, 53% were Caucasians, 22% were Mexican-American, 18% were African-American, and 7% other races, and 52% were women. Men had higher BMD and lower hs-CRP concentrations than women. BMD (total, subtotal, extremities, ribs, and trunk) was inversely associated with CRP quintiles both in men and women in a dose-dependent fashion (total BMD p for trend <0.001 for men and 0.001 for women). Lumbar spine BMD was inversely associated with CRP in women but not in men and there was no association at the thoracic spine and pelvis BMD subregions. The associations were independent of prescriptions medications use, comorbidities, and other potential confounders. Sensitivity analyses with further adjustment for vitamin D levels confirmed the results (Figures).

Conclusion: Among men and women in a large representative population-based sample, hs-CRP is inversely and independently associated with BMD (total and some subregions) in a dose-dependent fashion.





Disclosure: P. de Pablo, None; **C. Buckley**, None.

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Clinical Aspects: Co-morbidity - Prevention and Prevalence

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Rates and Predictors of Influenza, Pneumococcal, and Herpes Zoster Vaccination in Adult Patients with Rheumatic Diseases.

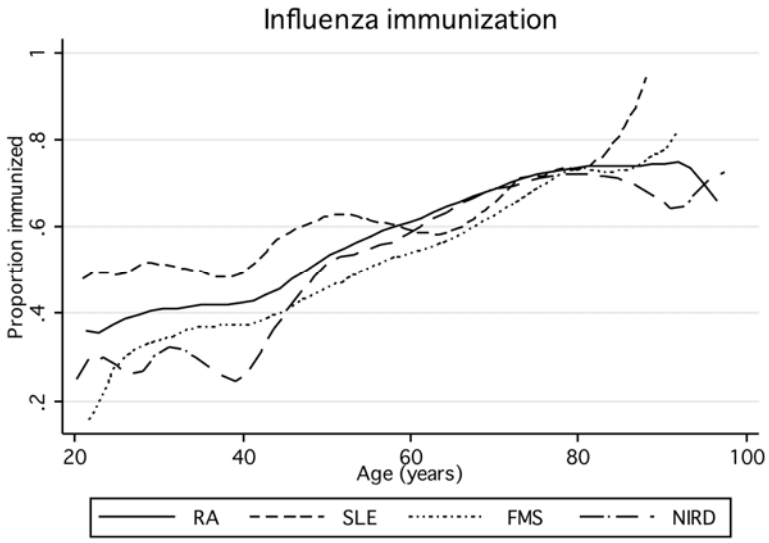
Frederick Wolfe[1] and Kaleb D. Michaud[2], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]University of Nebraska Medical Center and NDB, Omaha, NE

Purpose: Patients with chronic illnesses are at increased risk for, and have increased consequences of, illnesses such as influenza, pneumonia, and Herpes Zoster (Zoster). Public health authorities recommend immunization against influenza and pneumonia in the chronically ill, those over age 50 (influenza), and those who are immunocompromised; but there are not yet recommendations for the newer, expensive zoster vaccine. We studied rates and predictors of immunization in rheumatoid arthritis (RA) and other rheumatic diseases in light of public health recommendations and observed general population rates.

Methods: We studied 25,559 observations from 10,381 patients with RA, SLE, fibromyalgia, and non-inflammatory rheumatic disorders (NIRD) over a 2-year period ending in 2008. Patients self-reported immunizations for influenza (IV), pneumonia (PV), pneumonia in last 5 years (PV5), and zoster (ZV) in semi-annual questionnaires. We analyzed a series of predictors of immunization using Generalized Estimating Equations (GEE).

Results: In the most at risk group, age >=65, immunization rates for all patients were IV 70.2%, PV/PV5 78.8%/66.3%, and ZV 9.1% (table 1). Compared with RA, the SLE immunization rate was increased by 20% and the fibromyalgia rate was decreased by 30% after adjustment for age and sex. For PV5 these values were 42% increase and 56% decrease. For IV and PV5, rate differences between diagnostic groups were mostly in the <65 year age group (figure1). In multivariable analyses across all immunizations, rates increased by age, presence of diabetes, cardiovascular and pulmonary diseases, education level, household income, and majority ethnicity. In the multivariable RA analyses described above, prednisone (OR 1.14 (1.04, 1.25)) and biologic use (OR 1.27 (1.16, 1.39)) increased PV5 probability and biologic use increased IV probability (OR 1.21 (1.11,1.31)).

Age group	IV (Annual) %	PV (ever) %	PV (last 5 yrs) %	ZV (ever) %
<40	41.3 (37.4, 35.2)	29.5 (25.8, 33.2)	23.6 (20.2, 27.0)	-
40-65	56.3 (54.9, 57.6)	45.1 (43.7, 46.4)	37.1 (35.8, 38.4)	-
>=65	70.2 (68.9, 71.6)	78.8 (76.7, 79.2)	66.3 (64.9, 67.7)	9.1 (8.3,9.9)



Conclusion: Rates of immunization among rheumatic disease patients are similar to those of published studies of the general population but substantially lower than recommended by public health authorities. The use of ZV remains rare. Rheumatologists should pay more attention to immunization status of rheumatic disease patients.

Disclosure: F. Wolfe, None; **K. D. Michaud**, None.

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Inadequate Performance of Diagnostic Tests for Latent TB Infection in Elderly Rheumatoid Arthritis Patients: Study in a Population with a High Prevalence of Tuberculosis. Dario Ponce de Leon[1], Eduardo Acevedo-Vasquez[1], Sergio Alvizuri[1], Cesar Gutierrez[2], Mariano Cucho[1], Jose Alfaro[1], Risto Perich[1], Alfredo Sanchez-Torres[1], Cesar Pastor[1], Cesar Sanchez-Schwartz[1], Mariela Medina[1], Rocio Gamboa[1] and Manuel Ugarte-Gil[3], [1]Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru, [2]Universidad Nacional Mayor de San Marcos, Lima, Peru, [3]Universidad Cientifica del Sur, Lima, Peru

Purpose: More than 80% of Tuberculosis cases associated with biologic therapy are reported in patients older than 60 years being, in most cases the result of reactivation of latent tuberculosis infection (LTBI). The objective is to determine the performance of the tuberculin skin test (TST) and Quantiferon TB-Gold ® In Tube version (QFT-IT) (one of the two commercially available Interferon-g release assays) for detection of latent TB infection in elderly patients with rheumatoid arthritis (RA) and matched controls in an endemic TB population

Method: A controlled cross-sectional study of 101 consecutive RA patients and 93 immunocompetent controls was conducted at the Hospital Guillermo Almenara, where the incidence of TB in RA is 216/100,000. TST was deemed positive at ≥5mm (RA) and ≥10mm (Controls).The patients were stratified according to age groups in 20-40 years, 40-60 years and older than 60 years

Results: TST. We found a much lower TST positivity in RA patients older than 60 years (8/45; 17%) compared to controls from the same age group (29/41; 71%) (P<.001); this difference persisted for patients aged 40 to 60 (P<.001) but not in younger patients (aged 20–40) (45% vs 36%; P = 0.62).Fig 1

QFT-IT. We found a lower QFT positivity (18/45;40%) in RA patients older than 60 years compared to controls from the same age group (29/41;71%) (P =0.004).There was no difference between patients and controls in the younger age group. Fig. 2.

Conclusion: A decreased reactivity to the TST and the Quantiferon In Tube test is found in older RA patients compared to matched controls. Therefore, these results must be taken into account for decision making before initiation of biologic therapy in elderly RA patients, particularly in areas highly endemic for TB. These findings could be related to premature immunosenescence described in RA patients.

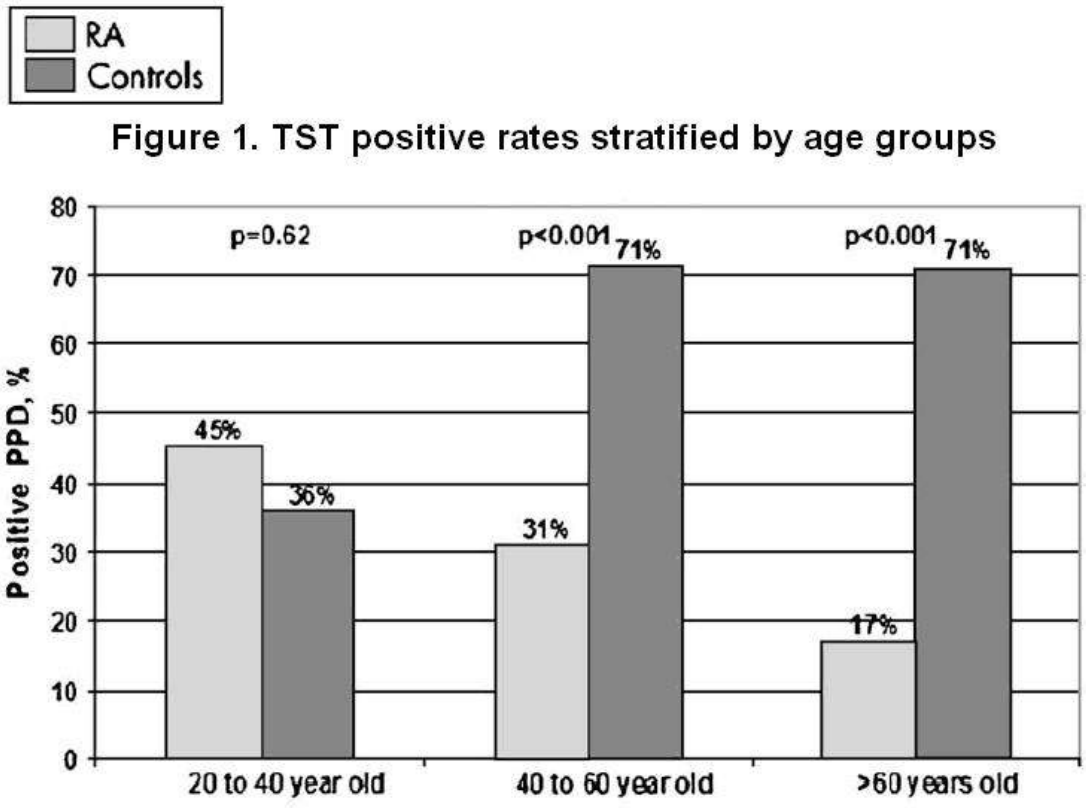

Figure 1. TST positive rates stratified by age groups

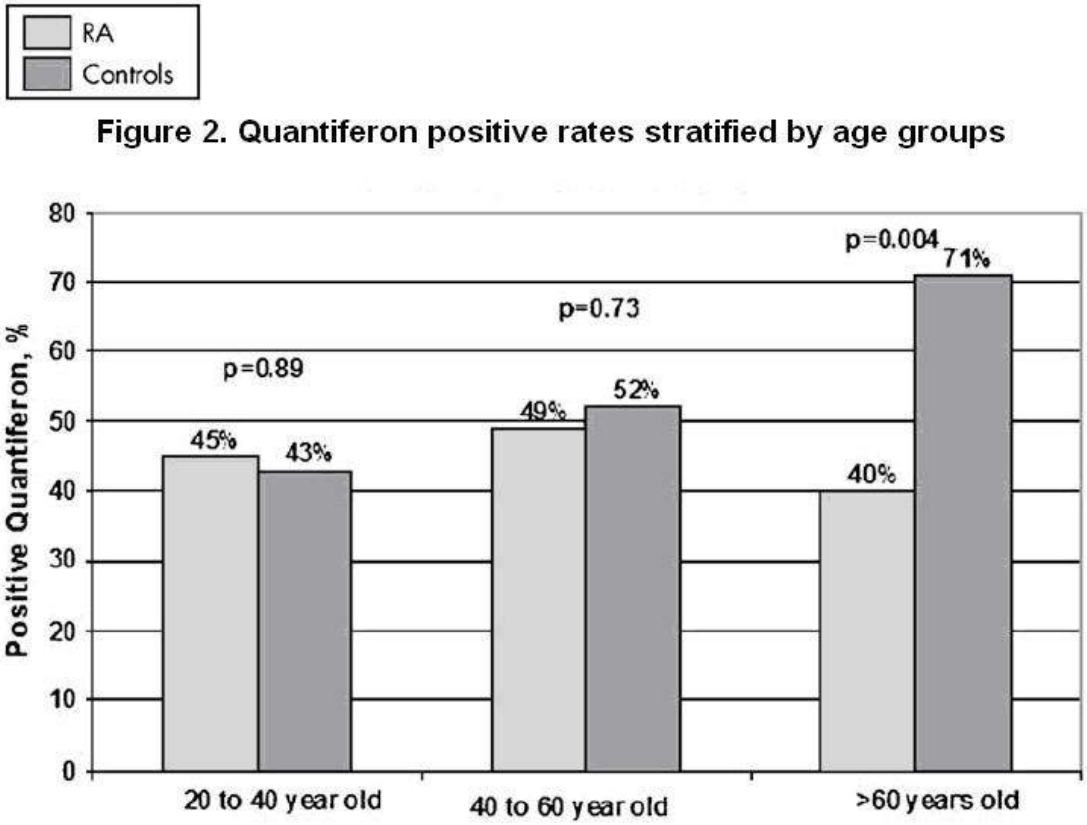

Figure 2. Quantiferon positive rates stratified by age groups

Disclosure: D. Ponce de Leon, None; **E. Acevedo-Vasquez**, None; **S. Alvizuri**, None; **C. Gutierrez**, None; **M. Cucho**, None; **J. Alfaro**, None; **R. Perich**, None; **A. Sanchez-Torres**, None; **C. Pastor**, None; **C. Sanchez-Schwartz**, None; **M. Medina**, None; **R. Gamboa**, None; **M. Ugarte-Gil**, None.

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Prevalence and Determinants of Vitamin D Insufficiency/Deficiency in U. S. Veterans with Rheumatoid Arthritis. Gail S. Kerr[1], John S. Richards[2], T. R. Mikuls[3], Iraj Sabahi[4], A.M. Reimold[5], Gw Cannon[6], Dannette S. Johnson[7] and Liron Caplan[8], [1]VAMC, Georgetown and Howard University Hospitals, Washington, DC, [2]VAMC, Geogetown University Hospital, Washington, DC, [3]U Nebraska, Omaha, NE, [4]Washington Hospital Center, Washington, DC, [5]VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [6]VA and University of Utah, Salt Lake City, UT, [7]University of MS Med Ctr, Jackson, MS, [8]Univ of CO Denver School of Med, Aurora, CO

Purpose: 25-hydroxy vitamin D (VitD) insufficiency/deficiency is increasingly reported in chronic diseases; rheumatic entities not exempted. However, its non-calcitropic and immunomodulatory role in rheumatoid arthritis (RA) disease severity, activity and outcomes remains to be defined. The purpose of this study was to evaluate the prevalence of VitD insufficiency/deficiency and their associations with disease activity, severity, body mass index (BMI), and all-cause mortality in a cohort of United States Veterans with rheumatoid arthritis (RA).

Method: Enrollment clinical data and banked plasma from RA patients entered in the Veterans Affairs Rheumatoid Arthritis Registry (VARA) (n=1,160), were available for study. Time of enrollment was stratified to season. VitD insufficiency was defined as < 30 ng/ml, deficiency as < 20 ng/ml. Demographics, body mass index (BMI), and parameters of disease severity and activity, were examined. Comorbidities and mortality were recorded. Chi-squared tests were performed for dichotomous variables, Student's t-test for continuous variables and Cox proportional hazards regression for mortality risk. Multivariate associations of patient factors with VitD status were examined using logistic regression, adjusting for age, gender, season of enrollment, and race.

Results: Patients (1,049 men, 77% Caucasian) had a mean (SD) age 64 (11) yrs. The prevalence of VitD insufficiency and deficiency were 84% and 45%, respectively (mean = 22.2 ng/ml, SD=25.9 ng/ml), and neither correlated with any season. There were 116 deaths with 2,067 patient-yrs of follow-up (mean follow-up period of 1.9 yrs.). Both VitD insufficiency (90% vs. 83%, p = 0.003) and deficiency (65% vs. 40%, p < 0.001) were more prevalent in non-Caucasians than Caucasians. Low VitD status (insufficiency and deficiency) was also more common among aCCP positive patients (85% vs 79%, p = 0.016, 48% vs 38%, p = 0.004, respectively), and was unchanged after adjustments for age, gender, race, and season of enrollment. VitD deficient patients were also significantly younger (62.9 vs. 65.2, p = 0.0009), while insufficient patients had a higher BMI (28.6 vs. 27.2, p = 0.013). There were no associations of other measures of RA disease activity or severity, nor select comorbidities or overall mortality, with VitD status.

Conclusion: In an elderly male RA population, VitD insufficiency was nearly universal, with deficiency affecting almost a half of the patients. With the increasing adverse health outcomes associated with VitD insufficiency/deficiency, screening and supplementation, particularly amongst young, minority and aCCP positive RA patients, should be performed.

Disclosure: G. S. Kerr, None; **J. S. Richards**, None; **T. R. Mikuls**, None; **I. Sabahi**, None; **A. M. Reimold**, None; **G. Cannon**, None; **D. S. Johnson**, None; **L. Caplan**, None.

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Carotid Intima Media Thickness in Rheumatoid Arthritis as Compared to Control Subjects: a Meta-Analysis. Alper M. van Sijl[1], Mike J.L. Peters[1], Dirk L. Knol[1], HC de Vet[1], Miguel A. Gonzalez-Gay[2], Yvo M. Smulders[1], Ben A.C. Dijkmans[1] and Michael T. Nurmohamed[3], [1]VU Medical Centre, Amsterdam, Netherlands, [2]Hospital Xeral-Calde, Lugo, Spain, [3]Jan van Breemen Institute, Amsterdam, Netherlands

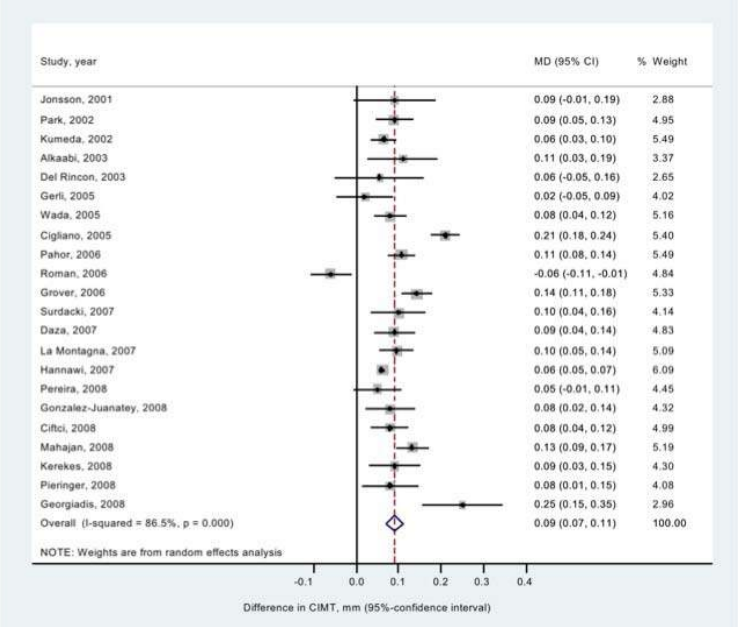
Purpose: Rheumatoid arthritis is associated with an increased risk of cardiovascular disease. Carotid intima media thickness (cIMT) is a frequently used measure to identify populations at risk for cardiovascular disease. A systematic literature search and meta-analysis were performed to evaluate the difference in cIMT between rheumatoid arthritis (RA) and control subjects.

Methods: The literature was screened to identify all available studies comparing cIMT in RA patients and control subjects. A random effects model meta-analysis was performed to estimate the overall mean difference in cIMT between both groups. Meta-regression was performed to assess the influence of the degree of comparability with regard to established cardiovascular risk factors, age, RA disease duration, and the disease activity score (DAS28) on the difference in cIMT.

Results: From 22 studies, cIMT data was obtained from 1,384 RA patients and 1,147 control subjects. In 17 out of 22 studies, RA patients had a significantly greater cIMT relative to controls. The overall mean cIMT difference was 0.09mm (95%-CI: 0.07-0.11). The degree of comparability of cardiovascular risk factors at baseline did not explain the observed heterogeneity of the cIMT difference between RA patients and controls. In addition, neither age nor RA disease duration had a significant influence on the cIMT difference among RA patients. With respect to disease activity, we found a borderline association of DAS28 with cIMT (b regression coefficient; 0.052, p-value; 0.05), which indicates that a higher DAS28 is associated with a greater cIMT. The funnel plot showed a typical inverse funnel shape suggesting publication bias (Egger's test, p = 0.07).

Conclusion: The findings of this systematic review indicate that cIMT is significantly higher in RA patients than in controls, supporting the current evidence base for an increased CV burden in this population.

Figure 1. Meta-analysis of 22 comparative CIMT studies between RA-patients and control subjects



Disclosure: A. M. van Sijl, None; **M. J. L. Peters**, None; **D. L. Knol**, None; **H. de Vet**, None; **M. A. Gonzalez-Gay**, None; **Y. M. Smulders**, None; **B. A. C. Dijkmans**, None; **M. T. Nurmohamed**, None.

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Discordance in the Association of Carotid with Coronary Atherosclerosis in Rheumatoid Arthritis Compared with Controls. Jon T. Giles[1], Wendy Post[1], Moyses Szklo[1], Roger S. Blumenthal[1], Michelle Petri[1], Allan Gelber[1], Joseph Polak[2] and Joan M. Bathon[1], [1]Johns Hopkins Univ, Baltimore, MD, [2]Tufts-New England Medical Center, Boston, MA

Purpose: Measures of carotid atherosclerosis have been used as surrogates for coronary atherosclerosis in many studies of cardiovascular disease (CVD) in RA. However, no studies have heretofore explored whether these measures are predictive of coronary atherosclerosis in RA patients to the same extent as in non-RA controls.

Methods: Men and women with RA enrolled in ESCAPE RA, a cohort study of subclinical CVD in RA, underwent ultrasonography of both common (CCA) and internal (ICA) carotid arteries and cardiac computed tomography (CT). The presence of carotid plaque, maximal intima-medial thickness (IMT) of the CCA and ICA, and extent of coronary arterial calcification (CAC) were compared to non-RA controls frequency matched on age, gender, and ethnicity from the Multi-Ethnic Study of Atherosclerosis. The associations of carotid measures with moderate subclinical atherosclerosis [CAC>100 (a cutpoint highly associated with CV events)] were compared between groups, with prevalence ratios (PRs) and 95% confidence intervals (CIs) calculated using multivariate Poisson regression with robust variance estimation.

Results: We compared 195 RA patients (60% female, 86% Caucasian, mean age 59 years) to 198 frequency matched non-RA controls. CV risk factors were similarly distributed, except for slightly higher mean systolic and diastolic blood pressures in the RA group. The prevalences of any CAC and carotid plaque, and median CAC and ICA-IMT values were significantly higher in RA patients vs. controls. Test characteristics (sensitivity, specificity, positive and negative predictive values) for carotid measures to predict CAC>100 were all lower in RA patients compared to controls. The weaker associations in the RA group were due to higher prevalences of CAC>100 for patients without plaque and with the lowest IMT values (Table); however, having plaque and higher IMT values were similarly associated with CAC>100 in the RA and control groups.

Conclusion: While the presence of plaque and increased IMT were similarly predictive of CAC>100 in RA patients and controls, RA patients without plaque or with low IMT were more likely to demonstrate CAC>100 than controls, suggesting that the absence of carotid atherosclerosis cannot rule out coronary atherosclerosis in RA. These findings may reflect differences in the underlying mechanisms of atherosclerosis between RA patients and controls.

Table. Crude and Adjusted Prevalences of CAC>100 According to Carotid Measures, RA vs. Control							
	Prevalence of CAC > 100 (%)		Prevalence Difference (%) RA vs. Control (Unadjusted)	RA vs. Control (Unadjusted)		RA vs. Control (Adjusted**)	
Carotid Measure	RA n = 195	Control n = 198		PR*	p	PR*	p
Plaque							
Plaque absent	34.0	19.0	+ 15.0	1.79	0.003	1.54	0.018
Plaque present	40.5	65.2	- 24.7	0.62	0.050	0.92	0.77
ICA-IMT Percentiles							
10^{th} (0.72 mm)	20.1	10.4	+ 9.7	1.93	0.015	2.10	0.012
25^{th} (0.82 mm)	22.8	12.8	+ 10.0	1.78	0.016	1.89	0.013
50^{th} (1.01 mm)	28.3	18.1	+ 10.2	1.56	0.021	1.60	0.019
75^{th} (1.41 mm)	40.2	31.7	+ 8.5	1.27	0.11	1.21	0.18
90^{th} (1.89 mm)	54.2	51.3	+ 2.9	1.06	0.72	0.96	0.81
CCA-IMT Percentiles							
10^{th} (0.68 mm)	19.3	6.9	+ 12.4	2.78	0.001	2.31	0.016
25^{th} (0.75 mm)	24.5	10.5	+ 14.0	2.33	0.001	1.97	0.015
50^{th} (0.83 mm)	32.3	17.1	+ 15.2	1.90	0.004	1.63	0.017
75^{th} (0.93 mm)	43.0	28.0	+ 15.0	1.54	0.004	1.35	0.052
90^{th} (1.05 mm)	58.3	47.6	+ 10.7	1.22	0.15	1.10	0.53
* PR = prevalence ratio (prevalence in the RA group divided by prevalence in the control group) ** Adjusted for age, gender, race/ethnicity, education, body mass index, hypertension and use of anti-hypertensives, smoking, diabetes, HDL, LDL, triglycerides, and use of lipid lowering medications							

Disclosure: J. T. Giles, None; **W. Post**, None; **M. Szklo**, None; **R. S. Blumenthal**, None; **M. Petri**, None; **A. Gelber**, None; **J. Polak**, None; **J. M. Bathon**, Crescendo Biosciences, 5 .

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The Apolipoprotein Complex LpAII:B:C:D:E Is Increased in Rheumatoid Arthritis and Is Associated with Carotid Atherosclerosis.

Petar Alaupovic[1], Jon T. Giles[2], Nicholas Knowlton[3], Adam Payne[1], G. Cavet[4], Micheal Centola[3] and Joan M. Bathon[2], [1]Oklahoma Medical Research Foun, Oklahoma City, OK, [2]Johns Hopkins University, School of Medicine, Baltimore, MD, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Crescendo Bioscience, Inc., South San Francisco, CA

Purpose: Conventional lipid measures do not account for the higher rates of cardiovascular disease (CVD) events and mortality in rheumatoid arthritis (RA). However, novel lipid parameters, such as loss of appropriate equilibrium among apolipoprotein complexes that traffic cholesterol, triglycerides, and fatty acids, may lead to atherogenic consequences in RA.

Method: Clinical and lab measures were assessed in 2 cohorts: 1) 94 RA patients and 79 age and sex matched controls (Cohort 1); 2) 39 RA patients from the ESCAPE RA CVD cohort study (Cohort 2). Cohort 2 patients were screened by carotid artery ultrasound to assess maximal intima-medial thickness (IMT) and plaque as surrogates of coronary atherosclerosis. Univarate comparisons were made using t-tests. Multivariate analyses were performed using linear and logistic regression.

Results: As previously observed, traditional risk factors, and plasma HDL and LDL, were not significantly increased in RA patients relative to age and sex matched controls (Cohort 1) and total cholesterol was only marginally increased. However, significant increases in the triglyceride carrier apolipoprotein complex LpAII:B:C:D:E and total triglyceride levels were observed in RA patients relative to controls (Table). For Cohort 2 patients, after adjusting for age, gender, and the anti-atherogenic apolipoprotein A-1, each standard deviation increase in LpAII:B:C:D:E was associated with a 0.15 unit increase in log-IMT ($p = 0.029$) and with a 4-fold increase in the odds of carotid plaque (OR 3.94; $p=0.048$). The magnitude and significance of the associations were unaffected by adjustment for Framingham score, or HDL, LDL, and triglyceride levels.

Table. Plasma Lipid, Apolipoprotein, and Apolipoprotein Complex Levels

	RA	Control	P-Value		RA	Control	P-Value
Lipids/Apolipoproteins				Apolipoprotein Particles			
HDL	59.5 (17.8)	56.9 (16.9)	0.422	LpA-I	35.7 (4.1)	35.1 (4.4)	0.432
Cholesterol	201.7 (46.9)	186.8 (36.8)	0.042	LpA-I:A-II	97.3 (11.6)	102.1 (14.6)	0.038
Triglycerides	163.1 (81.7)	113.1 (42.8)	<0.001	LpB	60.8 (7.6)	59.4 (7.4)	0.362
ApoA-I	133 (14.5)	138.7 (17)	0.039	LpB:C	8.7 (4.2)	10.5 (5.6)	0.038
ApoB	98.2 (15.5)	89.9 (12.8)	0.001	LpB:E+LpB:C:E	10.6 (5.1)	10 (5.5)	0.52
ApoC-III	12.1 (4.8)	10.2 (2.8)	0.007	LpA-II:B:C:D:E	18.2 (8.1)	10 (6)	<0.001

Values depicted are mean (standard deviation)

Conclusion: Compared to controls, RA was associated with a number of abnormalities in lipids, lipoproteins, and apolipoproteins known to be associated with atherogenesis. Among these, the apolipoprotein complex LpAII:B:C:D:E was the most strongly associated with measures of carotid atherosclerosis, suggesting that defects in apolipoprotein complex metabolism and triglyceride transport may mediate CVD in RA over and above the effects of commonly assessed lipoproteins (i.e. LDL, HDL). Moreover, this complex could form the basis of a standardized assay to detect patients at high risk of cardiovascular disease, thus targeting them for therapeutic intervention.

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ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Clinical Trials and Outcomes

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Reliability, Validity, and Minimally Important Differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC 2.0) Instrument. Dinesh Khanna[1], Ron Hays[1], Paul Maranian[2], James R. Seibold[3], Ann J. Impens[3], M. Mayes[4], Philip J. Clements[5], Nihal Fathi[6] and Daniel E. Furst[1], [1]UCLA, Los Angeles, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]University of Michigan, Ann Arbor, MI, [4]U.Texas Houston, Houston, TX, [5]UCLA School of Medicine, Los Angeles, CA, [6]Assiut University Hospital, Assiut, Egypt

Purpose: We developed a scleroderma gastrointestinal tract (SSC-GIT 1.0) instrument. The present study refines the SSC-GIT 1.0 by differentiating reflux symptoms from distention/bloating, adding a rectal incontinence scale, and creating a composite score of overall GIT burden of SSc In addition, we estimate minimally important differences of the new instrument.

Method: We administered the SSC-GIT 1.0 and SF-36v.2 to 152 patients with SSc at 3 scleroderma centers; 1 item was added to SSC-GIT 1.0 to assess rectal incontinence. In addition, subjects completed a rating of the severity of their GIT (very mild to very severe) and physicians noted the GIT diagnosis. We evaluated internal consistency reliability, test-retest reliability (1.1 week mean time interval in 25 patients) and performed multitrait scaling analysis. 115 of the 152 patients completed the questionnaires again at Time2 (25.2 week mean time interval). Patients also completed ratings of their overall, upper, and lower GIT involvement. For example: “Compared to your last visit, how would you rate your overall/upper/lower gastrointestinal symptoms? Much better, a little better, almost the same, a little worse, or much worse.” The minimally changed group was defined by those reporting they were a little better.

Results: Study participants (n=152) were female (84%) and Caucasian (81%); 55% had diffuse SSc and mean age was 51 years. Self-rated severity of GIT ranged from no symptoms to very mild (39%), to mild (21%), to moderate (31%), to severe or very severe (9%). Of an initial 53 items in SSC-GIT 1.0, 19 had low item-total correlations (<0.40) or poor discrimination among scales and were excluded, leaving a 34-item final instrument (UCLA SCTC GIT 2.0). Analyses supported 7 multi-item scales: reflux, bloating/ distention, diarrhea, soil, constipation, emotional well-being, and social well-being. Test-retest reliability estimates were >= 0.68 and coefficient alphas >=0.67. Participants who rated their GIT disease as mild had lower (better) scores on all 7 scales and those with "severe" had the higher scores on a 0-3 scale. In addition, symptom scales were able to discriminate subjects with corresponding clinical GIT diagnosis. The total GIT Score, developed by averaging 6 of 7 scales (excluding constipation), was reliable (test-retest 0.81 and Cronbach's alpha 0.71) provided discrimination between mild, moderate, and severe self-rated GIT involvement. MID estimates for improvement in the Total GIT score ranged from 0.16-0.28 (on a 0-3 scale; effect size estimates 0.40-0.52).

Conclusion: This study provides support for the reliability and validity of the UCLA-SCTC GIT 2.0, an improvement over the original instrument designed to assess GIT involvement in patients with SSc. An overall GIT Score was also developed to capture overall burden (severity) of SSc-associated GIT.

Disclosure: D. Khanna, Actelion Pharmaceuticals US, 2, Takeda Phamaceuticals, 2, Takeda Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, Gilead, 2, Gilead, 5, Fibrogen, 5, UCB, 5, Abbott Immunology Pharmaceuticals, 5, Savient Pharmaceuticals, 2, Savient Pharmaceuticals, 5, NIH, 2, Scleroderma Foundation, 2, ACR REF, 2 ; **R. Hays**, None; **P. Maranian**, None; **J. R. Seibold**, Fibrogen, 5, United Therapeutics, 2, Pfizer Inc, 5, Actelion Pharmaceuticals Ltd, 2, Bristol-Myers Squibb, 2, Actelion Pharmaceuticals US, 1, Actelion Pharmaceuticals Ltd, 5 ; **A. J. Impens**, None; **M. Mayes**, None; **P. J. Clements**, None; **N. Fathi**, None; **D. E. Furst**, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Genentech and Biogen IDEC Inc., 9, Gilead, 9, GlaxoSmithKline, 9, Nitec, 9, Novartis Pharmaceutical Corporation, 9, Roche Pharmaceuticals, 9, UCB, 9, Wyeth Pharmaceuticals, 9, Xoma Corporation , 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech and Biogen IDEC Inc., 9, gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9, Novartis Pharmaceutical Corporation, 9, Ucb, 9, Wyeth Pharmaceuticals, 9, Xoma, 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech and Biogen IDEC Inc., 9, Gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, UCB, 9 .

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Improving Survival Despite Greater Disease Burden in Systemic Sclerosis. Svetlana I. Nihtyanova[1], Edward C. Tang[1], Carol M. Black[1] and Christopher P. Denton[2], [1]Royal Free and University College Medical School, London, United Kingdom, [2]UCL Medical School, London, United Kingdom

Purpose: To determine whether the ascertainment of major organ complications of systemic sclerosis (SSc) has changed over time and if this is associated with better 5 year survival in two groups of cases seen a decade apart at a single tertiary SSc centre.

Methods: Subjects under regular review at our centre with a definite diagnosis of SSc were identified. We analysed patients with disease onset between years 1990 and 1993 (historical cohort) and patients with disease onset between 2000 and 2003 (contemporary cohort). Case notes were reviewed and demographic and clinical data were recorded. Kaplan-Meier estimates of survival and cumulative frequency of moderate to severe organ-based complications in the different subgroups observed over the first 5 years from disease onset were compared.

Results: A total of 520 SSc patients (234 in the historical cohort and 286 in the contemporary cohort) were included. As there was a significant difference between the two cohorts in terms of subset distribution, with the contemporary cohort having larger proportion of patients with the diffuse cutaneous (dc) subset compared to the historical cohort (45% v 32%, p=0.002), survival and frequency of organ complications were compared separately for the limited cutaneous (lc) SSc and dcSSc subjects. There were no significant differences between the historical and contemporary cohorts in terms of gender, age at onset or proportion of patients lost to follow-up.

We found reduction in all cause mortality among the dcSSc patients from the contemporary cohort with estimated 5-year survival probability of 85% compared to 69% for the historical cohort (p=0.012). There was no significant improvement in survival among the lcSSc patients (92% for the 2000-03 group and 91% for the 1990-93 group, p=0.639).

At 5 years from disease onset, a higher proportion of the patients from the contemporary cohort had a diagnosis of clinically significant pulmonary fibrosis (17% of the lcSSc and 39% of the dcSSc subjects) compared to 3% and 7% (limited and diffuse subset respectively) of the historical cohort, p<0.001. Similarly, the diagnosis of pulmonary arterial hypertension was more frequent among the patients from the contemporary cohort compared to those from the historical cohort over the first 5 years of disease (8% v 1%, p=0.002 for lcSSc and 7% v 1%, p=0.132 for dcSSc). Analysis of the proportion of patients who developed scleroderma renal crisis (SRC) or cardiac scleroderma during

the first five years of follow-up showed no significant difference between the historical and the contemporary cohorts. In particular among the dcSSc subjects, the cumulative incidence of SRC was 16% and 19% for the 2000-03 and 1990-93 cohorts respectively, p=0.815.

Conclusion: Despite the absence of proven disease modifying therapy, survival has substantially improved for dcSSc. There is also more complete ascertainment of lung complications of SSc, probably through greater awareness and more systematic annual screening for organ based complications.

Disclosure: S. I. Nihtyanova, None; **E. C. Tang**, None; **C. M. Black**, None; **C. P. Denton**, None.

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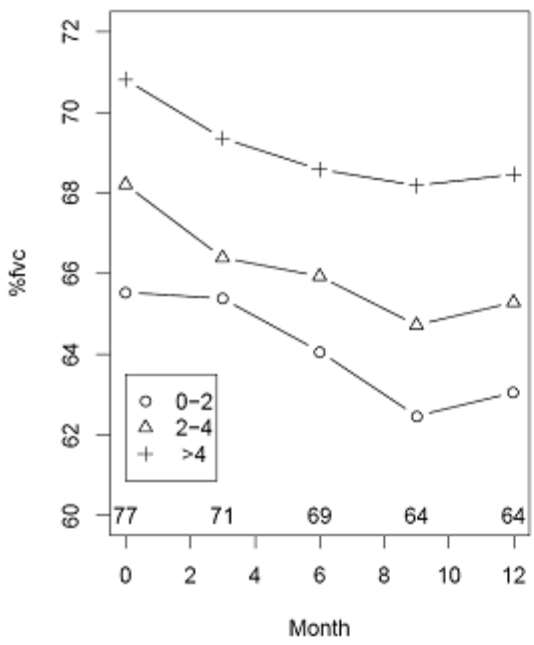
Course of Lung Physiology in Patients with Scleroderma and Active Interstitial Lung Disease: Results From the Scleroderma Lung Study (SLS). Dinesh Khanna[1], Niloofar Farmani[2], Chi-Hong Tseng[1], Philip J. Clements[2], Donald Tashkin[2], Michael Roth[2] and Daniel E. Furst[2], [1]University of California Los Angeles, Los Angeles, CA, [2]UCLA, Los Angeles, CA

Purpose: Patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) usually have the greatest decline in pulmonary function tests in early years of disease onset. Our objective was to assess the natural course of FVC% predicted and DLCO % predicted of 79 patients in the placebo (PLA) group of SLS stratified by 0-2, 2-4 and >4 years of SSc disease duration (defined from first non-Raynaud's symptoms).

Methods: We use 2-sample t-test to compare the rate of decline of FVC between 2 groups and ANOVA for the comparison of 3 groups. We also explored whether decline in the FVC% was different in patients with baseline FVC≥70% vs. < 70% and different degrees of fibrosis on HRCT. A mixed effects model repeated measurement analysis was carried out to compare the time trend FVC for patients with baseline FVC≥ 70% vs. < 70% and baseline fibrosis on HRCT (none to mild vs. moderate to severe) stratified by 0-2, 2-4 and >4 years of SSc disease duration.

Results: Of 79 patients, 77 had baseline disease duration. Of these, 22 (29%), 33 (43%) and 22 (29%) patients were in the 0-2, 2-4 and >4 years disease duration, respectively. There were no statistical differences in the baseline FVC% and DLCO% among 3 groups (p=0.6 for both). The mean (SD) decline in the FVC% predicted during the period of 12 months was -2.9 (8.3). Rate of decline in FVC at 12 month was not significantly different in the 3 groups (p value=0.75, Figures A and B). The mean (SD) decline in DLCO% predicted in the same time period was -3.4 (8.0), which was not significantly different in the 3 groups (p value=0.20). In the sensitivity analysis, rate of decline in the FVC% at 12 month was similar in patients with baseline FVC≥70% vs. < 70% (P value=0.62). However, a greater extent of baseline fibrosis was associated with greater decline in FVC% predicted (p=0.03). For analysis stratified by disease duration, we found significant time trend differences between patients with baseline FVC≥70% vs. < 70% for disease duration > 4 years and fibrosis on HRCT for disease duration 0-2 years, with greater declines in patients with FVC< 70% and greater fibrosis , respectively (p< 0.05).

Conclusion: SLS patients in the PLA group had the same rate of progression of lung disease irrespective of their disease duration or their baseline FVC % predicted. Baseline fibrosis on HRCT was associated with greater decline in FVC% over 12 months. This has implications in design of future SSc-ILD RCTs.



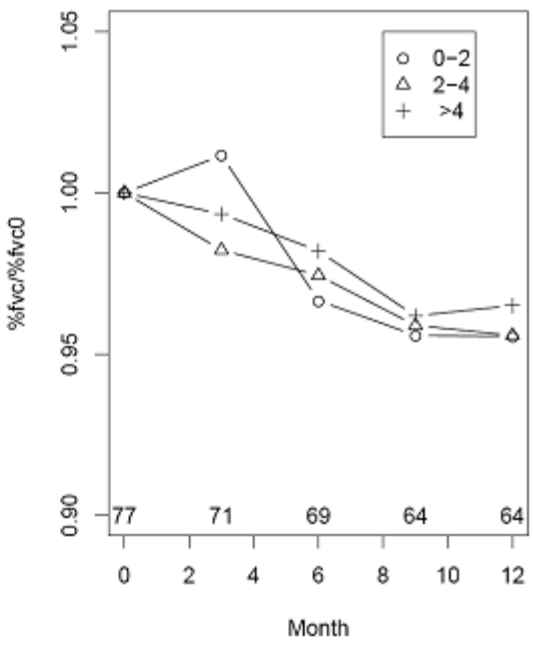


Figure A: Actual change in FVC% in 3 groups **Figure B:** Percent change in FVC% in 3 groups

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Imatinib Mesylate (Gleevec) in the Treatment of Systemic Sclerosis: Interim Results of a Phase IIa, One Year, Open Label Clinical Trial. Jessica Gordon[1], Jamie Mersten[1], S. Lyman[1], S.A. Kloiber[1], H. F. Wildman[2], M. K. Crow[1], K. A. Kirou[1] and R.F. Spiera[1], [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical College, New York, NY

Purpose: Imatinib mesylate has been shown in preclinical studies, mouse models, and case reports to decrease fibrosis in Systemic Sclerosis (SSc). We present here the interim results of an investigator initiated phase IIa, single center, single arm, open label clinical trial examining safety and efficacy of imatinib to treat patients with diffuse cutaneous (dc)SSc (NCT00555581.)

Methods: Patients with severe dcSSc are treated with imatinib 400 mg orally per day. Patients are evaluated monthly for 12 months during treatment and are seen in follow-up 3 months after discontinuing imatinib. The primary endpoint is safety as assessed by number of serious adverse events (SAEs) and adverse events (AEs.) Secondary endpoints are change in the Modified Rodnan Skin Score (MRSS), forced vital capacity (FVC), and diffusion capacity (DLCO.) Additional endpoints include the HAQ-DI, SF-36, echocardiogram, and skin histology.

Results: We have completed enrollment with 30 patients. Four patients (13.3%) are African American, and 26 (86.7%) are Caucasian, 4 of whom are Hispanic. Twenty patients have disease duration of less than 4 years and 10 have more than 4 years. Six patients have dropped out of the study.

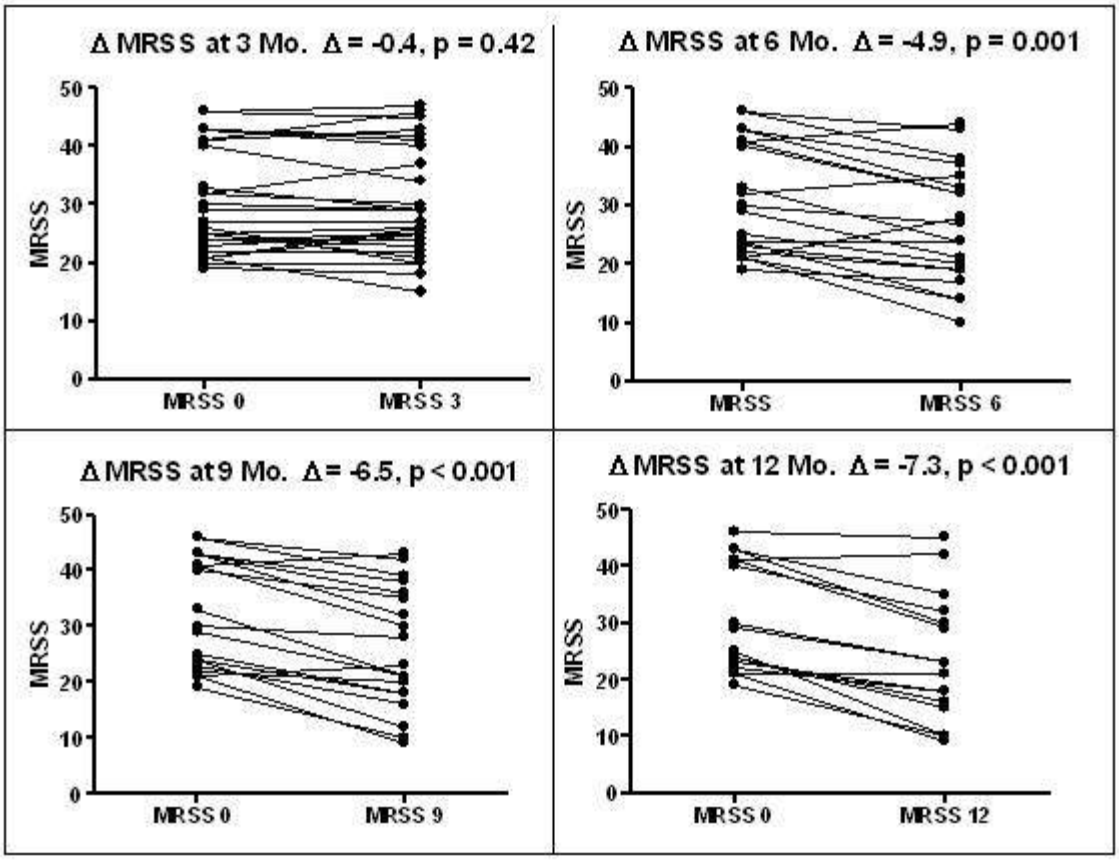
There have been 156 AEs at least possibly related to imatinib. There have been 24 SAEs including one death from community acquired pneumonia in a patient with preexisting severe pulmonary fibrosis. The most common AEs related to imatinib are fluid retention (80%),

nausea (73%), fatigue (53%), and elevation of creatine kinase (37%). These AEs are frequently self-limited or resolve with dose-adjustment, but fatigue led to discontinuance of drug in two patients.

In the 16 patients who have completed 12 months of treatment, mean MRSS improved from 30.8 ± 9.7 to 23.5 ± 11.1, ($p < 0.001$.) Improvements of MRSS are not seen at 3 months ($\Delta = -0.4 \pm 3.2$ points, $p=0.42$, $n = 26$), but were apparent beginning at 6 months ($\Delta = -4.9 \pm 5.0$, $p < 0.001$, $n = 21$), 9 months ($\Delta=-6.5 \pm 4.3$, $p < 0.001$, $n = 19$), and 12 months ($\Delta = -7.3 \pm 4.6$, $p < 0.001$, $n=16$.) Indices of pulmonary function improved at 1 year. Mean FVC improved from 84 ± 22 to 90 ± 23, $p = 0.039$. Mean DLCO improved from 80 ± 21 to 88 ± 27, $p = 0.037$. Skin histology showed improvement at the 12 month time point and is presented separately.

Conclusion: Our interim analysis demonstrates safety and efficacy of imatinib in the treatment of dcSSc. Imatinib is well-tolerated by most patients. Improvements in MRSS, FVC, and DLCO were observed. Translational investigations are ongoing to delineate mechanisms of action and predictors of response. Placebo-controlled investigation is warranted to better define the role of imatinib in the treatment of SSc.

Figure 1. Change in MRSS is seen starting at 6 months of treatment and further improves at 12 months of treatment.



Disclosure: J. Gordon, None; **J. Mersten**, Rudolph Rupert Scleroderma Research Program, 2 ; **S. Lyman**, None; **S. A. Kloiber**, None; **H. F. Wildman**, None; **M. K. Crow**, Rudolph Rupert Scleroderma Research Program, 2 ; **K. A. Kirou**, None; **R. F. Spiera**, Novartis Pharmaceutical Corporation, 2, Rudolph Rupert Scleroderma Research Program, 2 .

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Clinical Prediction of 5-Year Survival in Early Scleroderma:Validation of a Simple Prognostic Model in a Multi-Centre Study. J. Fransen[1], D. Diaconu[1], P. Airo[2], R. Hesselstrand[3], PE. Carreira[4], L. Beretta[5], G. Valentini[6], Murat Inanc[7], S. Ullman[8], Alexandra Balbir-Gurman[9], S. Sierakowski[10], L. Czirjak[11], V. Riccieri[12], R. Giacomelli[13], A. Gabrielli[14], G. Riemekasten[15], M. Matucci-Cerinic[16], D. Farge[17], N. Hunzelmann[18], Y. Allanore[19], Frank van den Hoogen[1] and MC. Vonk[1], [1]Rheumatology, Nijmegen, Netherlands, [2]Rheumatology, Brescia, Italy, [3]Rheumatology, Lund, Sweden, [4]Rheumatology, Madrid, Spain, [5]Rheumatology, Milan, Italy, [6]Rheumatology, Napoli, Italy, [7]Turkish Takayasu's Arteritis Study Group, Istanbul, Turkey, [8]Rheumatology, Copenhagen, Denmark, [9]B Shine Department of Rheumatology, Rambam Health Care Campus,. Rappaport Faculty of Medicine, Technion, Haifa, Israel, [10]Rheumatology, Bialystok, [11]Rheumatology, Pecs, Hungary, [12]Rheumatology, Roma, Italy, [13]Rheumatology, L'Aquila, Italy, [14]Rheumatology, Ancona, Italy, [15]Rheumatology, Berlin, Germany, [16]Rheumatology, Florence, Italy, [17]Rheumatology, Paris, France, [18]Dermatology, Cologne, Germany, [19]Rheumatology A, Cochin Hospital, Paris, France

Purpose: Systemic sclerosis (SSc) is associated with a significant reduction in life expectancy. A simple prognostic model to predict 5-year survival was developed in a British centre in 1999 in 280 patients, but it was not validated in other samples. Usually, a prognostic model is less accurate in new patients, especially from other centres or countries.

To validate the prognostic model to predict 5-year survival in SSc provided by Bryan et al. (1999) in other SSc centres throughout Europe.

Method: A European multi-centre cohort of SSc patients diagnosed before 2002 was established. Data were collected in clinical practice and stored in clinical charts or databases. Patients with Scleroderma according to the preliminary ACR criteria were eligible for this study when they were followed for at least five-years or shorter if they died. Patient-observation time started at the moment the diagnosis of SSc was secured (baseline) and ended at 5-years follow-up or at the moment of death, whichever came first. The primary outcome was 5-year survival after diagnosis of SSc. For the prognostic logistic regression model, the following baseline variables were used: age, gender, urine protein presence, ESR, and carbon monoxide diffusing capacity (DLCO).

Results: Data were available for N=1049 patients,119 (11.2%) of them died within 5 years after diagnosis. Of the patients there were 85% female, mean (SD) age at diagnosis was 50 (13.4), and 30% were classified as having diffuse SSc. At diagnosis, the median (P25-P75) ESR was 17 (9-33), elevated ESR (>25) was present in 298 (33.6%) patients, urine protein was present in 56 (6.5 %) patients, the median (P25-P75) DLCO in '% expected' was 75 (60-80), low DLCO (<70%) was present in 324 (42.8%) patients. The prognostic model with age (OR 1.03), gender (OR 1.93), urine protein (OR 2.29), elevated ESR (1.89) and low DLCO (OR 1.94) had an area under the ROC curve of 0.73. Of the patients with no risk factors, 9/232 (3.9%) died, with 1 risk factor 29/219 (14.2%) died, with 2 risk factors 20/93 (21.5%) died, and with 3 risk factors 4/16 (25%) died.

Conclusion: A simple prognostic model using 3 disease factors to predict 5 year survival at diagnosis in SSc showed reasonable discriminatory performance upon validation in a European multi-centre study. Update of the formula may increase discrimination and precision of the predictions.

Disclosure: J. Fransen, None; **D. Diaconu**, None; **P. Airo**, None; **R. Hesselstrand**, None; **P. Carreira**, None; **L. Beretta**, None; **G. Valentini**, None; **M. Inanc**, None; **S. Ullman**, None; **A. Balbir-Gurman**, None; **S. Sierakowski**, None; **L. Czirjak**, None; **V. Riccieri**, None; **R. Giacomelli**, None; **A. Gabrielli**, None; **G. Riemekasten**, None; **M. Matucci-Cerinic**, None; **D. Farge**, None; **N. Hunzelmann**, None; **Y. Allanore**, None; **F. van den Hoogen**, None; **M. Vonk**, None.

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A Proof of Concept Trial of Gleevec (Imatinib) in Active Diffuse Scleroderma (DSSc). Janet Pope[1], Donna L. McBain[2], Lisa Petrlich[1], Sharon Watson[1], Louise Bender[1], Faye Deleon[3] and Kelly Summers[4], [1]St Joseph Health Care, London, ON, [2]St Josephs Health Care, London, [3]McMaster University, Hamilton, ON, [4]University of Western Ontario, London, ON

Purpose: There has been interest in tyrosine kinase inhibitors in systemic sclerosis (SSc) due to the effects on PDGF, TGFbeta, adhesion molecules and other factors.

Method: We performed a 6 months proof of concept double blinded RCT of imatinib in active diffuse SSc with skin biopsies using 2mm biopsy on abdomen at time 0 and repeated beside original biopsy at 6 months; and plasma (0,3,6 months) analyzing PDGF, RANTES, E-Selectin, VCAM-1, ICAM-1, MMP-9, tPAI-1, IFN-gamma, IL-1alpha, IL-1beta, IL-4, 6, 10, 12p70, 13, 17; MCP-1,3, MIPs, CD40L, VEGF, TNFalpha, and TGFbeta, and patient and physician outcomes including HAQ, and modified Rodnan skin score (mRSS). We used 4:1

randomization and planned to enroll 20 patients, stratifying by presence or absence of stable background Methotrexate use. Novartis supplied imatinib and placebo for this investigator initiated study.

Results: After enrolling 10 patients mean age (9 active and one placebo);7 Female, mean age 51, 3.1 years disease duration (0.5 to 6 years) and mRSS skin score: 32 (SD 8), 3 had tendon friction rubs, patient global 66 (on 100 mm VAS), MD global 46, and HAQ 1.7; we found poor tolerability and high AEs (5 had to stop due to AEs or interrupting dose including fluid retention, weakness, nausea, vomiting, chest pain, worsening anemia, and hair loss), only 4 patients completed the 6 months on study drug at recommended dose. There was also one SAE (active drug marked fluid retention) so we stopped enrolling further subjects. Using ITT analysis, at 6 months, we found: no difference in any parameter with all p values (none were near significance) including: skin score (6 months mRSS 30. P=0.6), CRP, ESR, MD global (36) and patient global (39), HAQ (1.5), tissue (skin biopsy) and plasma cytokines and other factors. The 6 months health transition was rated by two who dropped out as much worse, and one more as much worse, another worse, 4 the same and 2 better. The plasma and tissue cytokines in those on active treatment were not statistically different from 0 to 6 months except sVCAM-1(plasma $p<0.001$) and sICAM-1 (tissue $p=0.009$).

Conclusion: In relatively early active disuse SSc, imatinib was not well tolerated and did not change any clinical or skin biopsy parameters over 6 months. It is unlikely that imatinib will be a feasible treatment for early SSc with respect to modifying skin sclerosis or inflammation.

Disclosure: J. Pope, Novartis , 5 ; **D. L. McBain**, None; **L. Petrlich**, None; **S. Watson**, None; **L. Bender**, None; **F. Deleon**, None; **K. Summers**, Novartis Pharmaceutical Corporation, 2 .

ACR REF Special Session

REF Marshall J. Schiff Memorial Lectureship: Inflammation and Joint Replacement

Sunday, October 18, 2009, 2:30 PM - 4:00 PM

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Glucocorticoid-Induced Fat Accrual Is Mediated by the Osteoblast. Holger Henneicke[1], Markus Herrmann[1], Janine Street[1], James Modzelewski[1], Frank Buttgereit[2], Hong Zhou[1] and Markus Seibel[1], [1]Bone Research Program, ANZAC Research Institute, The University of Sydney, Sydney, Australia, [2]Charite University Med-Berlin, Berlin, Germany

Purpose: Osteoblasts may be involved in the regulation of energy metabolism. To define whether the metabolic effects of glucocorticoids (GC) are mediated via the osteoblast, we used a transgenic mouse model in which a GC inactivating enzyme, 11ß-hydroxysteroid-dehydrogenase type 2 (11ßHSD2), has been targeted exclusively to mature osteoblasts via the 2.3kb collagen type Ia1 promoter. This transgene is expressed in osteoblasts/osteocytes but not in fat, pancreas, liver, muscle or the CNS.

Method: Transgenic (tg, n=16) and wild type (WT, n=16) mice received either corticosterone (CS) or placebo (PLC) via s.c. pellet implantation for 28 days. In a second experiment, WT mice (n=29) received either CS, CS + warfarin (1.25mg/L drinking water), PLC, or PLC + warfarin for 4 weeks. At day 28, body composition was measured by DXA. Gonadal (GF), retroperitonal (RF) and inter-scapular (IF) fat pads were dissected and weighed. Serum total and uncarboxylated (uc) osteocalcin (OCN), PINP (a marker of bone formation) and cholesterol were measured on day 0, 14 & 28.

Results: At day 28, CS treatment resulted in significant bone loss in WT but not in tg mice. Body weight gain over 28 days was greater in CS-treated WT mice (3.7g) than in CS-treated tg animals (1.9g). Fat masses (total body: 12.1 vs. 8.1g, $p< .01$; GF: 1.41 vs. 0.81g, $p< .01$; RF: 0.29 vs. 0.18, $p< .05$; IF: 0.60 vs. 0.36, $p< .01$) as well as serum cholesterol levels ($p<.05$) were all lower in CS-treated tg than in WT mice. None of these parameters differed significantly between PLC-treated tg and WT mice.

Serum OCN decreased in both CS-treated WT (-75%) and tg (-58%) animals, with total OCN levels remaining higher in tg than in WT mice during CS-treatment ($p< .01$). At day 28, serum ucOCN levels were reduced in CS-treated WT mice ($p<.01$) with no difference between CS-treated tg mice and controls (Fig.1). In contrast, serum PINP levels changed similarly in tg and WT animals during CS exposure.

In pilot studies, warfarin increased the ucOCN fraction from 29% to 54%. Total body fat (11.5 vs. 10.4; NS), GF (1.34 vs. 1.16, NS), RF (0.27 vs. 0.21, p< .05) and IF (0.43 vs. 0.36, p= .08) masses were lower in CS+warfarin-treated WT mice as compared to CS only-treated mice.

Conclusion: Osteoblast-targeted disruption of GC signalling attenuates GC-induced fat accrual and hyperlipidaemia in mice. Some of the effects of GC on energy metabolism appear to be, at least in part, mediated by osteocalcin.

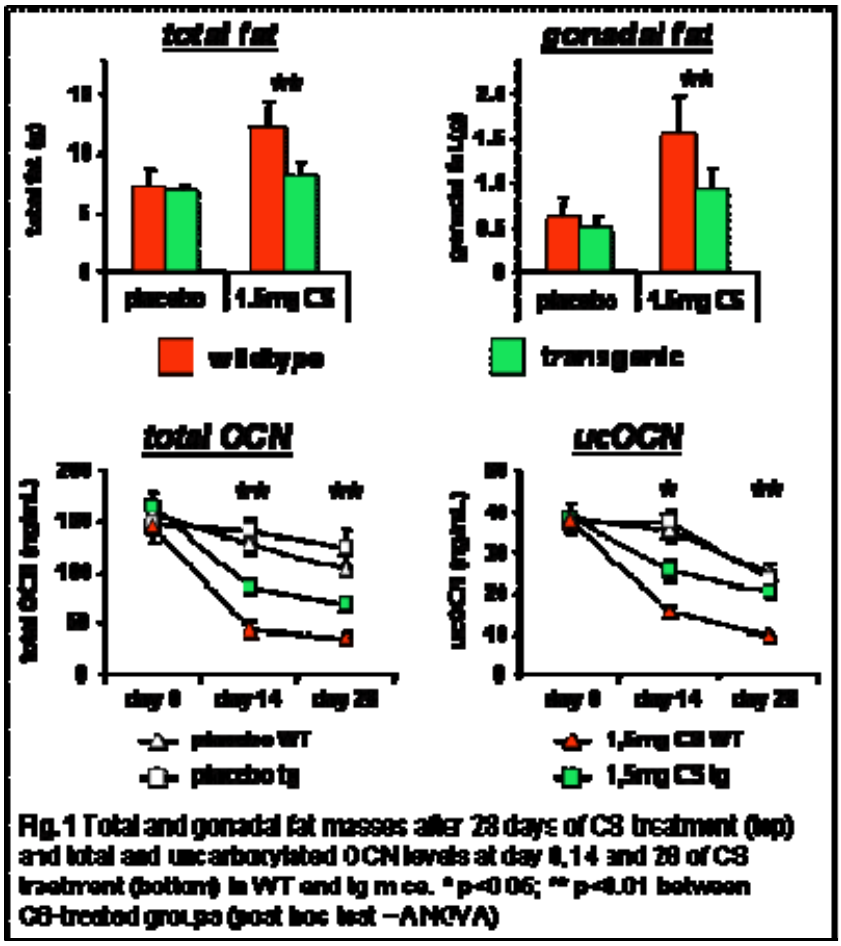

Fig.1 Total and gonadal fat masses after 28 days of CS treatment (top) and total and uncarboxylated OCN levels at day 0,14 and 28 of CS treatment (bottom) in WT and tg mice. * p<0.05; ** p<0.01 between CS-treated groups (post hoc test –ANOVA)

Disclosure: H. Henneicke, None; **M. Herrmann**, None; **J. Street**, None; **J. Modzelewski**, None; **F. Buttgereit**, None; **H. Zhou**, None; **M. Seibel**, None.

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The Surface Expression Level of DC-STAMP Defines the Fusogenic Potential of Osteoclast Precursors (OCP): RANKL-Induced DC-STAMPlo OCP Are the Master-Fusogens. Kofi A. Mensah[1], Yahui Grace Chiu[1], L. Xing[1], Christopher Ritchlin[2] and E.M. Schwarz[1], [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY

Purpose: Osteoclasts (OC) form by fusion of heterogeneous OC precursors (OCP). As OCP heterogeneity can be phenotyped by fusogenic potential (multinucleated master fusogens vs. mononuclear OCP donors) we hypothesized that DC-STAMP, a 7-transmembrane protein receptor required for OCP fusion, mediates this heterogeneity. To test this we evaluated the expression of fusogenic genes and the fusogenic potential of DC-STAMP^{hi} vs. DC-STAMP^{lo} OCP after culture with RANKL. We also evaluated DC-STAMP as an OCP biomarker in patients with inflammatory-erosive psoriatic arthritis (PsA).

Methods: FACS with a monoclonal antibody against DC-STAMP (1A2) was used to purify DC-STAMPlo and DC-STAMPhi RAW 264.7 cells and human peripheral blood mononuclear cells (PBMC). Gene expression before and after culture with RANKL was determined by real time RT-qPCR and flow cytometry. Fusogenic potential was determined by TRAP osteoclastogenesis assay. 2-color immunocytochemistry (ICC) for DC-STAMP and actin were performed on mouse and human OC cultures. Flow cytometry was also used to analyze PBMC from healthy controls (n=14) and PsA patients (n=21).

Results: Incubation of homogeneous DC-STAMPhi RAW cells for 3-days with RANKL produced DC-STAMPlo and DC-STAMPhi heterogeneous cultures. Independent RT-qPCR of these populations showed that *cd9*, *cd47*, and *oc-stamp* were up-regulated 1.5, 1.9, and 21-fold in DC-STAMPlo. These markers were down-regulated or unchanged in the DC-STAMPhi cells. *Trap* was significantly up-regulated 11.3 fold in the DC-STAMPlo population compared to the DC-STAMPhi group. In both groups, *rank* expression was down-regulated 97-99%, and *trem2* expression was up-regulated 7-10 fold. RANKL and M-CSF treatment of human PBMC generated similar DC-STAMP^{lo} and DC-STAMP^{hi} OCP. ICC of OC cultures confirmed that mononuclear OCP are DC-STAMP^{hi} and mature OC are DC-STAMP^{lo}. Consistent with this, we showed that only DC-STAMP^{lo} are pseudopodia producing OCP that have fusagenic potential, while DC-STAMP^{hi} can only serve as mononuclear donors. DC-STAMP+ freshly-isolated PBMC was significantly higher in PsA patients compared to controls (MFI = 3501±229 vs. 1259±85).

Conclusion: Although the DC-STAMP ligand remains unknown, this RANKL-induced factor delivers a critical signal to DC-STAMPhi mononuclear OCP, which induces the expression of genes involved in cell fusion while down-regulating DC-STAMP surface expression. The resulting DC-STAMPlo OCP are "master fusogens" that express higher levels of OC markers and pseudopods that seek out and attach to DC-STAMPhi OCP to form multinucleated OC. The higher frequency of DC-STAMP+ cells among PsA patients versus healthy controls suggests that DC-STAMP surface expression on PBMC, prior to RANKL exposure, may be a dynamic biomarker to assess the aggressiveness of erosive arthritis.

Disclosure: K. A. Mensah, None; **Y. G. Chiu**, None; **L. Xing**, None; **C. Ritchlin**, None; **E. M. Schwarz**, None.

ACR Concurrent Abstract Sessions

Epidemiology and Health Services

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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Anticonvulsant Use, Falls, Fractures and BMD : Findings From the Women's Health Initiative. Laura Carbone[1], Karen Johnson[2], John Robbins[3], Joseph Larson[4], J. David Curb[5], Kathleen Watson[6], Margery Gass[7] and Andrea LaCroix[8], [1]Univ of Tenn at Memphis, Memphis, TN, [2]University of TN, Memphis, TN, [3]University of California, Davis, CA, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, [5]University of Hawaii, HI, [6]University of Washington, Seattle, WA, [7]University of Cincinnatti, [8]Fred Hutchinson, Seattle, WA

Purpose: Anticonvulsants, particularly those that inhibit the cytochrome P450 enzyme- inducing system, may be associated with risks for fracture. The purpose of this study was to determine the relationship of anticonvulsant use to falls, fractures and bone mineral density (BMD) in postmenopausal women.

Methods: We included 138,667 women (1,385 users of anticonvulsants and 137,282 non users of anticonvulsants) aged 50-79 who enrolled in the Women's Health Initiative (WHI) from 1993-1998. Women who had BMD measurements at baseline and year 3 (84 anticonvulsant users and 8,677 non users of anticonvulsants) were also examined. Incident falls and fractures were determined over an average of 7.7 years of follow-up. BMD changes from baseline to year 3 at the total hip, lumbar spine and total body were calculated.

Results: After adjustment for covariates including age, ethnicity, BMI, calcium and vitamin D intake, prevalent fractures and falls, medication use, smoking and alcohol use, parental history of hip fractures, age of menopause, physical activity levels, physical function, self reported health, other medical conditions and WHI trial participation, use of anticonvulsants was positively associated with total fractures (HR 1.44 (95% CI 1.30,1.61), site specific fractures including hip fractures (HR 1.51 (95% CI 1.05, 2.17), clinical vertebral (HR 1.60 (95% CI 1.20, 2.12), lower arm or wrist (HR 1.40 (95% CI 1.11, 1.76) and other clinical fractures (HR 1.46 (95% CI 1.29, 1.65) and 2 or more falls ((HR 1.62 (95% CI 1.50, 1.74) but not with baseline BMD or changes in BMD at the total hip, lumbar spine or total body ($p \geq 0.064$ for all sites). Use of more than one and use of enzyme-inducing anticonvulsants were significantly associated with total fractures (HR 1.55 (1.15, 2.09) and (HR 1.36 (95% CI 1.09, 1.69) respectively.

Conclusion: After adjustment for potential confounders, users of anticonvulsants had an increased risk for total fractures and site specific fractures including hip, clinical vertebral and wrist fractures. The association of anticonvulsant use with fractures was stronger with use of more than one anticonvulsant, and use of enzyme-inducing anticonvulsants. Whether the association of anticonvulsants with fractures is a function of the drug itself or rather, the condition it is being prescribed for merits further study. In clinical practice, however, postmenopausal women who use anticonvulsants should be considered at increased risk for fracture, and attention to fall prevention in these women may be particularly important.:

Disclosure: L. Carbone, None; **K. Johnson**, None; **J. Robbins**, None; **J. Larson**, None; **J. D. Curb**, None; **K. Watson**, None; **M. Gass**, None; **A. LaCroix**, None.

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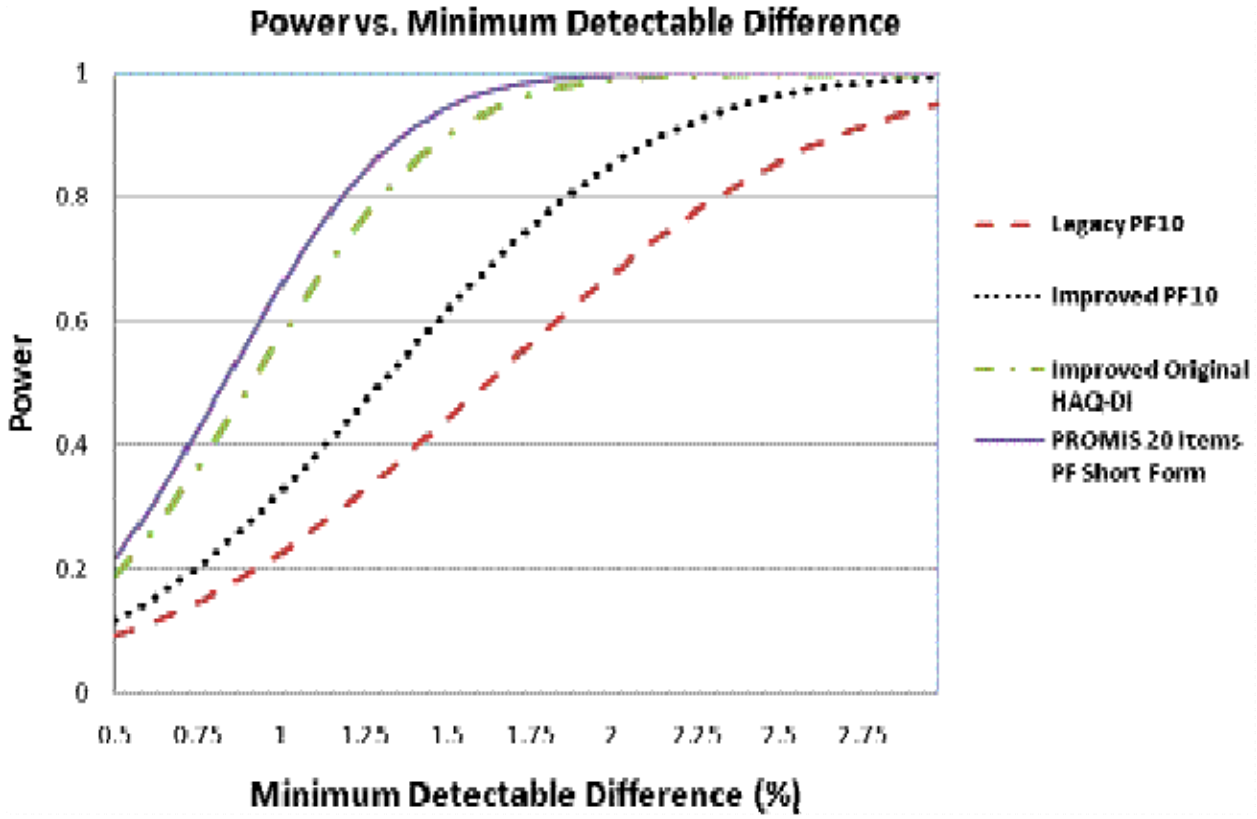
Improved Responsiveness of Physical Function (Disability) Scales Based Upon Item Response Theory (IRT). James F. Fries[1], Eswar Krishnan[2], Matthias Rose[3], Bharathi Lingala[4] and Bonnie Bruce[5], [1]Stanford Univ Medical Ctr, Palo Alto, CA, [2]Stanford University School of Medicine, Palo Alto, CA, [3]QualityMetric, Inc., Waltham, MD, [4]Stanford University, CA, [5]Stanford Dept of Medicine, Palo Alto, CA

Purpose: The original Health Assessment Questionnaire (HAQ-DI) and PF-10 items from the SF-36 have yielded familiar, sensitive and valid clinical Physical Function (PF) endpoints. Now, Item Response Theory (IRT) permits major instrument improvements. IRT analyses can calibrate items with the greatest information content for deployment in more powerful instruments. The NIH Patient Reported Outcomes System (PROMIS) is charged with development of improved IRT-based tools. We compare the original HAQ and PF-10 instruments with successor IRT-based instruments

Methods: We compared six PF (Disability) scales (Original PF-10, Original HAQ, IRT-improved PF-10 and IRT-based HAQ, and the PROMIS 20-item Short-Form using items selected by IRT for maximal information content. We assessed sensitivity to detect six-month longitudinal self-reported improvement, and intensification of treatment in patients with Rheumatoid Arthritis (RA). Metrics for sensitivity were the p-value, the Standardized Response Mean (SRM), Cohen and Guyatt Effect Sizes, minimally detectable differences, and required sample sizes. Questionnaires each contained all items from all instruments but the order of original and new items was randomized to eliminate order effects. Of 521 subjects, 467 (90 %) completed baseline and six-month assessments.

Results: Patients met ACR criteria, averaged 65 years of age and 14 years of education, were 80 % female and 87 % Caucasian, and had baseline original HAQ scores of 0.9 with an SD of 0.7. All instruments were sensitive to changes over time, with p-values ranging from 0.04 to 0.0002 and SRM and Effect Size computations mirroring these results. The most sensitive to change were the improved 20-item Short Forms, regardless of the scoring algorithm or endpoint used. Under study conditions, IRT-Improved instruments could detect a 1.2 % difference with 80 % power, while reference instruments could detect only a 2.3 % difference ($p < 0.01$). The Figure compares instruments on the minimally detectable difference as a function of study power. Under test conditions, detection of a 2.3 % difference with IRT-improved instruments required only 26 % of the sample sizes of the reference instruments (106 vs. 404).



Conclusion: Development of outcome assessment instruments from IRT-calibrated items results in greater sensitivity and efficiency. This can improve the science of outcome assessment, the precision of results from clinical studies, and reduce sample size requirements, thereby reducing recruitment time and reducing costs, and markedly improving study efficiency.

Disclosure: J. F. Fries, None; **E. Krishnan**, None; **M. Rose**, None; **B. Lingala**, None; **B. Bruce**, None.

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Does the Benefit of Medication Adherence Relate More to a Drug Effect or the Behavior Itself? Quantifying the Effect of Adherence Behavior Using Data From the Placebo Arms of the WHI. Jeffrey Curtis[1], Joseph Larson[2], Elizabeth Delzell[1], Suzanne Judd[1], Monika M. Safford[1], Andrea LaCroix[2] and Rowan Chlebowski[3], [1]UAB, Birmingham, AL, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, [3]UCLA, Los Angeles, CA

Purpose: The relationship between medication adherence and various outcomes including fracture is of substantial interest, particularly in the osteoporosis community. The extent to which adherence to medications as a behavior is a proxy for other healthy behaviors that affect outcomes is unclear. To better understand the magnitude of the effect of adherence as a behavior, we examined the relationship between adherence to placebo in the hormone therapy (HT) arm of the Women's Health Initiative (WHI) on the risk of fracture, cardiovascular events, malignancy and death.

Method: We used data from those randomized to placebo in the HT arm of the WHI. Adherence was represented as time-varying based upon pill counts and quantified as a medication possession ratio (MPR). Outcome events were identified and validated using medical records as per the original WHI protocol. Confounders were selected a-priori and based upon the ability to adjust the main exposure-outcome relationship by > 10%. Cox proportional hazards models were used to evaluate the relationship between adherence (≤ 50%, 50-80%, ≥ 80%) and each of the various outcomes, with low adherence as referent. Analyses were censored at the first event specific to each outcome.

Results: A total of 13485 women were randomized to placebo in the HT arm of the WHI and were under observation for 86091 person-years (without respect to censoring). The median (IQR) cumulative adherence to placebo at the end of the trial was 91.3% (81.4, 96.0%). There was a consistent relationship between adherence to placebo and a protective effect of all outcomes that was strongest for death and hip fracture, although not all results were statistically significant (see table). Results were not substantially affected by multivariable adjusted for various confounders.

Conclusion: Medication adherence appears to be a proxy for other unmeasured behaviors and health habits that have important effects on numerous outcomes. The magnitude of this effect was greatest for hip fracture and death. Results of future studies evaluating outcomes related to adherence to specific medications should be interpreted cautiously in light of these results.

Table: Relationship between Medium & High Adherence to Placebo and Various Events, referent to Low Adherence

	Medium Adherence (MPR 50—80%)		High Adherence (MPR >= 80%)	
	Crude HR	Adjusted* HR	Crude HR	Adjusted* HR
Death	0.81 (0.61, 1.08)	0.82 (0.62, 1.10)	0.48 (0.38, 0.60)	0.51 (0.41, 0.64)
Hip fracture	0.76 (0.41, 1.41)	0.66 (0.36, 1.23)	0.61 (0.39, 0.96)	0.50 (0.32, 0.79)
Clinical vertebral fracture	1.06 (0.54, 2.10)	1.02 (0.51, 2.02)	0.92 (0.54, 1.57)	0.81 (0.48, 1.39)
Non-hip, non-vertebral fracture	1.11 (0.87, 1.41)	1.10 (0.86, 1.41)	1.17 (0.97, 1.42)	1.11 (0.92, 1.34)
Cardiovascular event (e.g. AMI)	0.96 (0.63, 1.47)	0.93 (0.61, 1.42)	0.90 (0.65, 1.24)	0.91 (0.65, 1.26)
Invasive breast cancer	1.00 (0.62, 1.59)	0.98 (0.61, 1.56)	0.75 (0.52, 1.08)	0.72 (0.50, 1.05)
Total breast cancer	0.84 (0.54, 1.31)	0.83 (0.53, 1.29)	0.80 (0.57, 1.11)	0.76 (0.55, 1.06)
Colorectal cancer	2.35 (1.08, 5.11)	2.32 (1.07, 5.04)	1.44 (0.72, 2.86)	1.40 (0.70, 2.80)

MPR = medication possession ratio; HR = hazard ratio; AMI = acute myocardial infarction. All models are stratified by randomization arm of the WHI Dietary Modification trial (Active, Comparison, Not Randomized) and prevalent condition.

* adjusted for age, ethnicity, body mass index, self-reported health, education, current smoking, and history of fracture after 55.

Disclosure: J. Curtis, Proctor & Gamble Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, 8, Centocor, Inc., 5, Amgen, 5, Proctor & Gamble Pharmaceuticals, 5, UCB, 5, Roche Pharmaceuticals, 5, Centocor, Inc., 2, Roche Pharmaceuticals, 2, Eli Lilly and Company, 2, Proctor & Gamble Pharmaceuticals, 2, Amgen, 2, Novartis, 2, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8, CORRONA, 2 ; **J. Larson**, None; **E. Delzell**, Amgen, Inc, 2; **S. Judd**, None; **M. M. Safford**, None; **A. LaCroix**, None; **R. Chlebowski**, None.

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Farm History, Insecticide Use and Risk of Autoimmune Rheumatic Disease in the Women's Health Initiative Observational Study.

Christine G. Parks[1], Brian T. Walitt[2], Mary Pettinger[3], Jiu-Chiuan Chen[4], Anneclaire de Roos[3], Julie Hunt[3], Gloria Sarto[5] and Barbara V. Howard[6], [1]National Institute of Environmental Health Science, Research Triangle Park, NC, [2]Washington Hospital Center, Washington, DC, [3]Fred Hutcinson Cancer Research Center, Seattle, WA, [4]USC Keck School of Medicine, Los Angeles, [5]University of Wisconsin Medical Center, Madison, [6]Medstar Research Institute, Washington, DC

Purpose: Farming has been previously associated with the autoimmune rheumatic diseases (ARD), including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The exposure(s) underlying this association are not well-understood, and few studies have directly addressed the role of pesticides, including personal and residential insecticide use. **Method:** Using data from the Women's Health Initiative Observational Study (n=76,861, aged 50-79 years), we examined self-reported lifetime personal or commercial residential insecticide use and having lived or worked on a farm in relation to risk of incident ARD, confirmed by use of disease modifying anti-rheumatic drugs at year 3 of follow-up (n=213; 178 with RA only, 27 with SLE only, and 8 with both RA and SLE), and excluding unconfirmed cases. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated by multivariate models adjusting for age and covariates, including race, region, education, occupation, history of smoking, asthma, other autoimmune diseases, co-morbidity, and reproductive factors. **Results:** Compared with never use, personal insecticide use (mixing or applying) was associated with ARD risk, with stronger associations among those with a greater frequency (age-adjusted HR=2.47; 95%CI 1.51, 4.03 for ≥ 6 times per year) and duration of use (age-adjusted HR=2.07; 95% CI 1.31, 3.25 for ≥ 20 years). Increasing cumulative insecticide use (years X applications) also showed a significant trend of association (p=0.0004) with ARD risk, and these associations persisted after adjusting for farming and covariates. Having lived or worked on a farm was also associated with ARD risk (age-adjusted HR=1.97; 95% CI 1.14, 3.42 for ≥20 years), but the effect size was diminished after adjusting for covariates and insecticide use. Despite the small number of SLE cases, disease-stratified analyses indicated similar associations as seen for RA. In those who had lived or worked on a farm, frequent commercial application to home or garden was also associated with ARD risk, even after adjusting for covariates and personal insecticide use (adjusted HR=2.73; 95%CI 1.1, 6.78 for ≥6 times per year). Long-term commercial residential insecticide exposure was significantly associated with ARD risk regardless of farming history (age-adjusted HR=1.85; 95% CI 1.13, 3.04 for ≥20 years). **Conclusion:** Insecticide exposure may increase risk of ARD in post-menopausal women. These findings, based on self-report, provide rationale for further investigation of specific personal and environmental insecticide exposures in relation to ARD.

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The Relationship Between Bisphosphonate Adherence and Fracture: Is It the Behavior or the Medication? - Results From the Placebo Arm of the Fracture Intervention Trial. Jeffrey R. Curtis[1], Suzanne Judd[1], Doug Bauer[2], Dennis Black[2], Elizabeth Delzell[1], Kristine Ensrud[3], Monika M. Safford[1] and Ann Schwartz[2], [1]UAB, Birmingham, AL, [2]UCSF, San Francisco, CA, [3]University of Minnesota Medical School, Minneapolis, MN

Purpose: Several observational studies have demonstrated a relationship between compliance to osteoporosis medications and fracture. While medication compliance would be expected to reduce risk, compliance may also be a surrogate for other healthy behaviors that affect fracture risk. Little is known about the size of this potential effect; thus we evaluated the relationship between compliance to placebo and clinical fractures among women participating in the Fracture Intervention Trial (FIT).

Method: Compliance to placebo among participants in the placebo arm of the FIT was evaluated using pill counts. Women were defined as having high compliance if they took ≥ 80% of dispensed placebo. Cox proportional hazards models analyzed the relationship between placebo compliance and various types of clinical fractures. Factors that could affect fracture outcomes were included in multivariable models and included age, baseline bone mineral density, height, body mass index, general health, smoking status, calcium intake, prior clinical fracture, and baseline radiographic vertebral fracture.

Results: Among 3169 women randomized to placebo, 81.8% had high compliance. Among placebo treated women, there were 45 hip, 111 wrist, 75 clinical vertebral and 489 total clinical fractures over a median follow-up period of 4.03 years. For wrist, hip or spine fractures combined, high compliance was associated with a statistically significant 30% lower fracture incidence after adjustment, with similar trends for individual fracture types (Table).

Conclusion: Women participating in a clinical trial of alendronate that were highly compliant to placebo had significantly reduced risk for wrist, hip or clinical spine fractures, suggesting that adherence may be a proxy for other behavior that confers benefit independent of the effect of the medication. Previous observational studies that have reported benefit of bisphosphonates may in part be confounded by healthy behaviors associated with medication adherence.

Table: Relationship between compliance* and fracture

	Crude fracture rate per 100 person years		Hazard Ratio unadjusted	Hazard Ratio adjusted‡
	Compliant	Non-compliant		
Hip fracture	0.35	0.52	0.65 (0.34, 1.31)	0.82 (0.40, 1.69)
Wrist fracture	0.90	1.10	0.82 (0.52, 1.29)	0.75 (0.47, 1.19)
Spine fracture	0.55	1.00	0.55 (0.33, 0.91)	0.66 (0.93, 1.11)
Wrist, hip or spine fracture	1.68	2.51	0.67 (0.49, 0.92)	0.70 (0.51, 0.96)
Any clinical fracture	4.31	4.90	0.88 (0.71, 1.10)	0.90 (0.72, 1.13)

‡ adjusted for age, baseline BMD, height, BMI, general health, smoking status, baseline calcium intake, baseline vertebral fracture, other clinical fracture after age 45

* compliance measured using ≥ 80% threshold

Disclosure: J. R. Curtis, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 2, Amgen, 2, Merck Pharmaceuticals, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly, 2, Roche Pharmaceuticals, 2, Corrona, 2, Novartis Pharmaceutical Corporation, 8, Procter and Gamble, 8, Eli Lilly, 8, Roche Pharmaceuticals, 8, Merck Pharmaceuticals, 8 ; **S. Judd**, None; **D. Bauer**, None; **D. Black**, Nycomed, 5, Zosano Pharma, 5, Novartis Pharmaceutical Corporation, 2, Roche Pharmaceuticals, 2 ; **E. Delzell**, Amgen, Inc, 2 ; **K. Ensrud**, None; **M. M. Safford**, None; **A. Schwartz**, Merck Pharmaceuticals, 5, Schering Plough, 2, Amgen, 2 .

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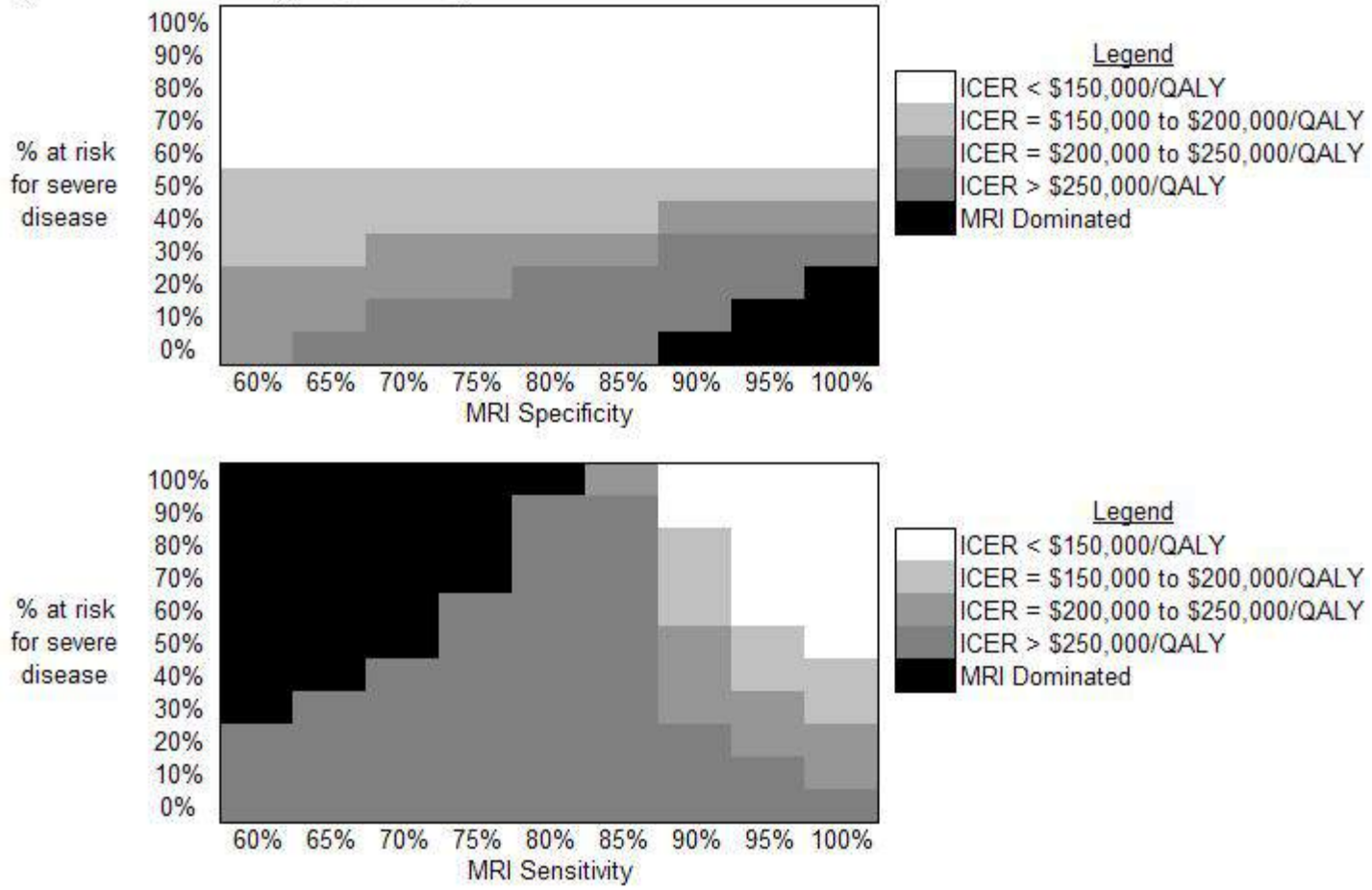
Examining the Cost-Effectiveness of Adding MRI to Early RA Management. L.G. Suter[1], L. Fraenkel[1] and R. S. Braithwaite[2], [1]Yale University, New Haven, CT, [2]Veterans Affairs Health Care System, West Haven, CT

Purpose: Data supports that early treatment for rheumatoid arthritis (RA) improves outcomes, but this approach requires accurate risk stratification to identify those most likely to benefit and avoid over-treatment. MRI has been suggested as a potential tool for risk stratifying early RA patients. Our objective was to explore the cost-effectiveness of adding MRI to standard early RA prognostic markers.

Methods: Using TreeAge® decision analysis software (v. 1.0.2), we created a simulation model of early RA management comparing the addition of MRI to standard assessment (i.e., RF status, CCP antibodies, baseline disease activity) in a population with disease duration <2 years and no erosions on plain radiographs. The model estimated total costs (in 2007 USD) and quality adjusted life years (QALYs). Clinical assessments were performed at 3 month intervals to determine the need for treatment escalation based on disease activity (DAS28) and change over time (ACR50). Adverse events (AEs) were classified as mild (with no associated cost or mortality) or moderate to severe (e.g., requiring treatment or hospitalization and resulting in cost and mortality increases). Cost, quality of life, treatment response, and AE estimates represent the range of data published in randomized trial and observational studies. The model was constructed from the societal perspective with 3% discounting. Sensitivity analyses examined the impact of varying all input estimates, in addition to best and worst case scenarios.

Results: In the base analysis, adding MRI to standard testing increased average per person costs for the first year of treatment from $7,079 to $7,835 and quality of life from 0.810 to 0.815 QALYs, yielding an incremental cost-effectiveness ratio (ICER) of $151,200/QALY gained. Increasing the proportion of individuals at risk for severe disease or increasing the proportion of individuals receiving more aggressive treatment (e.g., by decreasing MRI specificity or improving sensitivity) improved the cost-effectiveness of MRI (Figure 1).

Figure 1. ICERs for adding MRI, according to % at risk for severe disease and MRI characteristics



Conclusion: This model provides a formal framework for evaluating the cost-effectiveness of MRI in early RA management. Short-term analyses suggest that, despite conferring small quality of life gains in the first year of treatment, MRI is unlikely to be cost-effective in the short-term at currently acceptable thresholds among individuals at low risk for severe disease (e.g., very early RA or undifferentiated inflammatory arthritis). Longer-term analyses are needed to better define the populations, treatment regimens and MRI characteristics for which MRI is cost-effective.

Disclosure: L. G. Suter, NIH, AF, 2 ; **L. Fraenkel**, NIH, AF, 2 ; **R. S. Braithwaite**, None.

ACR Concurrent Abstract Sessions

Inflammatory Diseases of Childhood: Genetics and Pathogenesis

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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Chronic TLR9 Activation Initiates Secondary Macrophage Activation Syndrome without Hemophagocytes and in the Absence of Foreign Antigen. Edward M. Behrens[1], Tara T. Donnelly[2], Portia A. Kreiger[3], Michele Paessler[2] and Gary A. Koretzky[4], [1]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, [2]Children's Hospital of Phila, Phila, PA, [3]A.I. DuPont Hospital, Wilmington, DE, [4]Univ of PA School of Medicine, Phila, PA

Purpose: Macrophage Activation Syndrome (MAS) is a potentially fatal complication of many rheumatic illnesses, most notably Systemic Juvenile Idiopathic Arthritis. Previous animal models suggest that an inability to adequately clear foreign antigen (Ag) presented to CD8+ T-cells results in MAS. These models are limited by the fact that they require infection to generate disease, making it difficult to separate infectious pathology from MAS pathology. Furthermore, they all require a background of genetic defects in CD8+ T-cell cytotoxicity, defects not generally found in the secondary MAS seen in humans. We describe the first animal model of secondary, non-infectious MAS utilizing chronic TLR9 stimulation.

Method: Mice were treated with every other day i.p. injections of 50 μg of CpG (TLR9 agonist) +/- Ag (ovalbumin (OVA), 100 μg). Complete blood counts were done on day 9, and mice were taken for necropsy on day 11. The following parameters were measured: splenic weight and cellularity; splenic leukocyte numbers and activation status; bone marrow, spleen, and liver histology; CD163 immunostaining of bone marrow and spleen; and serum ferritin and IFNγ levels. Statistical analysis used t-tests or Mann-Whitney tests where appropriate.

Results: Mice treated with repeated doses of CpG, but not a single dose, nor with PBS developed the following: splenomegaly, pancytopenia, hyperferritinemia, fibrin microthrombi consistent with consumptive coagulopathy, without evidence of malignancy (all $P < 0.05$). Thus, these mice developed 5/8 necessary criteria for MAS, sufficient for diagnosis. Also consistent with MAS were elevated serum IFNγ, splenic architecture disruption, and hepatic inflammation (all $P < 0.05$). Chronic CpG treatment led to CD8+ T-cell activation as measured by $CD69^{hi}CD62L^{lo}$ surface markers ($P < 0.05$), CD4+ T-cells and B-cells were unaffected. Total spleen cell counts were increased. Although absolute numbers of lymphocytes and macrophages were unaffected, splenic dendritic cells were decreased in chronic CpG treated mice ($P < 0.05$). Surprisingly, hemophagocytes (HPCs) were not observed in the bone marrow of CpG treated mice, and CD163 immunostaining was negative, separating the presence of HPCs from the initiation of disease. Addition of the foreign Ag OVA resulted in the additional activation of CD4+ T-cells and B-cells, but still did not result in HPCs.

Conclusion: Chronic TLR9 activation leads to a clinical syndrome indistinguishable from MAS. Surprisingly, these mice develop MAS without developing HPCs. Therefore, with this model we have separated bonafide MAS from the development of HPCs, arguing against a role for HPCs in disease initiation. Current models propose that prolonged antigemia leads to MAS. Based on our results we suggest that adjuvantemia, particularly TLR9 adjuvants, may lead to MAS. Intriguingly, this may explain the association of EBV infection, a DNA virus capable of triggering TLR9, with the development of MAS.

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Shared Loci Between Juvenile Idiopathic Arthritis and Other Autoimmune Diseases. Susan D. Thompson[1], Paula S. Ramos[2], Marc Sudman[1], Miranda C. Marion[2], Cornelia Mueller[3], Johannes-Peter Haas[4], Sampath Prahalad[5], Andrew S. Zeft[6], John F. Bohnsack[6], Carol A. Wise[7], Marilynn G. Punaro[7], Carlos D. Rosé[8], Jasmin Divers[2], Carl D. Langefeld[2] and David N. Glass[1], [1]Childrens Hospital Med Ctr, Cincinnati, OH, [2]Wake Forest University Health Sciences, Winston-Salem, NC, [3]University Hospital, Greifswald, Germany, [4]German Centre for Rheumatology in Children and Adolescents, Garmisch-Partenkirchen, Germany, [5]Emory University, Atlanta, GA, [6]University of Utah, Salt Lake City, UT, [7]Texas Scottish Rite Hospital for Children, Dallas, TX, [8]duPont Hospital for Children, Wilmington, DE

Purpose: The basis for susceptibility to common autoimmune diseases (AD) including Juvenile Idiopathic Arthritis (JIA) is a complex interplay between multiple genetic and environmental risk factors. The use of genome-wide association studies has identified both disease-specific mechanisms and common pathways across diseases. This study tests for association between JIA and SNPs reported in AD studies.

Method: A list of SNPs reported in the AD literature (not including the MHC region) was compiled. After adjusting population substructure, association testing was done for the candidate SNPs using Affymetrix SNP6.0 GeneChip data comprising 809 JIA subjects (ILAR revised criteria; European ancestry), 531 regionally matched controls and 3004 out-of-study controls (Wellcome Trust Consortium, Affymetrix 500K data). SNPGWA was used for association testing. Missing data proportions, minor allele frequency and departure from HWE were calculated. Replication of statistically significant SNPs ($p < 0.005$) utilized independent JIA (n=1006) and control cohorts (n=1340) from Centers in the U.S. and Germany.

Results: Evidence for association was seen for SNPs within or near genes encoding intracellular signaling molecules PTPN2: rs2847297 ($p=1.29x10^{-6}$, OR=1.34), rs7234029 ($p=7.19x10^{-11}$, OR=1.74), PTPN22: rs6679677 ($p=8.66x10^{-8}$, OR=1.57), rs2488457 ($p=5.05 \times 10^{-5}$, OR=1.39), rs1132200 ($p=1.13x10^{-4}$, OR=0.71) and TRAF1: rs2416804 ($p=2.46x10^{-4}$, OR=1.24), rs10984447 ($8.79x10^{-4}$, OR=1.26). In addition, evidence was also found for SNPs within or near cytokine/cytokine receptor genes including the IL2-IL21locus: rs17388568 ($p=1.59x10^{-4}$, OR=1.16), rs13143866 ($p=8.87x10^{-3}$, OR=0.87), IL23R: rs10489629 ($p=7.58x10^{-6}$. OR=0.83), and IL2RA: rs2104286 ($p=3.83x10^{-5}$, OR=0.74), rs12251307 ($p=9.18x10^{-5}$, OR=0.69). Finally, evidence of association was found for SNPs located outside of genes included: rs1010824 ($4.92x10^{-3}$, OR=0.78) which is near the gene ANGPT1, rs17696736 ($3.26x10^{-3}$, OR=1.38) on chr12, rs7151781 ($p=1.55x10^{-4}$, OR=1.27) and on chr14. The associated alleles are the same and odds ratios are similar to those seen in other autoimmune diseases. **Conclusion:** These data support the idea that AD share common biological mechanisms; albeit, in most cases the causal SNP has not been unequivocally identified. Therefore additional studies are needed to determine the mechanism by which these polymorphisms contribute to JIA specifically and to AD as a whole.

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Putative Autoimmune Susceptibility Loci: TENR-IL2-IL21, AFF3 and CTLA4, Are Associated with Juvenile Idiopathic Arthritis.

Anne Hinks[1], S. Eyre[1], Anne Barton[1], Paul Martin[1], Edward Flynn[1], Xiayi Ke[1], Jon Packham[2], J. Worthington[1] and W. Thomson[1], [1]University of Manchester, Manchester, United Kingdom, [2]University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom

Purpose: The strategy of utilising information from autoimmune disease genome wide association studies or candidate gene studies has facilitated the search for novel JIA susceptibility loci. Indeed two recently identified confirmed JIA susceptibility loci, *PTPN22* and *IL2RA* are putative autoimmune susceptibility genes as they show association to rheumatoid arthritis, type 1 diabetes, and Graves' disease. Several novel putative autoimmune susceptibility loci have recently been identified with association to more than one autoimmune disease. We hypothesise that SNPs within these genes may also be associated with susceptibility to JIA. The aim of the study was to test whether markers at four putative autoimmune susceptibility loci, *TENR-IL2-IL21*, *CTLA4*, *AFF3* and *IL7R*, are associated with JIA.

Method: Previously associated SNPs for each of the four regions (4 SNPs in total) were selected for investigation. Genotyping was performed using Sequenom MassArray. DNA was available for 1054 UK Caucasian JIA cases and 3531 controls. Genotype frequencies were compared between cases and controls using the trend test implemented in PLINK.**Results:** Strong evidence for association was seen for both *TENR-IL2-IL21* (rs6822844 OR 0.78 95%CI 0.67-0.9, ptrend= 0.0006) and *AFF3* (rs1160542 OR 1.25 95%CI 1.13-1.39, ptrend=2.05 x 10^{-5}). The *CTLA4* SNP, rs3087243 showed suggestive evidence for association with JIA (OR 0.9 95% CI 0.81-1.0, ptrend=0.05). The *IL7R* SNP, rs6897932, showed a trend towards association with JIA (OR 0.9 95% CI 0.8-1.01, ptrend=0.06). In all cases the associated allele is the same and odds ratios similar to those seen in other autoimmune diseases.

Conclusion: We present evidence for two novel JIA susceptibility loci, *TENR-IL2-IL21 and AFF3* which will require validation in independent JIA datasets. In addition, we present evidence supporting *IL7R* and *CTLA4* as JIA susceptibility genes. *CTLA4* has been investigated previously in JIA with conflicting results. This may reflect true genetic heterogeneity at this locus or may be due to the modest sample sizes used in previous investigations. For all genes the causal SNP has not been unequivocally identified and therefore fine mapping and functional studies will be required to elucidate how these polymorphisms contribute to JIA and autoimmune disease as a whole.

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B-Cell Signature in Patients with JIA Is Associated with Age of Onset Suggesting Biologically Relevant Classification Criteria. Michael G. Barnes[1], Susan D. Thompson[1], Thomas A. Griffin[1], Alexei A. Grom[1], David N. Glass[1] and Robert A. Colbert[2], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]NIAMS/NIH, Bethesda, MD

Purpose: Genetic differences influence age of onset in juvenile arthritis but are not currently considered in the JIA classification. Gene expression data were analyzed to determine if there are patterns associated with early (< 6 years) or late (= 6 years) disease onset in patients with juvenile idiopathic arthritis (JIA).

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from 39 oligoarticular and 45 polyarticular subjects with recent onset JIA, and 56 control subjects. Patient samples were collected prior to treatment with DMARD or biologic agents. PolyA RNA was labeled using NuGEN Ovation and hybridized to Affymetrix HG U133 plus 2.0 arrays. Data were preprocessed using robust multichip analysis and statistics used a false discovery rate of 5%.

Results: Gene expression analysis identified 832 probe sets (of 54,676 total) detecting differential expression between early (n=23) and late (n=16) onset oligoarticular JIA patients. B-cell related markers (CD19, CD22, CD38, CD40, CD72, CD79A, CD79B, CD200), B-cell transcription factors (TCF3, EBF, EIF5B), and other B-cell related genes (BCL7A, BCL11A, BCNP1, BLNK, BRDG1, BTLA, BANK1, SP100, Ig's) were highly represented in the 324 probe sets with increased expression in early onset oligoarticular patients. As expected, the 832 probe sets were able to segregate the patients by age at onset. Unexpectedly, when both oligoarticular and polyarticular patients were analyzed together, the early onset JIA patients (oligoarticular, n = 23; polyarticular, n = 18) clustered together regardless of the number of joints involved. On the other hand, of the late onset polyarticular patients (n=27) some had expression patterns that resemble early onset oligoarticular while others had patterns that resemble late onset oligoarticular patients.

To ensure the differences were not simply due to the age of the donor, samples taken from controls before (n=20) or after (n=36) age 6 were compared and identified only 22 probe sets (12 overlapping) detecting differential expression. The 22 probe sets separated either control or patient samples by age indicating that it is possible to identify a different set of gene expression changes related to age.

Conclusion: PBMC gene expression differences, in part representing a B-cell signature, were able to distinguish early and late onset JIA. The genes were able to identify early onset but not late onset polyarticular patients. These results suggest underlying pathologic mechanisms independent of the currently defined JIA criteria and could lead to alternative treatment options for early onset JIA patients. Age of onset should be considered in revising classification criteria.

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A Systems Biology Analysis of PFAPA Syndrome Reveals a Distinct Disease Entity with Interferon-Inducible Protein 10 (IP-10) and Interleukin-1 (IL-1) as Novel Links for Pathogenesis and Therapy. Silvia Stojanov[1], Sivia Lapidus[1], Puja Chitkara[1], Henry Feder[2], Juan C. Salazar[2], Michael M. Ward[1], Robert A. Colbert[1], Geryl Wood[1], Ivona Aksentijevich[1], R. Goldbach-Mansky[1], Beverly K. Barham[1], Balu H. Athreya[3], Karyl S. Barron[4] and Daniel L. Kastner[1], [1]NIAMS/NIH, Bethesda, MD, [2]University of Connecticut Health Sciences Center/Connecticut Children's Medical Center, Hartford, CT, [3]duPont Hospital for Children/Thomas Jefferson University, Wilmington, DE, [4]NIAID/NIH, Bethesda, MD

Purpose: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) attacks are associated with an aberrant cytokine profile, suggesting a dysregulated innate and adaptive immune response. Using a systems biology approach we attempted to shed more insights into pathogenesis and treatment.

Method: We collected blood samples from three pediatric cohorts: PFAPA patients whose genetic testing excluded hereditary periodic fevers (HPFs) during flares and asymptomatic intervals (N=21), healthy controls (N=21), and HPF patients with flare (N=12). We performed analyses using whole blood microarray, quantitative PCR (qRT-PCR), serum cytokines, and lymphocyte immunophenotyping**.**

Results: Principal component analysis of the overall mRNA expression revealed that PFAPA flares were remarkably distinct from asymptomatic intervals and HPF flares. Genes that were significantly overexpressed in PFAPA attacks compared to inactive PFAPA included interferon-induced (*IP-10*) and IL-1-related (*IL-1B, CASP1*), as well as complement (*C1QB, C2, SERPING1*) genes, whereas T

cell-associated transcripts (*CD3, CD8B*) were downregulated. Leukocytosis with neutrophilia and monocytosis during PFAPA flares was accompanied by a relative reduction of T lymphocytes. Serum IP-10, a chemokine for activated T lymphocytes, was significantly increased during flares and correlated with a decrease in circulating CD4+/CD25+ lymphocytes (Spearman r = -0.8257, p = 0.0001). Serum G-CSF, IL-18, IL-6 and MIP-1b were significantly elevated during PFAPA flares, with IP-10 and G-CSF being the strongest flare predictors. Based on our results, two patients were treated with the IL-1 receptor antagonist, anakinra, during febrile attacks with a prompt clinical response.

Conclusion: Gene expression profiling revealed PFAPA as a distinct entity from HPFs. The overexpression of complement genes suggests an infectious trigger with a strong IP-10, and IL-1/IL-18-mediated response of the innate immune system. Activation and probable recruitment of T cells to peripheral tissues underline the involvement of the adaptive immunity in the pathogenesis of PFAPA, with IP-10 as a potential new biomarker. Preliminary results of the clinical response in two patients support IL-1 inhibition for treatment of PFAPA attacks.

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Genetic Polymorphisms in Key Methotrexate (MTX) Pathway Genes Associated with Response to MTX Treatment in Juvenile Idiopathic Arthritis. Anne Hinks[1], Halima Moncrieffe[2], Paul Martin[1], S.D. Lal[1], Simona Ursu[2], Laura Kassoumeri[2], L. R. Wedderburn[2] and W. Thomson[1], [1]University of Manchester, Manchester, United Kingdom, [2]UCL Institute of Child Health, London, United Kingdom

Purpose: The primary disease modifying therapy in use in juvenile idiopathic arthritis (JIA) is methotrexate (MTX). However, around 35% of children will fail to respond to MTX treatment. The main determinates of MTX response in JIA remain unclear although evidence suggests there may be a genetic component. Genes within the MTX metabolic pathway represent good candidates as predicators of response.

Objectives: To investigate the effect of SNPs across 13 MTX pathway genes on the efficacy of MTX in patients with JIA.

Methods: Subjects were recruited from the SPARKS Childhood Arthritis Response to Medication Study (SPARKS CHARMS) whose response to MTX had been determined over a 6 month period. The cohort included 314 UK Caucasian children whose response was measured using the ACR Paediatric response criteria. Patients were included if they were either ACR Ped 70 (n=72) or non-responders (n=51). Tagging SNPs were selected for ABCG2, ADORA2A, AMPD1, ATIC, DHFR, FPGS, GGH, ITPA, MTHFD1, MTHFR, SHMT1, SLC19A1 (RFC) and TYMS using an r^2 cutoff ≥ 0.8 and MAF ≥ 0.05 within 10kb up and down stream of each gene giving an average coverage after QC of >89%. Genotyping was performed using the Sequenom iPlex® MassARRAY platform. Genotype frequencies were compared between non-responders and responders (ACR70) using the trend test implemented in PLINK and allelic Odds ratios with 95 % confidence intervals calculated in STATA 9.2.

Results: Of the 193 SNPs tested, 3 were found to be significantly associated (pTREND ≤ 0.05) with MTX response. Interestingly 2 of these (rs12995526 & rs4673990) were found in the 5-aminoimidazole-4-carcoxamide ribonucleotide transformylase (ATIC) gene which encodes an enzyme that is important in the de novo purine synthesis pathway. Individuals carrying these SNPs had an increased risk of not responding to MTX (OR 1.79, 95% CI 1.07-3.00 and OR 1.69, 95% CI 1.01-2.83, respectively). Another association was found in the ITPA gene (rs2295553) which again conferred an increased risk of not responding to MTX (OR 1.73, 95%CI 1.03-2.89). In addition there were a further 10 SNPs with a trend towards association ($p<0.1$) in the genes encoding MTHFR, AMPD1, ATIC, DHFR, SHMT1, ITPA and SLC19A1, which are worthy of further follow up.

Conclusion: Genetic variations in a number of key MTX pathway genes have been found to be significantly associated with MTX response in JIA patients. Further studies will be required to validate these findings. If confirmed these results could contribute towards a better understanding of and ability to predict MTX response in JIA. .

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ACR Concurrent Abstract Sessions

Insights from Innate Immunity

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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Beyond MyD88 and TRIF: Syk/SLP-76 Signaling as a Third Adaptor Pathway Downstream of Toll-Like Receptors. Sheila Rao[1], Edward M. Behrens[2], Tara T. Donnelly[2], Gregory Wu[1], Terri M. Laufer[1], Uma Sriram[2], Stefania Gallucci[2] and Gary A. Koretzky[1], [1]Univ of PA, Philadelphia, PA, [2]Childrens Hospital of Phil, Philadelphia, PA

Purpose: Toll-like Receptors (TLRs) are important initial sensors of pathogens in infections. TLR activation leads to pro-inflammatory responses including cytokine release, type I interferon responses, and antigen presenting cell activation. Two major signaling pathways have been well characterized downstream of TLRs, named for their respective adaptors MyD88 and TRIF. We have characterized a third pathway for TLR signaling in dendritic cells (DCs) that utilizes the tyrosine kinase Syk and its adaptor molecule SLP-76.

Method: DCs were generated from the bone marrow of mice by 6 days of culture in medium conditioned with 3 ng/mL of GM-CSF. DCs were stimulated with TLR4 agonist (LPS, 100 ng/mL),TLR9 agonist (CpG, 10 μg/mL), or TLR3 agonist (pI:C,10 μg/mL). Production of TNFα, IL-12, and IL-6 were analyzed by ELISA in cell supernatants. IFNβ production was assessed by real time RT-PCR. Phosphorylation of ERK1/2 and Akt were assessed by western blotting of cell lysates with phospho-specific antibodies. Syk phosphorylation was assayed by Syk immunoprecipatation, followed by immunoblotting with phospho-specific Syk antibody. T-cell proliferation was assessed by CFSE dilution.

Results: Syk is phosphorylated between 2 and 5 minutes after stimulus with TLR3, 4, or 9 ligands. Inhibition of Syk with piceatannol prevents TLR4 induced TNFα and IL-6 secretion, but does not affect IFNβ production after 3 hours of stimulation. Syk inhibition prevents TNFα, IL-6 and IL-12 secretion after overnight stimulation of both TLR4 and TLR9. SLP-76 deficient DCs have attenuated TNFα and IL-12 secretion after TLR4 stimulation, but not TLR9. IL-6 and IFNβ are not affected by SLP-76 deficiency. Either MyD88 deficiency or Syk inhibition leads to attenuation of ERK phosphorylation downstream of TLR4 or TLR9; Syk inhibition combined with MyD88 deficiency results in complete abrogation of ERK phosphorylation in both TLRs. Akt phosphorylation is Syk dependent, MyD88 independent downstream of TLR4, but requires both pathways downstream of TLR9. SLP-76 deficient DCs are suboptimal in inducing antigen specific CD4+ T-cell responses, however this occurs in a TLR independent fashion, suggesting SLP-76 also has TLR independent functions in antigen presentation.

Conclusion: Syk signaling is important for multiple TLR signaling events and functions, however its degree of crosstalk with other TLR pathways differs between different TLRs. Absence of SLP-76 results in deficiency in a subset of these functions, suggesting a role for other Syk adaptors in TLR signaling. These results provide new potential pharmacologic targets for the modulation of TLR function in inflammatory disease states.

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The Role of Uric Acid in Inflammation to Sterile Cell Death. Hajime Kono[1], Chun-Jen Chen[2], Fernando Ontiveros[1] and Kenneth L. Rock[1], [1]UMass Med School, Worcester, MA, [2]National Taiwan Univ., Taipei, Taiwan

Purpose: When cells undergo necrosis *in vivo*, they stimulate acute inflammatory responses. Neutrophils are the first cells to be recruited to the site of necrosis followed by monocytes. Inflammation to necrotic cell death is medically important because it contributes to the pathogenesis of a number of diseases. It is thought that necrosis stimulates inflammation because dying cells release proinflammatory molecules that are recognized by the immune system. However, there is relatively little known about the molecular identity of these molecules and even less about their contribution to responses *in vivo*. We had previously found that uric acid released from dying cells acts as an adjuvant to promote the generation of adaptive immune responses through dendritic cells. Independent of this, monosodium urate crystal can evoke gout, an acute inflammatory condition characterized by neutrophil infiltration to the affected joint. Here we investigate the role of uric acid in the inflammatory response to necrotic cells *in vivo*.

Method: We recently developed 2 lines of transgenic mice that express intracellular or secreted uricase gene under the beta-actin promoter to deplete uric acid intracellularly and/or extracellularly. We also utilized recombinant uricase (Rasburicase) or Allopurinol to reduce the amount of uric acid *in vivo*. Neutrophil recruitment towards the sites of cell death was examined by monitoring the neutrophil numbers in the peritonium 15 hours after injection of sterile necrotic cells, or by measuring the myeloperoxidase activity of liver in mice that received 300 mg/kg of Acetaminophen to induce sterile necrosis of hepatocyte.

Results: We find that dead cells not only release intracellular stores of uric acid but also produce it in large amounts *post mortem* as nucleic acids are degraded. The production of uric acid from dying cells depends on xantine oxidase activity. Using the uricase transgenic mice that have reduced levels of uric acid either intracellularly and/or extracellularly, we find that uric acid depletion significantly reduces the cell death-induced inflammatory responses. Myeloperoxidase activities in liver of Acetaminophen challenged mice were 157±20 mOD/min in WT, 73±15 in secreted uricase Tg, 36±4 in intracellular uircase Tg, and 15±3 in PBS control ($P<0.001$, One-way ANOVA with Tukey's test). These results were confirmed with pharmacological treatments that reduced uric acid levels either by blocking its synthesis (Allopurinol) or hydrolyzing it in the extracellular fluids (Rasburicase). Importantly, uric acid depletion selectively inhibited inflammation to dying cells but not to microbial molecules.

Conclusion: Collectively the data identify uric acid as a proinflammatory molecule released from dying cells that contributes significantly to the cell death-induced acute inflammatory responses *in vivo*.

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Correlation of Disease Activity Change Due to Anti TNF Alpha Treatment with Galactosylation Status of Serum IgG in Inflammatory Arthritis. Emily S. Collins[1], Jodie L. Abrahams[2], Marie Galligan[2], Chin Teck Ng[1], Matthew P. Campbell[2], Barry Bresnihan[1], Douglas J. Veale[1], Pauline M. Rudd[2] and Oliver M. FitzGerald[1], [1]St Vincent's University Hospital, Dublin, Ireland, [2]National Institute for Bioprocessing Research and Training, Dublin, Ireland

Purpose: Previous studies have identified a relationship between decreased galactosylation of IgG and inflammatory arthritis (IA)(1). The extent of the decrease has been shown to correlate with disease severity in rheumatoid arthritis (RA) and to reverse in remission. Traditionally IgG galactosylation has been measured by purification of IgG from serum. The effect of anti-TNFα therapy on the galactosylation status of serum IgG of IA patients was investigated using a method developed in the Dublin–Oxford Glycobiology Laboratory, NIBRT, for the analysis of whole serum (2). We were aiming to establish whether the decreased galactosylation observed in IA reverses upon anti-TNFα treatment and whether the changes in the level of IgG G0 correlate with disease response and thus could be a useful biomarker.

Method: Serum samples were collected from a cohort of 56 inflammatory arthritis patients on anti-TNFα therapy at baseline, 1 month and 1 year after starting treatment and clinical data were collected over this time. Serum samples were analysed using HPLC-based analysis of serum N-glycans after enzymatic release and labelling of N-glycans from whole serum by an in-gel block method(2). The galactosylation of IgG was calculated using a ratio between the IgG FG0 core fucosylated nongalactosylated and FG1 core fucosylated monogalactosylated HPLC peak volumes and is given as a ratio G0/G1 with an increased value indicating a decrease in galactosylation of IgG.

Results: The G0/G1 ratio for IgG decreased following anti-TNFα therapy (indicating an increase in galactosylation) and showed a greater decrease in patients who responded to therapy compared to non-responders, with levels returning to those expected for healthy individuals. Responders: average G0/G1 ratio at baseline=0.91 at 1 year=0.72 ($p=2.4x10-6$); Non-responders: average G0/G1 ratio at baseline =1.08 at 1 year=1.05 ($p=0.76$). The change in G0/G1 by 1 month is very small and no correlation with response is seen. Similar results were obtained when the patients were grouped according to disease type.

The galactosylation level of IgG correlated with disease activity (DAS 28) and severity (HAQ) at baseline ($r2= 0.96$ and 0.92 respectively) and at 1 year ($r2= 0.82$ and 0.92 respectively).

Conclusion: The change in galactosylation of IgG of IA patients on anti-TNFα therapy is correlated to their decrease in disease activity over 1 year. This indicates that the status of IgG galactosylation using whole serum could be a useful marker of disease response.

References: 1)Parekh RB et al., Association of rheumatoid arthritis and primary osteoarthritis with changes in the glycosylation pattern of total serum IgG, Nature 316 (1985) 452–457.
2) Royle et al., HPLC-based analysis of serum N-glycans on a 96-well plate platform with dedicated database software. Anal Biochem. 2008 May 1;376(1):1-12.

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Interaction Between ASC and Estrogen in the Regulation of Inflammation in Murine Arthritis. Laeticia Kolly[1], Sharmal Narayan[1], Jurg Tschopp[2], Alexander K. So[3] and Nathalie Busso[1], [1]Service of Rheumatology, Lausanne, Switzerland, [2]University of Lausanne, Lausanne, Switzerland, [3]CHUV, Lausanne, Switzerland

Purpose: The inflammasome is a multiprotein complex that triggers caspase dependent activation of IL-1b. ASC (apoptosis-associated speck-like protein), a common component of the inflammasome, functions as an adaptor for caspase recruitment, and the NLR (Nod-like receptor) acts as the sensor of the complex. The inflammasome is implicated in inflammatory and autoimmune diseases, including gout and vitiligo. Some of these diseases show a strong gender effect. To determine whether ASC differentially modulates inflammation in males and females mice in models of experimental arthritis.

Method: K/BxN serum transfer-induced arthritis (KRN) and Antigen-Induced Arthritis (AIA) was induced in 8-10 weeks old ASC-deficient mice and their corresponding +/+ littermates (all in a C57Bl/6 background). The severity of arthritis was assessed by clinical scoring (in KBN) and technetium uptake measurement (for AIA). Histological analysis and serum amyloid A (SAA) ELISA were also performed.

Results: In the KRN model, ASC deficiency conferred protection to female mice, as female ASC -/- mice, but not male ASC-/-, had a significant delay in onset of arthritis compared to the corresponding +/+ mice. To investigate whether estradiol is directly responsible for this difference, we castrated female and male ASC -/- mice and supplemented half of them with estradiol. Castration removed the protective effect of ASC deficiency, and supplementation with estradiol restored the protective effect of ASC deficiency.

The effect of estrogens was further confirmed in the AIA model. ASC -/- mice showed a significant decrease of technetium uptake in the arthritic knee. Upon ovariectomy, female ASC -/- mice had the same severity of arthritis as female ASC+/+ mice. Furthermore, supplementation of ovariectomized female ASC -/- mice with estradiol decreased the severity of AIA.

In both models, caspase-1 activation did not seem to have a major role since the levels of active caspase-1 were similar between arthritic male and female mice and since caspase-1 deficiency did not lead to decreased arthritis severity in both the KRN and the AIA model.

Conclusion: ASC, a component of the inflammasome complex, modulates synovial inflammation in females in both the KRN and AIA models. This effect is mediated by estrogens and is independent of caspase-1 activity. These findings suggest that ASC interacts with other proteins beside the classical inflammasome complex in regulating inflammatory responses *in vivo*.

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FK506 Pretreated Dendritic Cells Induce Enduring T Cell Hyporesponsiveness. Dana E. Orange[1], Nathalie Blachere[2] and Robert Darnell[2], [1]HSS, New York, NY, [2]Rockefeller University, New York, NY

Purpose: It has become clear over the past several years that dendritic cells (DCs) play a critical role in peripheral tolerance. In the periphery, immature DCs are particularly efficient at phagocytosing dying cells. Low dose antigen captured from these dying cells is constantly being processed and presented in the context of MHC to delete self-reactive T cells. However, if a DC has been licensed, the immunologic outcome of antigen presentation is T cell activation. In searching for compounds that modulate this outcome, we have discovered that FK506 abrogates CD4 and CD8 T cell activation by directly interfering with cross-talk occurring at the T cell - DC interface. Furthermore, FK506 treated DCs induce a lasting effect on the T cell population, rendering an enduring hyporesponsive state despite subsequent antigen encounter. This study reveals a pharmacologically sensitive pathway that can be exploited to induce antigen-specific tolerance to self-reactive cells.

Method: Healthy donor PBMCs were cultured with IL 4 and GMCSF. Immature DCs phagocytosed flu infected apoptotic 3T3 cells and were then matured with TNF and PGE2 and treated with either no drug treatment or FK506. DCs were analyzed by flow cytometry for markers of maturation. Antigen presenting DCs were then cocultured with MACS purified CD8 or CD4 T cells and either plated in an IFNγ elispot directly or cultured for seven days. At the end of a week, the cocultured T cells are assayed for IFNγ production in response to a directly influenza infected DC via elispot.

Results: DCs pretreated with FK506 were blocked in their ability to activate CD4 and CD8 T cell responses to exogenously acquired antigen in the IFNγ elispot assay. To evaluate whether this lack of response was because those T cells remained ignorant or whether they had been actively tolerized, the T cells were kept in culture for seven days. One week later they were recultured with flu infected DCs. If they remained ignorant the expected outcome upon subsequent antigen encounter with such a maximally inflammatory stimulus would be activation. However, T cells which had been previously cocultured with an FK506 pretreated DC, remained blocked in their ability to respond, indicating that they had indeed been tolerized.

Conclusion: This work implies a novel therapeutic approach to tolerizing antigen specific T cells through manipulation of DCs. Previously it has been shown that immature DCs presenting antigen lead to tolerance, but these DCs do not express CCR7 or traffic to lymph nodes. The FK506 pretreated DCs used in the above assays have been matured ex-vivo and despite expression of all markers of maturation, lend a tolerogenic phenotype which endures even upon subsequent stimulation with a maximally inflammatory stimulus. The significance of this project is that it is possible that FK506 pretreated DCs could be used as a vaccine which upon injection, would allow for DCs which would traffic to lymph nodes and efficiently tolerize aberrant T cell responses.

Disclosure: D. E. Orange, None; **N. Blachere**, None; **R. Darnell**, None.

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Regulatory Natural Antibodies to Apoptotic Cell Membrane Determinants Inhibit Pro-Inflammatory Responses to Activating IgG Autoantibody Immune Complexes Implicated in Autoimmune Pathogenesis. Jaya Vas, Caroline Gronwall and Gregg J. Silverman, UC San Diego, La Jolla, CA

Purpose: Immune complexes (IC) containing Fc-receptor activating IgG autoantibodies, in combination with released nuclear antigens released from dying cells, have been implicated in autoimmune pathogenesis. We have recently demonstrated that naturally arising IgM antibodies (NAbs) to apoptotic cell membrane (ACM) determinants, such as phosphorylcholine, recruit early complement factors and suppress pro-inflammatory responses of dendritic cells and macrophages to purified agonists to TLR3, TLR4, TLR7 and TLR9. A monoclonal IgM PC-specific anti-ACM antibody was also shown to inhibit in vivo TLR responses and block the induction of collagen-induced arthritis. To better understand the potential functional roles of regulatory anti-ACM NAbs, we investigated the effects on IgG autoantibody-IC driven responses.

Method: For in vivo studies, we assessed the effect on IgG anti-collagen type II (CII) induced inflammatory arthritis. For in vitro analyses, we investigated the effects on IgG IC- that result from dual stimulation through activating FcgR and TLR9, in which bone marrow-derived DC dendritic cells (BMDCs) were stimulated with titrated concentrations of the anti-chromatin Moabs PL2-3(IgG2a) or PL2-8(IgG2b).

Results: In a standard passive transfer model in which arthritis was induced by i.v. administration of 2 mg of IgG anti-CII mixture, weekly treatment with 2 mg of the IgM anti-ACM regulatory antibody significantly prevented the development of clinical arthritis in BALB/c mice, compared to saline or isotype control treatment. These effects correlated with inhibition of cartilage destruction and boney erosions. For in vitro studies, we found that either the IgG2a and IgG2b anti-chromatin Moabs, or supernatants from primary necrotic cells alone, induced TNF-alpha and IL-6 production from BMDCs, with further increases induced by co-stimulation with IgG autoantibody and necrotic supernatants. Importantly, incubation with IgM anti-ACM NAb, but not isotype control, significantly blunted the production of TNF-a and IL-6 by DCs induced by necrotic cell supernatants, and also inhibited these responses to IgG anti- chromatin autoantibodies, or incubation with both IgG anti-chromatin antibody and necrotic cell supernatant. The level of cytokine inhibition by the regulatory anti-ACM Ab was comparable to that associated with dexamethasone, a potent glucocorticoid.

Conclusion: Our studies demonstrate that regulatory IgM anti-ACM NAb can suppress inflammatory arthritis induced by pathogenic IgG autoantibody-immune complexes, and similarly inhibit autoantibody-mediated activation and cytokine production by conventional dendritic cells. These studies support a potential physiologic role for regulatory anti-ACM NAbs for maintaining homeostasis and for opposing pathogenic IgG autoantibody-IC mediated inflammatory responses.

Disclosure: J. Vas, None; **C. Gronwall**, None; **G. J. Silverman**, None.

ACR Concurrent Abstract Sessions

Osteoarthritis Epidemiology & Imaging
Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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The Relationship Between Weight Maintenance and Incident Radiographic Knee Osteoarthritis: The Johnston County Osteoarthritis Project. Lauren M. Abbate[1], June Stevens[1], Todd A. Schwartz[1], Leigh F. Callahan[1], Jordan B. Renner[1], Charles G. Helmick[2] and Joanne M. Jordan[1], [1]The University of North Carolina, Chapel Hill, NC, [2]Centers for Disease Control and Prevention, Atlanta, GA

Purpose: On average, adults gain weight throughout most of their life span. Weight loss is difficult to achieve, and it is possible that weight maintenance is a more attainable goal for some individuals. The purpose of this study is to determine if weight maintenance is an effective strategy to reduce the risk of incident radiographic knee osteoarthritis (rKOA).

Methods: Data were from the Johnston County Osteoarthritis Project, a longitudinal study of African-Americans and Whites aged 45 years and older in Johnston County, NC from T_0 (1990-1998) to T_1 (1999- 2003 (n=1,480). Weight change was defined as change from initial weight and was coded as a 5-level variable with categories defined as: ≥5% loss, >3 to <5% loss, ± 3%, >3 to <5% gain, and ≥5% gain. Indicator variables were used to make contrasts between ≥5% loss (weight loss), ± 3% (weight maintenance), and ≥5% (weight gain) with weight gain as the referent. Incident rKOA was defined as Kellgren-Lawrence (K-L) grade of 0 or 1 at T_0 and K-L ≥ 2 at T_1. Knee-based Weibull proportional hazards models with adjustment for the correlation between knees were used to calculate hazard ratios and 95% confidence intervals for the association between weight change incident rKOA. All models were adjusted for age, race, sex, height, and the mean of weights from T_0 and T_1.

Results: Of the 1,480 individuals, 63.2% were female and 25.9% were African-American with mean (SD) age and BMI of 59.4 (9.4) years and 28.6 (5.5) kg/m^2, respectively. Mean (SD) follow-up time was 5.9 (1.3) years (range 3.6 to 13.2), during which rKOA developed in 415 (14.9%) of 2,788 knees. Compared to those who gained weight (31.4%), those who maintained weight (32.8%) were no less likely to develop incident rKOA [HR=1.02 (95% CI=0.77, 1.35)], but those who lost weight (16.7%) were at reduced risk [0.71 (0.49, 1.01)].

Conclusion: Weight loss, but not weight maintenance, may be an effective strategy to reduce the risk of incident rKOA.

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Incidence of Severe Knee and Hip Osteoarthritis in Relation to Dietary Intake of Antioxidants Beta–Carotene, Vitamin C, Vitamin E and Selenium: a Population-Based Prospective Cohort Study. Gunnar Engström[1], Maria Gerhardsson de Verdier[2], Peter M. Nilsson[3], Elisabet Wirfält[3], Carl Mellström[2], Jan Rollof[2] and Stefan Lohmander[3], [1]Lund University, Sweden, [2]AstraZeneca R&D, Lund, Sweden, [3]Lund University, Lund, Sweden

Purpose: The relationship between dietary factors, in particular antioxidants, and osteoarthritis (OA) remains unclear. This prospective population-based study explored the relationships between intake of antioxidants and incidence of severe hip and knee osteoarthritis.

Method: The Malmö Diet and Cancer cohort (n=28098, age 45-73 years, 61% women) was established between 1991 and 1996. A modified diet history method was used to assess dietary habits. Incidence of severe knee and hip OA, defined as new cases of arthroplasty due to hip or knee OA, was monitored until 2005, in relation to energy-adjusted intakes of Vitamin C, Vitamin E, β–carotene and selenium.

Results: A total of 465 incident cases of knee OA and 554 of hip OA occurred during the follow-up. After adjustments for risk factors, high dietary intake of Vitamin C and selenium was significantly associated with incidence of hip OA [hazards ratio: 1.45 (95%CI:1.09-1.9) and 1.32 (95%CI: 1.01-1.7), respectively, for the highest versus lowest quintile of the antioxidant]. When consumption of antioxidant

supplements was taken into account, high selenium intake was significantly associated with incidence of both hip and knee OA. There was no evidence of any protective effect for any of the antioxidants.

Table 3. Intake of four antioxidants in relation to knee or hip OA during follow-up.

	Knee OA			**Hip OA**		
	yes	**no**	**P**	**yes**	**No**	**P**
N	465	27196		544	27055	
Beta-carotene	4.1+3.6 (3.2)	3.8+3.4 (2.8)	0.03	4.0+3.1 (3.2)	3.8+3.4 (2.8)	0.11
Beta-carotene*	4.2+3.6 (3.2)	3.9+3.9 (2.8)	0.05	4.1+3.4 (3.2)	3.9+3.9 (2.8)	0.10
Vitamin E	10.4+4.2 (9.6)	10.6+4.3 (9.8)	0.26	10.5+4.0 (9.5)	10.6+4.3 (9.8)	0.94
Vitamin E*	17.1+27 (10.9)	16.1+28 (11.1)	0.14	15.4+16 (11)	16.1+28 (11)	0.90
Vitamin C	114+62 (103)	110+62 (98)	0.01	116+59 (105)	110+62 (98)	0.01
Vitamin C*	174+243 (124)	175+267 (116)	0.24	166+194 (120)	176+268 (116)	0.39
Selenium	40.3+14 (38)	39.3+14 (37)	0.007	41.7+16 (39)	39.2+14 (37)	<0.001
Selenium*	49.1+27 (41)	46.9+26 (40)	0.02	51.8+29 (43)	46.8+26 (40)	<0.001

*including supplements

Values are crude mean±SD (median). Log transformed values used for calculation of p-values, adjusted for age, sex, method, log energy, season

Conclusion: In this population-based study, there was no evidence of a protective effect of antioxidants against severe knee or hip OA leading to arthroplasty. The association between high intake of Vitamin C and selenium and incidence of severe OA needs to be confirmed by other prospective studies with data on diet and intake of supplements.

Disclosure: G. Engström, AstraZeneca, 3 ; **M. Gerhardsson de Verdier**, AstraZeneca, 3 ; **P. M. Nilsson**, None; **E. Wirfält**, None; **C. Mellström**, AstraZeneca, 3 ; **J. Rollof**, AstraZeneca, 3 ; **S. Lohmander**, AstraZeneca, 2 .

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Association of Osteoarthritis-Related Knee Pain with a Functional Polymorphism of the Catechol-O-Methyltransferase Gene. T. Neogi[1], K. Wang[1], C. Kammerer[2], R. Ferrell[2], M. Garcia[3], C. K. Kwoh[2], T. Harris[3], S. Satterfield[4], P. Caserotti[3] and M.C. Nevitt[5], [1]BUSM, Boston, MA, [2]UPittsburgh, Pittsburgh, PA, [3]NIA, Bethesda, MD, [4]UofTennessee, Memphis, TN, [5]UCSF, San Francisco, CA

Purpose: Pain related to musculoskeletal complaints is the most common reason for outpatient visits, with knee being the primary site of pain, yet little is understood about pain in musculoskeletal conditions. It is well known that in osteoarthritis (OA) there are individuals in whom their symptoms appear to be discordant with the degree of disease on radiographs. Some of this between-person variability may be related to genetic factors that contribute to the experience of pain. Recently, a functional polymorphism of the catechol-O-methyltransferase (*COMT*) gene has been reported to be associated with pain sensitivity, as well as hip-OA related pain. We evaluated the association of a functional polymorphism of *COMT* with knee pain, particularly OA-related knee pain, among well-functioning older adults.

Methods: Health, Aging and Body Composition Study is a longitudinal study of well-functioning elders. Genotypes of the Val158Met (rs4680) *COMT* polymorphism were determined by the TaqMan procedure (Applied Biosystems, Inc), with 5% blind duplicate procedures, and quality control with direct sequencing of a subset of samples. At baseline, participants were asked whether they had knee pain on most days: 1) of a month in the past 12 months; 2) of the past 30 days; or 3) moderate or worse pain with any activity by WOMAC. Those with knee pain and selected controls had knee x-rays. Presence of radiographic OA was defined as Kellgren and Lawrence grade ≥2 or presence of patellofemoral OA. We evaluated the association of having ≥1 methionine (Met) allele of the rs4680 SNP (dominant mode of inheritance) with presence of knee pain on most days of the month in the past 12 months, and of the past 30 days using logistic regression, adjusting for age, sex, BMI, depressive symptoms (CES-D), race and presence of radiographic OA.

Results: There were 1128 individuals who had x-rays taken (mean age 74.6±2.9, 58.5% female, mean BMI 27.7±5 kg/m^2, 66% with ≥1 Met allele, 50% with knee OA). Having ≥1 Met allele in the rs4680 SNP was associated with presence of knee pain on most days of a month of the past 12 months (adj OR 1.44, 95% CI 1.09-1.91), as well as pain on most days of the past 30 days (adj OR 1.43 95% CI 1.08-1.89), with effects attenuated after adjustment for race due to allele frequency differences (past 12 months: adj OR 1.31 (0.98-1.74); past 30 days adj OR 1.26 (0.95-1.68)), but with no effect measure modification by race noted (similar effect estimates in both races). Similar effects were noted for pain among those with knee OA ((past 12 months: adj OR 1.29 (0.84-1.99), past 30 days: adj OR 1.27 (0.83-1.95)).

Conclusion: The Val158Met functional polymorphism of *COMT* was associated with knee pain. This *COMT* polymorphism may explain in part the observed variation in pain and structural abnormalities noted in persons with OA, and needs to be replicated in larger samples.

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Pain in One Knee Increases the Risk of Tibiofemoral Osteoarthritis in the Contralateral Knee: The MOST Study. J. Niu[1], David T. Felson[2], M. Nevitt[3], P. Aliabadi[1], C. Lewis[4], B. Sack[1], J. Torner[5] and Yq. Zhang[1], [1]BUSM, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]UCSF, San Francisco, CA, [4]UAB, Birmingham, AL, [5]UIowa, Iowa City, IA

Purpose: Several studies have reported that painful nonosteoarthritic knees have an increased risk of radiographic tibiofemoral osteoarthritis (TF OA). As gait usually changes when a person develops knee pain, we expect the risk of TF OA would also increase in a contralateral nonpainful knee due to unloading of the painful side. We examined the relationship of knee pain on one side to the risk of TF OA on the contralateral side in the Multicenter Osteoarthritis (MOST) Study.

Method: The MOST Study is a NIH-funded longitudinal observational study of subjects who have or are at high risk for knee OA. PA and lateral view knee X-rays were taken at baseline and 30-month follow-up. Among knees without whole knee OA (K/L grade <2 and no patellofemoral (PF) OA) at baseline, we defined a knee as having incident TF OA if its K/L grade ≥2 at 30-month or had knee replacement during follow-up period. Frequent knee pain (FKP, pain on most days of the past 30 days) and severity of knee pain (SKP, WOMAC knee pain subscale, categorized as 0, 1-5, 6-20) were collected at baseline. We divided knees into 4 groups based on which side was affected by FKP and 9 groups based on the side of their SKP. We examined the relation of FKP and SKP categories to the risk of TF OA using logistic regression model adjusting for age, sex, BMI, history of knee injury and surgery, depression (CES-D≥16), whole knee OA status of the contralateral side at baseline while accounting for the correlation between two knees using GEE. We repeated the analyses among the knees without any OA feature at TF and PF joints at baseline (i.e., K/L grade, osteophyte, joint space narrowing score =0).

Results: Of 3094 knees (from 1844 subjects, mean age 61.3 years, mean BMI 29.6 kg/m^2, 57.2% women) without whole knee OA at baseline, 191 developed TF OA over 30-month period. Compared with those without FKP on both sides, odds ratios (OR) of developing TF OA were 4.7 (95% CI: 2.9, 7.4) in the ipsilateral knee and 2.1 (95% CI: 1.3, 3.2) in the contralateral knee among persons with unilateral knee pain, while the OR was 2.7 (95% CI 1.8, 4.1) among persons with bilateral knee pain. A similar pattern was also observed for SKP (see Table). Results did not change much when analyses were restricted to the knees without any OA feature at baseline.

Conclusion: We confirmed that knees with pain had a higher risk of TF OA than those without pain. In addition, we observed that the contralateral knee in persons with unilateral knee pain was also at higher risk of TF OA than the knees in persons without knee pain. Our findings provide support for the concept that knee pain may change knee loading and increase the risk of TF OA in a contralateral nonpainful knee.

Table. Severity of knee pain and risk of TF OA

Severity of pain in the same knee	Severity of pain in the other knee		
	0	1-5	6-20
0	1.0 (Ref)	1.8 (0.9, 3.7)	2.3 (1.0, 5.3)
1-5	2.8(1.3, 6.0)	2.2(1.2, 3.8)	3.8 (2.0,7.2)
6-20	11.9 (5.2, 27.2)	7.8 (4.1, 15.1)	4.1 (2.2, 8.0)

Disclosure: J. Niu, None; **D. T. Felson**, None; **M. Nevitt**, None; **P. Aliabadi**, None; **C. Lewis**, None; **B. Sack**, None; **J. Torner**, None; **Y. Zhang**, None.

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Bone Mineral Density Is Associated with Dynamic Joint Loads in Osteoarthritis Predisposed Knees. Anisha Dua[1], Laura E. Thorp[1], Joel A. Block[1] and Najia Shakoor[2], [1]Rush-University Med Ctr, Chicago, IL, [2]Rush University Medical Center, Chicago, IL

Purpose: We have previously shown that subjects with endstage unilateral hip osteoarthritis (OA) more commonly develop endstage OA of the contralateral knee rather than the ipsilateral knee, and that these subjects have higher dynamic joint loads at the contralateral knee than the ipsilateral knee. Local bone mineral density (BMD) reflects the loading history of that bone; hence, BMD may be a marker of excessive loading of the knee joint as well as of early asymptomatic OA. Here, we evaluated subjects who had unilateral hip OA but who were asymptomatic at their knees, to test the hypothesis that asymmetric loading of the knees induced by unilateral hip OA results in elevated BMD at the medial tibial plateau of the contralateral knee compared with the ipsilateral knee, and that these BMD asymmetries correlate with dynamic joint loading at the knees.

Method: Fifty subjects with symptomatic unilateral hip OA and asymptomatic knees were evaluated. Subjects had moderate to severe radiographic unilateral hip OA using the Kellgren Lawrence (KL) grading system. Subjects were asymptomatic at the knees (WOMAC pain during walking <20 mm out of 100 mm). Subjects underwent DXA scanning of bilateral knees and these scans were evaluated in a blinded manner by a trained investigator using a previously validated method. The BMD of the medial and lateral regions of the tibial plateau and the distal tibial shaft were measured in each knee. Subjects also underwent gait analyses using an optoelectronic camera system and multicomponent force plate. Inverse dynamics were used to calculate dynamic joint loads and the peak external knee adduction moment, a validated marker of medial compartment knee loading, was used as the primary load parameter. Paired t-tests were used to evaluate differences in BMD and loading between the knees and Spearman correlations were used to evaluate correlations between BMD and loading. $p<0.05$ was considered significant.

Results: Bone mineral density was significantly increased at the contralateral medial tibial plateau compared with the ipsilateral medial tibial plateau (0.912g/cm^2±0.208 vs 0.869g/cm^2±0.196 p=0.040). Furthermore, a direct correlation was found between the medial knee load (peak external knee adduction moment) and BMD at the contralateral medial knee (rho=0.381, p=0.008). No significant differences were noted for BMD at the lateral compartments of the two knees.

Conclusion: This study demonstrates that unilateral hip OA is associated with increased BMD at the contralateral medial knee when compared with the ipsilateral medial knee, that BMD alterations are directly correlated with loading alterations at the OA-predisposed knee (contralateral knee), and that these events occur even in asymptomatic, clinically uninvolved knees. These findings suggest that BMD alterations may be a surrogate marker for joint loading and OA progression, even in asymptomatic subjects. Although further investigation is necessary to delineate causal relationships, BMD may be a useful tool to follow structural progression in longitudinal OA studies.

Disclosure: A. Dua, None; **L. E. Thorp**, None; **J. A. Block**, None; **N. Shakoor**, None.

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The Association Between Patella Alta and Structural Features of Patellofemoral Joint Osteoarthritis (OA) On MRI: The MOST Study. J.J. Stefanik[1], Y. Zhu[1], A.C. Zumwalt[1], K.D. Gross[2], M. Clancy[1], J. A. Lynch[3], L.A. Frey Law[4], C.E. Lewis[5], F.W. Roemer[1], C.M. Powers[6], A. Guermazi[1] and David T. Felson[7], [1]BUSM, Boston, MA, [2]MGH Inst Health Prof, Boston, MA, [3]UCSF, San Francisco, CA, [4]UIowa, Iowa City, IA, [5]UAB, Birmingham, AL, [6]University of Southern California, Los Angeles, CA, [7]Boston University School of Medicine, Boston, MA

Purpose: Research on risk factors for patellofemoral joint (PFJ) osteoarthritis (OA) has focused on PFJ alignment and trochlear morphology. Patella alta (PA), a high riding patella, has received much less attention despite being a known risk factor for patellar subluxation and dislocation in young persons. PA is measured by the Insall-Salvati ratio (ISR), the ratio between the length of the patellar tendon and length of the patella. One possible mechanism for PFJ OA development is decreased contact area between opposing joint surfaces causing increased stress on cartilage and bone. Recently the ISR, but not patellofemoral alignment, has been shown to be associated with decreased contact area in the PFJ. The purpose of this study was to examine the relation of the ISR to prevalence of cartilage damage and measures of bone damage, specifically bone marrow lesions (BMLs) and subchondral bone attrition (SBA), in the lateral PFJ compartment.

Methods: The MOST study is an NIH funded cohort study of persons aged 50-79 years with or at risk for knee OA. We measured the ISR on the baseline flexed and weight bearing lateral radiographs in 486 knees, one knee per subject. Cartilage damage, BMLs, and SBA were graded at baseline on MRI using the WORMS scale (0-6, 0-3, and 0-3 respectively) on the patellar and trochlear facets. We divided the ISR into quartiles and dichotomized cartilage damage (≥2), BMLs (≥1), and SBA (≥1) into presence or absence of pathology. We examined the association between the ISR and cartilage damage, BMLs, and SBA in the lateral PFJ using logistic regression with GEE to account for the correlation between patellar and trochlear readings from the same knee. All analyses were adjusted for age, sex, and BMI.

Results: The mean age of the sample was 62, mean BMI 30, mean ISR 1.10, and 60% of subjects were female. Of the 486 knees studied, 35% had cartilage damage, 21% BMLs, and 14% SBA. Compared with subjects in the lowest ISR quartile, those in the highest quartile had 2.7 (95% CI 1.8, 4.4), 3.2 (1.9 5.4), and 6.0 (3.0, 12.4) times more likely to have lateral PFJ cartilage damage, BMLs, and SBA respectively.

Conclusion: Subjects with a high ISR, indicative of patella alta, are more likely to have cartilage damage, BMLs, and SBA in the lateral PFJ, supporting the hypothesis that subjects with an increased ISR have increased PFJ stress. Future research is needed to evaluate whether a high ISR increases the risk of PFJ OA and to investigate the association between the ISR, measures of PFJ alignment, PFJ OA, and pain.

Insall-Salvati Ratio (ISR)

	Quartile 1	Quartile2	Quartile 3	Quartile 4	P for trend
	0.64-0.99	1.00-1.08	1.09-1.20	1.21-1.58	(continuous ISR)
	n=128 knees	n=106 knees	n=128 knees	n=124 knees	
	(low)			(high)	
Cartilage Damage					
% WORMS ≥2	25	36	32	46	
Adjusted OR (95% CI)	1.0 (reference)	1.7 (1.0, 2.7)	1.5 (0.9, 2.3)	2.7 (1.8, 4.4)	<0.0001
Bone Marrow Lesions					

% WORMS ≥1	14	19	18	32	
Adjusted OR (95% CI)	1.0 (reference)	1.4 (0.8, 2.6)	1.3 (0.7, 2.3)	3.2 (1.9 5.4)	<0.0001
Subchondral Bone Attrition					
% WORMS ≥1	6	17	10	25	
Adjusted OR (95% CI)	1.0 (reference)	3.3 (1.6, 7.0)	1.7 (0.8, 3.7)	6.0 (3.0, 12.4)	<0.0001

Disclosure: J. J. Stefanik, None; **Y. Zhu**, None; **A. C. Zumwalt**, None; **K. D. Gross**, None; **M. Clancy**, None; **J. A. Lynch**, None; **L. A. Frey Law**, None; **C. E. Lewis**, None; **F. W. Roemer**, None; **C. M. Powers**, None; **A. Guermazi**, BICL, LLC, 4, Synarc, Inc., 1, GE Healthcare, 2, MerckSerono, Facet Solutions, 5 ; **D. T. Felson**, None.

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Therapy: Biologic Therapy

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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Smoking Is Associated with Non-Response to Methotrexate and to Anti-TNF Treatment in Patients with Rheumatoid Arthritis. Results From the Swedish EIRA Study. Saedis Saevarsdottir[1], Sara Wedrén[2], Maria Seddighzadeh[2], Johan Askling[1], Leonid Padyukov[2], Lars Alfredsson[2] and Lars Klareskog[1], [1]Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden

Purpose: Smoking is a well established risk factor for rheumatoid arthritis (RA), and the aim of this study is to evaluate whether smoking influences response to methotrexate (MTX) and anti-TNF therapy.

Methods: Clinical data for patients participating in a Swedish population-based study of incident RA (Epidemiological Investigation of Rheumatoid Arthritis, EIRA), who have received routine care, where retrieved from the Swedish Rheumatology and Biologics Registers (SRR/ARTIS, n=1756). Cigarette smoking (never, past or current and pack-years), RF and anti-CCP positivity and the presence of the shared epitope allele (SE) was defined by standard procedures. The primary endpoint was non-response to MTX or anti-TNF therapy at 3 months according to the EULAR response criteria, which is defined as less than 0.6 DAS28 units improvement or DAS28>5.1. Clinical data and information about anti-CCP, RF and SE status were available for 815 out of 965 patients started on MTX monotherapy at baseline and for 320 out of 375 patients that had started anti-TNF therapy as the first biological treatment until the end of the follow-up period. The data were analysed using logistic regression with uni- and multivariate models and presented as odds ratios with 95% confidence interval (OR[95%CI]).

Results: Smoking was associated with non-response to both MTX and anti-TNF treatment. For MTX treatment, 40% of current smokers and 28% of never smokers were non-responders (OR 1.8[1.2-2.7]). However, no clear dose response effect was observed between number of pack-years and response. For anti-TNF therapy, 40% of current smokers and 25% of never-smokers were non-responders (OR 2.0[1.1-3.7]). Whether the patients had concurrent MTX therapy did not influence these findings. When the patients were grouped according to number of pack-years of cigarette smoking into 0, 1-15, 16-30 and >30 pack-years; the frequency of non-response to anti-TNF therapy was 25%, 31%, 40% and 43%, respectively (OR: Ref., 1.3[0.72-2.5], 2.0[1.0-4.0] and 2.3[1.0-5.4]). The risk associated with smoking was significant after adjustment for clinical co-variables, anti-CCP, RF and SE in a multivariate model.

Conclusion: Cigarette smokers had a higher risk of non-response to both MTX and to anti-TNF treatment in this population based study on incident RA receiving real-life care.

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Rituximab in Combination with Methotrexate (MTX) Significantly Inhibits Joint Damage and Improves Clinical Outcomes in Patients with Early Active RA Who Are Naïve to MTX: A Randomized Active Comparator Placebo-Controlled Trial (IMAGE). Paul P. Tak[1], William F. C. Rigby[2], Andrea Rubbert-Roth[3], Charles G. Peterfy[4], Ronald F. van Vollenhoven[5], William Stohl[6], Eva Hessey[7], Annie C. Chen[8], Helen Tyrrell[7] and Tim M. Shaw[7], [1]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, [3]University of Cologne, Cologne, Germany, [4]Synarc Inc., San Francisco, CA, [5]The Karolinska Institute, Stockholm, Sweden, [6]Univ Southern California, Los Angeles, CA, [7]Roche Products Ltd, Welwyn Garden City, United Kingdom, [8]Genentech, Inc, South San Francisco, CA

Purpose: To evaluate clinical and radiographic outcomes with rituximab (RTX) plus MTX compared with MTX alone in patients (pts) with active rheumatoid arthritis (RA) not previously treated with MTX.

Methods: Key inclusion criteria were: no prior exposure to MTX; disease duration <4 years; swollen and tender joint count each ≥8; C-reactive protein (≥1.0 mg/dL), rheumatoid factor positive, or erosive damage. Pts were randomized to either placebo (Plc) + MTX, RTX (2 x 500mg) + MTX or RTX (2 x 1000 mg) + MTX. MTX was initiated in all groups at 7.5 mg/wk and titrated to 20 mg/wk by Wk 8. RTX was given by IV infusion on Days 1 and 15 with a 24-week repeat treatment schedule based on DAS28≥2.6. Radiographs, taken at screening, Wks 24 and 52, were read centrally using the Genant-modified Sharp method (mTSS). The primary endpoint was the change from screening in the mTSS at Wk 52. Secondary endpoints included Major Clinical Response (MCR; ACR70 maintained for at least 6 months).

Results: 755 pts were randomized (715 radiographically evaluable). Groups were balanced at baseline (mean RA duration of 0.9 years and DAS28 >7). At 52 wks, only RTX (2 x 1000 mg) + MTX was associated with both a significant decrease in radiographic progression and improved clinical outcomes as compared with Plc + MTX (Table). Notably, the radiographic and clinical benefits in the RTX (2 x 1000mg) + MTX group were observed by Week 24 with evidence of increased inhibition of joint damage from Wk 24–52.

	Plc + MTX	**RTX (2 x 500 mg) + MTX**	**RTX (2 x 1000 mg) + MTX**
Radiological	n=232	n=239	n=244
Mean change in mTSS at 24 wks	0.70	0.58	0.33*
Mean change in erosion score at 24 wks	0.49	0.40	0.22**
Mean change in mTSS at 52 wks	1.08	0.65	0.36**
Mean change in erosion score at 52 wks	0.74	0.45	0.23***
Clinical	n=249	n=249	n=250
ACR50 (%)	41.8	59.4***	64.8***
ACR70 (%)	24.9	42.2***	46.8***
MCR (%)	8.0	17.3*	18.4**
DAS remission (%)	12.6	25.4**	30.5***
Mean change in DAS28	n=244	n=247	n=248
	-2.06	-3.05***	-3.21***

**p<0.05, **p<0.001, ***p<0.0001 compared with Plc + MTX.*

Safety data were consistent with those previously reported. The rate of serious infections was 6.09, 4.61 and 3.73 events/100 pt-years in the Plc + MTX, RTX (2 x 500 mg) and RTX (2 x 1000 mg) groups, respectively. Three deaths occurred (pneumonia [2] and cerebral infarct): all were in the Plc + MTX arm.

Conclusion: In pts with early active RA, RTX (2 x 1000 mg) + MTX significantly improved clinical outcomes and inhibited joint damage, compared with MTX alone.

Disclosure: P. P. Tak, Roche Pharmaceuticals, 2, Merck-Serono, 2, Roche Pharmaceuticals, 5, Genentech and Biogen IDEC Inc., 5 ; **W. F. C. Rigby**, Genentech and Biogen IDEC Inc., 5, Genentech and Biogen IDEC Inc., 8 ; **A. Rubbert-Roth**, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Abbott Laboratories, 5, UCB, 5, Essex, 5, Bristol-Myers Squibb, 5, Chugai, 5 ; **C. G. Peterfy**, Synarc, Inc., 4 ; **R. F. van Vollenhoven**, Schering-Plough, 2, Abbott Immunology Pharmaceuticals, 2, Wyeth Pharmaceuticals, 2, Roche, 2 ; **W. Stohl**, Xencor, Inc., 2, Xencor, Inc., 5 ; **E. Hessey**, Roche Pharmaceuticals, 3, Roche Pharmaceuticals, 1 ; **A. C. Chen**, Roche Pharmaceuticals, 1, Genentech and Biogen IDEC Inc., 1, Genentech and Biogen IDEC Inc., 3 ; **H. Tyrrell**, Roche Pharmaceuticals, 3 ; **T. M. Shaw**, Hoffmann-La Roche, 3, Hoffmann-La Roche, 1 .

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LITHE: Tocilizumab Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis (RA) Patients (Pts) at 2 Yrs with Increasing Clinical Efficacy Over Time. Roy Fleischmann[1], R. Burgos-Vargas[2], P. Ambs[3], E. Alecock[4] and J. Kremer[5], [1]Metroplex Clinical Research Center, Dallas, TX, [2]Hospital General de México, México, Mexico, [3]Roche, Basel, Switzerland, [4]Roche, Welwyn, United Kingdom, [5]Albany Medical College, Albany, NY

Purpose: To report results of a 2-yr planned analysis of a double-blind, randomized controlled, phase 3 trial of TCZ in pts with moderate to severe RA who remained on MTX despite inadequate response.

Method: Pts were randomized (1:1:1) to receive TCZ + MTX (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or placebo + MTX (control [CON]) every 4 wks. Stepwise rescue therapy starting at wk 16 was allowed if pts did not respond (<20% improvement in SJC and TJC). At wk 52, all pts were required to initiate open-label TCZ8 for yr 2, unless they had achieved ≥ 70% improvement in SJC and TJC, allowing them to continue the blinded therapy they were receiving at the end of yr 1 to wk 104. Primary 2-yr end points were change from baseline in Genant-modified Total Sharp Score (GmTSS) and physical function (AUC of change from baseline in HAQ-DI). Linear extrapolation (GmTSS) or standardization (change in HAQ-DI) was used for missing data (post-rescue data set to missing). To examine impact of 2 yrs of treatment, efficacy end points were assessed over time for pts randomized to TCZ8, with LOCF for SJC and TJC for pts who received rescue therapy or withdrew from that time point.

Results: The ITT population consisted of 398 TCZ8, 399 TCZ4, and 393 CON pts. At 2 yrs, exposure rate per pt-yrs (PY) were 1320, 521.9, and 284.8 in TCZ8, TCZ4, and CON pts. More CON pts required rescue vs TCZ pts, and more TCZ pts remained on initial randomized therapy (Table A). At yr 2, pts in the TCZ8 group had significantly less radiographic progression (81% inhibition) vs CON pts (based on linear extrapolation of mean change in GmTSS on initial treatment for post-rescue data). Significantly more TCZ8 pts had no radiographic progression vs CON pts ($p \leq 0.0001$). AUC of change from baseline in HAQ-DI showed significant improvement in physical function in TCZ4 and TCZ8 vs CON pts (Table A). In pts initially randomized to TCZ8, low disease activity score (LDAS; DAS28 □3.2) was seen in >60%, and DAS28 remission (DAS28 <2.6) rates were ~50% at wk 52 and continued to increase to wk 104 (Table B). By wk 52, in pts treated with TCZ8, clinically significant improvements in SJC occurred (–10) that were maintained through wk 104. Rates/100PY for adverse events (AEs) were higher in TCZ8 and TCZ4 (263.6, 275.4) vs CON pts (251.4) while rates for serious AEs were comparable (11.4, 12.1, 10.9). Rates per 100PY of AEs leading to withdrawal and treatment modification were higher in TCZ8 and TCZ4 (7.4 and 32.5; 8.4 and 30.7) vs CON pts (4.8 and 20.4) and rates for death were comparable (0.6, 0.2, 0.4).

Conclusion: TCZ + MTX continues to inhibit radiographic progression and improve physical function with a clinical effect, as evidenced by improving DAS28 remission, LDAS, and SJC at 2 yrs and with a manageable safety profile.

Table A. Disposition and selected endpoints at 2 yr in ITT pts

	Initial Randomized Therapy		
	Placebo + MTX	**TCZ 4 mg/kg+MTX**	**TCZ 8 mg/kg+MTX**
Randomized, n	393	399	398
Disposition			
Withdrawals, % (n)	27 (104)	22 (89)	22 (88)
Completed, % (n)	73 (289)	78 (310)	78 (310)
Rescue, % (n)	50 (197)	24 (96)	15 (60)
Open-label TCZ8 at Week 52, % (n)	68 (267)	63 (252)	62 (248)
Remained on randomized therapy at Week 52, % (n)	9 (34)	20 (78)	21 (85)
Mean GmTSS change from baseline	1.96	0.58[a]	0.37[a]
No GmTSS progression, % (n/n)	66 (195/294)	75 (256/343)[b]	83 (292/353)[a]
Adjusted mean AUC of HAQ DI change from baseline	-139.4	-287.5[a]	-320.8[a]

[a] $p \leq 0.0025$ vs placebo +MTX. [b] $p=0.0239$. (n/n)=pts with response/evaluable pts.

Table B. Clinical efficacy data in pts initially randomized to TCZ8

	Baseline TCZ 8 mg/kg+MTX	**Week 52 TCZ 8 mg/kg+MTX**	**Week 104 TCZ 8 mg/kg+MTX**
LDAS, % (n/n)		64 (176/275)	76 (184/241)
DAS remission, % (n/n)		48 (132/275)	65 (156/241)
Mean SJC*	17 (n=398)	7 (n=397)	6 (n=397)
Mean TJC*	29 (n=398)	14 (n=397)	12 (n=397)

(n/n)=pts with response/evaluable pts. Post-rescue data set to missing. LOCF for missing SJC and TJC

Disclosure: R. Fleischmann, Amgen, Wyeth, Centocor, Abbott, Genentech, BiogenIdec, UCB, Regeneron, Lilly, Pfizer, 2, Amgen, Wyeth, Centocor, Abbott, Genentech, Biogen Idec, UCB, AstraZeneca, Pfizer, Lilly, 5, Amgen, Wyeth, Abbott, 8 ; **R. Burgos-Vargas**, Roche Pharmaceuticals, 5 ; **P. Ambs**, Roche Pharmaceuticals, 3 ; **E. Alecock**, Roche Pharmaceuticals, 3 ; **J. Kremer**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 .

Disease Remission Is Achieved within Two Years in Over Half of Methotrexate Naive Patients with Early Erosive Rheumatoid Arthritis (RA) Treated with Abatacept Plus MTX: Results From the AGREE Trial. R. Westhovens[1], M. Robles[2], S. Nayiager[3], J. Wollenhaupt[4], P. Durez[5], J. Gómez-Reino[6], W. Grassi[7], B. Haraoui[8], W. Shergy[9], SH Park[10], H. Genant[11], C. Peterfy[12], J.-C. Becker[13], A. Covucci[13], R. Helfrick[13] and J. Bathon[14], [1]UZ Gasthuisberg, KU Leuven, Leuven, Belgium, [2]Centrol Medico Toluca, Mentpec, Mexico, [3]St Augustine's Hospital, Durban, South Africa, [4]Klinikum Eilbek, Hamburg, Germany, [5]Univ Catholique de Louvain, Brussels, Belgium, [6]Hospital Clinico Univ De Santiago, A Coruna, Spain, [7]Univ Politecnica delle Marche, Ancona, Italy, [8]Institut de Rhumatolgie de Montreal, Montreal, QC, [9]Univ of Alabama, Huntsville, AL, [10]Kangnam St Mary's Hosp, Seoul, South Korea, [11]University of California, San Francisco, CA, [12]SYNARC, Inc, San Francisco, CA, [13]Bristol-Myers Squibb, Princeton, NJ, [14]Johns Hopkins Univ Sch of Med, Baltimore, MD

Purpose: Intensive treatment of patients early in the RA disease process is becoming a standard of care making disease remission, as a treatment goal, more attainable. Here we report the clinical and safety outcomes in methotrexate naïve patients with early erosive RA treated with a combination of abatacept + methotrexate through 24 months.

Method: The AGREE trial was a 24 month study with a 12 month double-blind period (DB) and 12 month open label period (OL). During DB, patients were randomized to ABA (~10 mg/kg dose based on weight range) + MTX (dosed up to 20 mg) or placebo (PLA) + MTX. All patients completing DB and entering OL received ABA + MTX. Safety was assessed in all pts receiving ≥1 dose of ABA in OL. Clinical outcomes evaluated included DAS28 remission (DAS28 <2.6), low disease activity state (LDAS, DAS28 <= 3.2), and ACR responses.

Results: All 459 pts completing DB entered OL; 94.3% completed OL. Remission, LDAS, and ACR responses were sustained or increased from 12 to 24 months in original ABA + MTX arm (Table), with over half (55.2%) in remission at 24 months. Proportion achieving these outcomes in the original MTX alone arm increased after initiating ABA in OL, with 44.5% in remission at 24 months. Rates (per 100 pt yrs) of serious AE (6.42 vs 8.35) and serious infections (1.73 vs 2.04) were similar in the OL vs DB respectively. Autoimmune events occurred at a similar rate in OL as in DB (1.30 vs 2.47, respectively). Two deaths occurred. No malignancies or TB were reported.

Clinical Outcomes, (%)

	ABA + MTX (DB & OL) (N=232)		**MTX Alone (DB) → ABA + MTX (OL) (N=227)**	
	Baseline to Yr 1	**Yr 1 to Yr 2**	**Baseline to Yr 1**	**Yr 1 to Yr 2**
DAS(28) Remission	46.1	55.2	26.9	44.5
LDAS	60.8	71.1	43.2	60.4
ACR 50	64.7	74.1	50.2	67.0
ACR 70	48.3	53.9	31.7	49.8
ACR 90	18.5	22.0	7.5	22.9

Conclusion: Sustained disease remission is an achievable goal for many patients with early RA when treatment with combination of ABA + MTX is initiated early. Consistent with the long-term safety experience in patients with longer standing disease no new or unexpected safety signals occurred in this population. These data support the use of ABA + MTX in an early RA population.

Disclosure: R. Westhovens, Bristol-Myers Squibb, 8, Bristol-Myers Squibb, Schering-Plough, Centocor, Roche, 5, UCB , 2 ; **M. Robles**, None; **S. Nayiager**, None; **J. Wollenhaupt**, Bristol-Myers Squibb, 5 ; **P. Durez**, UCL, 3, Bristol-Myers Squibb, Roche, Centocor, Abbott, Wyeth, 5, UEMS, Royal Belgian Society of Rheumatology, 6, Bristol-Myers Squibb, 8 ; **J. Gómez-Reino**, Wyeth, Schering-Plough, Bristol-Myers Squibb, Roche, 6, Abbott, Wyeth, Roche, Bristol-Myers Squibb, Schering-Plough ; **W. Grassi**, Abbott Immunology, Wyeth, 2, Bristtol-Myers Squibb, Abbott Immunology, Schering-Plough, 5, Bristol-Myers Squibb, Abbott Immunology, General Electric, Esaote, Schering-Plough, Roche, Wyeth, Abbott Immunology, Wyeth, 2, Bristtol-Myers Squibb, Abbott Immunology, Schering-Plough, 5, Bristol-Myers Squibb, Abbott Immunology, General Electric, Esaote, Schering-Plough, Roche, Wyeth ; **B. Haraoui**, Abbott, Amgen, Bristol-Myers Squibb, Roche, Shering-Plough, UCB, Wyeth, 5, Abbott, Amgen, Bristol-Myers Squibb, Roche, Shering-Plough, UCB, Wyeth, 2, Abbott, Amgen, Bristol-Myers Squibb, Roche, Shering-Plough, UCB, Wyeth, 8 ; **W. Shergy**, Amgen, Wyeth, Abbott, Bristol-Myers Squibb, Centocor, Genentech, Biogen-Idec, 9 ; **S. Park**, None; **H. Genant**, Synarc, Inc., 1, Bristol-Myers Squibb, Roche, Genentech, Pfizer, Amgen, Merck, Servier, Biogen-Idec, Lilly, 2, Bristol-Myers Squibb, Roche, Merck, Lilly, Genentech, Amgen, Servier, Synarc, 5 ; **C. Peterfy**, Synarc, Inc., 1, Synarc, Inc., 3 ; **J. -. C. Becker**,

Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **A. Covucci**, Bristol-Myers Squibb, 3 ; **R. Helfrick**, Bristol-Myers Squibb, 3 ; **J. Bathon**, Biogen-Idec, Merck Serono, 2, Crescendo Biosciences, Roche, UCB, 5 .

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Reduced Radiographic Progression in Patients with Early Rheumatoid Arthritis (RA) Treated with Abatacept + Methotrexate Compared to Methotrexate Alone: 24 Month Outcomes. J. Bathon[1], H. Genant[2], S. Nayiager[3], J. Wollenhaupt[4], P. Durez[5], J. Gómez-Reino[6], W. Grassi[7], B. Haraoui[8], W. Shergy[9], SH Park[10], M. Robles[11], C. Peterfy[12], J.-C. Becker[13], A. Covucci[13], R. Helfrick[13] and R. Westhovens[14], [1]Johns Hopkins Univ Sch of Med, Baltimore, MD, [2]University of California, San Francisco, CA, [3]St Augustine's Hospital, Durban, South Africa, [4]Klinikum Eilbek, Hamburg, Germany, [5]Univ Catholique de Louvain, Brussels, Belgium, [6]Hospital Clinico Univ De Santiago, A Coruna, Spain, [7]Univ Politecnica delle Marche, Ancona, Italy, [8]Institut de Rhumatolgie de Montreal, Montreal, QC, [9]Univ of Alabama, Huntsville, AL, [10]Kangnam St Mary's Hosp, Seoul, South Korea, [11]Centrol Medico Toluca, Mentpec, Mexico, [12]SYNARC, Inc, San Francisco, CA, [13]Bristol-Myers Squibb, Princeton, NJ, [14]UZ Gasthuisberg, KU Leuven, Leuven, Belgium

Purpose: Radiographic progression early in the course of RA disease may translate into long term detrimental outcomes. Here we report the 24 month radiographic outcomes in methotrexate (MTX)-naïve patients with early, erosive RA and poor prognostic factors who are treated early with abatacept (ABA) + MTX compared to MTX alone.

Method: The AGREE trial was a 24-month study, with a 12-month double-blind (DB) and a 12-month open-label (OL) period, in adult MTX-naïve patients with early, erosive RA and poor prognostic factors. During the DB, patients were randomized to ABA (~10 mg/kg dose based on weight range) + MTX (dosed up to 20 mg) or placebo (PLA) + MTX. All pts received ABA + MTX during the OL. Radiographic outcomes were assessed using Genant-modified Sharp scores. Changes in erosions [ES], joint space narrowing [JSN] and total score [TS] are reported. A change in TS <= 0 defined nonprogressors.

Results: Of the 459 pts completing DB and entering OL, 94.3% completed the study. Changes in radiographic outcomes from baseline to year 1 and year 1 to year 2 are presented in the table. From baseline through 24 months, patients originally randomized to the ABA + MTX arm experienced less progression of structural damage as measured by change in TS (0.84 vs 1.75) and a greater proportion of nonprogressors (56.8% vs 43.8%) compared to those originally randomized to MTX monotherapy. Moreover, among patients originally randomized to ABA + MTX arm, there was an increasing degree of inhibition of progression seen in year 2 compared to year 1 (TS = 0.18 vs 0.66, respectively, P<0.0001), with 91.1% of year 1 nonprogressors remaining nonprogressors in year 2 compared to patients initiated on MTX alone.

Radiographic Outcomes*				
Mean change Genant-modified Sharp Score	**ABA + MTX (N=213)**		**MTX Alone (DB) → ABA + MTX (OL) (N=192)**	
	Baseline to Yr 1	**Yr 1 to Yr 2**	**Baseline to Yr 1**	**Yr 1 to Yr 2**
ES	0.50	0.09	1.26	0.13
JSN	0.16	0.09	0.22	0.12
TS	0.65	0.18	1.48	0.25
* Data are reported as observed for all treated subjects in open label				

Conclusion: Early use of combination therapy with ABA and MTX results in greater long-term sustainable radiographic benefit in MTX-naïve early RA patients than MTX alone and supports the use of abatacept earlier in the RA disease process.

Disclosure: J. Bathon, Biogen-Idec, Merck Serono, 2, Crescendo Biosciences, Roche, UCB, 5 ; **H. Genant**, Synarc, Inc., 1, Bristol-Myers Squibb, Roche, Genentech, Pfizer, Amgen, Merck, Servier, Biogen-Idec, Lilly, 2, Bristol-Myers Squibb, Roche, Merck, Lilly, Genentech, Amgen, Servier, Synarc, 5 ; **S. Nayiager**, None; **J. Wollenhaupt**, Bristol-Myers Squibb, 5 ; **P. Durez**, UCL, 3, Bristol-Myers Squibb, Roche, Centocor, Abbott, Wyeth, 5, UEMS, Royal Belgian Society of Rheumatology, 6, Bristol-Myers Squibb, 8 ; **J. Gómez-Reino**, Wyeth, Schering-Plough, Bristol-Myers Squibb, Roche, 6, Abbott, Wyeth, Roche, Bristol-Myers Squibb, Schering-Plough, 9 ; **W. Grassi**, Abbott Immunology, Wyeth, 2, Bristtol-Myers Squibb, Abbott Immunology, Schering-Plough, 5, Bristol-Myers Squibb, Abbott Immunology, General Electric, Esaote, Schering-Plough, Roche, Wyeth, 9 ; **B. Haraoui**, Abbott, Amgen, Bristol-Myers

Squibb, Roche, Shering-Plough, UCB, Wyeth, 2, Abbott, Amgen, Bristol-Myers Squibb, Roche, Shering-Plough, UCB, Wyeth, 5, Abbott, Amgen, Bristol-Myers Squibb, Roche, Shering-Plough, UCB, Wyeth, 8 ; **W. Shergy**, Amgen, Wyeth, Abbott, Bristol-Myers Squibb, Centocor, Genentech, Biogen-Idec, 9 ; **S. Park**, None; **M. Robles**, None; **C. Peterfy**, Synarc, Inc., 1, Synarc, Inc., 3 ; **J. -. C. Becker**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, Bristol-Myers Squibb ; **A. Covucci**, Bristol-Myers Squibb, 3 ; **R. Helfrick**, Bristol-Myers Squibb, 3 ; **R. Westhovens**, Bristol-Myers Squibb, 8, Bristol-Myers Squibb, Schering-Plough, Centocor, Roche, 5, UCB , 2 .

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Golimumab and Radiographic Progression in Rheumatoid Arthritis: Results of GO-BEFORE and GO-FORWARD Studies. P. Emery[1], R. Fleischmann[2], Désirée M.F.M. van der Heijde[3], Edward C. Keystone[4], M. C. Genovese[5], P. G. Conaghan[6], E. C. Hsia[7], W. Xu[8], A. Baratelle[9], A. Beutler[8] and M. U. Rahman[7], [1]Univ Leeds, Leeds, United Kingdom, [2]U of Texas Southwest Med Center, Dallas, TX, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Professor of Medicine/University of Toronto, Toronto, ON, [5]Stanford University, Palo Alto, CA, [6]U of Leeds, Leeds, United Kingdom, [7]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [8]Centocor R&D, Inc, Malvern, PA, [9]Centocor, Malvern, PA

Purpose: To evaluate the effect of golimumab (GLM) on radiographic progression in pts with RA.

Methods: In both GO-BEFORE (MTX-naïve pts; n=637) and GO-FORWARD (MTX-inadequately responding (IR) pts; n=444) pts were randomized to PBO+MTX, GLM 100mg+PBO, GLM 50mg+MTX, or GLM 100mg+MTX. Subcutaneous injections were administered q4 wks. The GO-BEFORE had a control period of 52 wks with early escape [EE] at wk 28 and GO-FORWARD had a control period of 24 wks with EE at wk 16. Pts. in control grps meeting EE criteria start receiving GLM 50 mg + MTX. Radiographs of hands and feet at baseline, wk 24 (wk 16 for EE pts) and wk 52 in GO-FORWARD, and baseline, wk 28, and wk 52 in GO-BEFORE were scored by 2 independent readers and an adjudicator using the van der Heijde -Sharp score (vdHS). Different readers were used for the two trials. Linear extrapolation was used for radiographs taken at EE visits.

Results: In the MTX-naïve population, vdHS changes from baseline to wk 52 (co-primary endpoint) in both the 50mg and 100mg GLM+MTX grps were significantly lower compared with those in the PBO+MTX grp (Table). In the MTX-IR population, vdHS changes from baseline to wk 24 (primary analysis) were minimal in all grps, preventing any significant effect of GLM to be detected. The proportion of pts with change in vdHS above the smallest detectable change (SDC=2.58 for the study) was 4 % in the PBO+MTX grp. The lack of progression in the PBO grp may have been due to the short placebo-control period (in PBO+MTX gr 32% EE at wk 16 and remaining pts crossed over at wk 24 to receive GLM) and relatively less active pt population (median CRP of 0.9, lower joint counts, lower baseline vdHS scores) than in previously reported trials in similar populations.

Conclusion: Both GLM 50 + MTX & 100 mg + MTX demonstrated statistically significant and comparable inhibition of radiographic progression in MTX-naïve population compared with MTX alone. In the MTX-IR population the minimal radiographic progression in the MTX alone grp prevented any effect of GLM to be detected.

Table: Total vdHS for pts in GO-BEFORE and GO-FORWARD

	PBO + MTX	GLM 100 mg + PBO	GLM + MTX 50 mg	GLM + MTX 100 mg	GLM + MTX Combined
MTX-naïve (GO-BEFORE)					
Pts randomized	160	159	159	159	318
Total vdHS					
Baseline					
Mean ± SD	19.71±35.44	20.42±30.90	18.69±32.39	18.22±35.47	18.45±33.92
Median (IQR)	5.25 (2.00-18.10)	6.00 (2.50-26.50)	5.50 (2.00-19.50)	6.00 (2.50-18.00)	6.00 (2.00-18.00)
Change from baseline to wk 28					
Mean ± SD	1.11±3.88	0.61±3.55	0.71±3.77	0.01±1.47	0.36±2.88
Median (IQR)	0.0 (0.00-1.00)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
p value		0.054	0.065	0.003	0.005
Change from baseline to wk 52					
Mean ± SD	1.37±4.56	1.25±6.16	0.74±5.23	0.07±1.83	0.41±3.93
Median (IQR)	0.00 (0.00-1.50)	0.00 (0.00-1.00)	0.00 (-0.50-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
p value		0.266	0.015	0.025	0.006
MTX-IR (GO-FORWARD)					
Pts randomized	133	133	89	89	175
Total vdHS					
Baseline					
Mean ± SD	36.70±52.06	37.42±52.45	29.67±39.29	39.57±56.09	34.59±48.49
Median (IQR)	17.50 (1.50-49.50)	15.25 (2.50-49.00)	9.50 (2.00-49.64)	17.00 (3.00-47.00)	14.00 (2.50-49.28)
Change from baseline to wk 24					
Mean ± SD	0.55±2.35	0.27±1.60	0.6±2.74	0.23±1.34	0.41±2.16
Median (IQR)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
p value		0.361	0.953	0.293	0.551
Change from baseline to wk 52					
Mean ± SD	1.10±4.68	0.89±3.37	0.93±4.86	0.15±1.64	0.54±3.64
Median (IQR)	0.00 (0.00-1.10)	0.00 (0.00-1.00)	0.00 (0.00-0.50)	0.00 (0.00-0.85)	0.00 (0.00-0.50)
p value		0.967	0.855	0.221	0.390

P values for comparisons between GLM and PBO+MTX grps, using an analysis of variance on the van der Waerden normal scores.

Disclosure: P. Emery, Centocor Research and Development, Inc, 9 ; **R. Fleischmann**, Centocor Research and Development, Inc, 9 ; **D. M. F. M. van der Heijde**, Centocor Research and Development, Inc., 2 ; **E. C. Keystone**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, 5, Centocor Research and Development, Inc, 9, Centocor Research and Development, Inc, 8 ; **M. C. Genovese**, Centocor, Inc., 2, centocor, 5, Centocor, Inc., 8 ; **P. G. Conaghan**, Centocor, Inc., 5, Novartis Pharmaceutical Corporation, 5, BMS, 5, Roche Pharmaceuticals, 5 ; **E. C. Hsia**, Centocor Research and Development, Inc., 3 ; **W. Xu**, Centocor Research and Development, Inc., 3 ; **A. Baratelle**, None; **A. Beutler**, Centocor, Inc., 3 ; **M. U. Rahman**, Centocor, Inc., 3 .

ACR REF Special Sessions

REF Edmond L. Dubois Memorial Lectureship

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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Mononuclear Phagocytes That Upregulate ITGAM Are Markers of SLE Nephritis Onset and Remission. Ramalingam Bethunaickan, Meera Ramanujam, Haiou Tao and Anne Davidson, Feinstein Institute for Medical Research, Manhasset, NY

Purpose: The onset of lupus nephritis is associated with activation of renal mononuclear phagocytes. Macrophage/DC populations in the nephritic kidney are heterogeneous and may have different effector functions. Our goal was to characterize the major subpopulations of these cells in pre-nephritic, nephritic and remission kidneys of 3 lupus prone murine models that develop different forms of the disease.

Methods: We used multiparameter flow cytometry to phenotype renal CD11b cells and immunohistochemistry to localize the cell types. We sorted the major subpopulations and performed electron microscopy and real time PCR studies. Turnover rate of the subpopulations was determined using BrDU. We used a fluorescent sensor for cathepsin to stain staining of kidneys in vivo. We labeled peripheral blood monocytes in vivo with fluorescent beads and analyzed kidneys by flow cytometry 96 hrs later.

Results: Microarray analysis of nephritic SLE kidneys from mice and humans revealed a macrophage/DC activation signature with marked upregulation of ITGAM (α chain of CD11b) in both mice and humans. Young kidneys contained two CD11b+ populations, a dominant $CD11b^{hi}/F4/80^{hi}/CD11c^{int}/Gr1^{lo}/CD62L^{lo}/VLA\text{-}4^{int}$ population and a much smaller $CD11b^{hi}/F4/80^{int}/CD11c^{int}/Gr1^{hi}/VLA\text{-}4^{hi}$ population, previously described as renal dendritic cells (rDC) and inflammatory macrophages respectively. The rDC population had small dendrites and was located in the renal interstitium in all three strains. Phenotypic analysis of nephritic kidneys showed global activation and expansion of these rDCs with marked upregulation of ITGAM, F4/80 and Ox-40L in all three strains, that reversed completely after remission induction. rDCs became very swollen at onset of proteinuria with large numbers of vacuoles and they secreted inflammatory chemokines and cytokines and displayed increased cathepsin activity. The onset of proteinuria in NZB/W and NZW/BXSB mice with proliferative nephritis was also associated with renal influx of $CD11b^{hi}/CD11c^{hi}/F/480^{int}/GR1^{lo}/CD43^{hi}/CD62L^{lo}/VLA\text{-}4^{hi}$ ($CD11c^{hi}$) cells that disappeared upon remission induction. This population had a veiled cell morphology typical of myeloid DCs. $CD11c^{hi}$ cells secreted inflammatory cytokines but did not become vacuolated or display cathepsin activity. They were located in lymphoid aggregates in NZB/W mice, in glomeruli in NZW/BXSB mice but were rare in NZM2410 mice that have only glomerulosclerosis. BrDU labeling indicated that the rDCs had a turnover rate of 45-60 days whereas the $CD11c^{hi}$ cells turned over in 15 days. Fluorescent bead labeling indicated that rDCs derive from circulating $Gr1^{lo}$ monocytes whereas the $CD11c^{hi}$ DCs derive from a different source.

Conclusion: Lupus nephritis, unlike acute inflammatory nephritis in which there is an influx of $Gr1^{hi}$ inflammatory macrophages, is associated with reversible activation of intrinsic renal dendritic cells expressing increased levels of ITGAM. In mice with proliferative nephritis myeloid dendritic cells migrate into the kidneys, turn over rapidly and disappear upon remission. These two cell types constitute different targets for therapeutic intervention.

Disclosure: R. Bethunaickan, None; **M. Ramanujam**, 33 , Centocor, Inc. ; **H. Tao**, None; **A. Davidson**, None.

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Novel Proteasome Inhibitors Have a Beneficial Effect in Murine Lupus. Travis Ichikawa[1], Tony Muchamuel[2], Jing Jiang[2], Teresa Owen[1], Christopher J. Kirk[2] and Jennifer H. Anolik[3], [1]University of Rochester Medical Center, Rochester, NY, [2]Proteolix, Inc., South San Francisco, CA, [3]University of Rochester, Rochester, NY

Purpose: Most therapies currently used to treat systemic lupus erythematosus (SLE) and B cell targeted therapies under development do not effectively target plasma cells and autoantibodies. We postulated that proteasome inhibition, particularly selective targeting of the immunoproteasome, may be useful in the treatment of SLE by targeting plasma cells and other immune cells critical to disease pathogenesis.

Method: Nephritic NZB/W F1 lupus-prone female mice were treated with the proteasome inhibitors (targeting both the constitutive β5 and immunoproteasome LMP7 subunits) carfilzomib (twice in 24-hour interval) and bortezomib (twice in 36-hour interval), the LMP7-selective inhibitor PR-957 (3 times in 48-hour intervals), or vehicle control intravenously. Spleen (SP) and bone marrow (BM) lymphocytes were

harvested and analyzed by flow cytometry using standard markers, including intracellular kappa light chain and CD138 for identification of plasma cells (PCs). Nephritis was monitored by proteinuria (Uristix) and kidney harvest. Serum anti-dsDNA levels were measured by ELISA (IgG, Alpha Diagnostic International). Total IgG and dsDNA antibody secreting cells (ASC) were measured by ELIspot. MRL/lpr mice with active proteinuria (age 11 weeks) were also treated with proteasome inhibitors for 13 weeks.

Results: Lupus prone mice with active nephritis had a lower tolerance for the dual targeted proteasome inhibitors than previously reported while immunoproteasome inhibition was well tolerated in these animals. Short-term treatment of NZB/W F1 mice with established nephritis (durable proteinurea >=3 or 300mg/dl) with carfilzomib (twice in 24-hour interval), PR-957 (3 times in 48-hour intervals), or bortezomib (twice in 36-hour interval) had profound effects on plasma cells. Specifically, carfilzomib and PR-957 reduced the SP PCs 2.4 and 2.1-fold respectively (1.95% carfilzomib treated vs. 2.2% PR-957 treated vs. 4.71% untreated [n=5]). Strikingly, carfilzomib and PR-957 reduced the frequency of total IgG and anti-dsDNA IgG secreting cells by up to 90% in the spleen (dsDNA ASC frequency: 1.4/10E5 for carfilzomib vs. 10.6/10E5 for PR-957 vs. 21.5/10E5 cells for untreated mice). Anti-dsDNA IgG secreting plasma cells in the BM were reduced to undetectable levels after proteasome inhibitor treatment. The effects of longer term treatment on nephritis are under investigation in this model. However, all 3 agents prevented progression to severe proteinuria in MRL/lpr mice. Bortezomib and PR-957, but not carfilzomib, significantly reduced the levels of serum autoantibodies.

Conclusion: Carfilzomib and PR-957 significantly decrease autoreactive plasma cells in lupus prone mice. Of note, inhibition of the immunoproteasome was equally efficacious to dual targeting agents in preventing lupus disease progression. These results support the utility of proteasome inhibition in the treatment of SLE.

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Gender Specific Association of X-Linked TLR7 with Male SLE. N. Shen[1], Q. Fu[2], Y. Deng[1], J. Zhao[2], X. X. Qian[1], K M. Kaufman[3], Y J. Tang[1], J Y. Chen[4], W L. Yang[5], A. Kawasaki[6], N. Tsuchiya[6], Y. Kawaguchi[7], C Y. Yu[8], H S. Howe[9], Mok MY[5], Y K. Sung[10], J B. Harley[3], J M. Guthridge[3], J M. Grossman[2], R M. Cantor[2], Y W. Song[11], S C. Bae[10], S L. Chen[1], B H. Hahn[2], Y L. Lau[5] and BP. Tsao[2], [1]Ren Ji Hosp, Shanghai, [2]UCLA, LA, CA, [3]Oklahoma Medical Res Fnd, [4]Chang Gung Memorial Hosp, Taiwan, [5]UHK, Hk, [6]Univ of Tsukuba, [7]Tokyo Women's Medical Univ, [8]Ohio State Univ, [9]Tan Tock Seng Hosp, Singapore, [10]Hanyang Univ, [11]Seoul National Univ

Purpose: Duplicated *Tlr7* promotes lupus-like disease in male BXSB-*Yaa* mice, prompting us to evaluate *TLR7* in SLE patients especially in males.

Method: SNP genotyping was conducted using the Illumina Infinium platform in the discovery panel, and Taqman or pyrosequencing in replication panels. Relative expression of *TLR7* mRNA in PBMC was measured by RT-qPCR.

Results: Fine-mapping the 23-kb *TLR7* region using 11 SNPs in 1434 SLE cases of Eastern Asian (EA) descent vs. 1591 EA controls showed association of 2 *TLR7* SNPs with SLE (rs5935436 in the promoter, $p=1.8\times10^{-3}$; rs3853839 in the 3'UTR, $p=6.7\times10^{-4}$). In this discovery panel, the association signal of the 3'UTR SNP was mainly found in Chinese (cases/controls; 563/522, $p = 6.3\times10^{-6}$) with a higher OR in males than females (OR = 5.6 vs. 1.5), but not detected in Koreans (845/1022). This association with SLE with a stronger male effect was replicated in both independent panels of Chinese (2133/2069, $p = 1.8\times10^{-5}$, OR = 3.1 vs. 1.3) and Japanese (560/913, p=0.007, OR = 3.5 vs. 1.2). In the combined analysis of 4127 cases and 4573 controls, the G allele of the 3'UTR SNP was associated with SLE ($p = 2.4 \times 10^{-12}$) exhibiting a higher OR in males than females (OR = 2.5[1.7-3.5]) vs. 1.3[1.2-1.4]). Healthy Chinese controls of either gender carrying only the risk G allele had significantly higher mRNA level of *TLR7* in PBMC than those carrying allele C only, which was similarly found in female Chinese SLE patients, suggesting regulation of *TLR7* expression by this SNP or its linked variants.

Conclusion: Association between the X-linked *TLR7* SNP and SLE with a stronger male effect was identified in EA and replicated in independent Chinese and Japanese panels. This risk allele may confer elevated expression of the RNA-binding TLR7, predisposing to the development of SLE, especially in male Chinese or Japanese.

Association of rs3853839 with SLE in EA population.

Ethnicity	**Panels**	**Sex**	**Case/Control**	G Allele Frequency	**P**	**OR(95%CI)**

				Case	Control		
Eastern Asian*	**Discovery**	**M**	**126/229**	**0.83**	**0.73**	**0.04**	**1.8[1.0-3.1]**
		F	**1308/1362**	**0.79**	**0.76**	**3.0E-03**	**1.2[1.1-1.4]**
		All	**1434/1591**	**0.80**	**0.76**	**6.7E-04**	**1.2 [1.1-1.4]**
Chinese	**Discovery**	**M**	**61/145**	**0.93**	**0.72**	**7.0E-04**	**5.6[1.9-16.7]**
		F	**502/377**	**0.83**	**0.76**	**2.0E-04**	**1.5[1.2-2.0]**
		All	**563/522**	**0.83**	**0.75**	**6.3E-06**	**1.7[1.3-2.1]**
	Replication	**M**	**181/819**	**0.92**	**0.80**	**8.3E-05**	**3.1[1.7-5.6]**
		F	**1952/1250**	**0.83**	**0.80**	**4.4E-04**	**1.3[1.1-1.4]**
		All	**2133/2069**	**0.84**	**0.80**	**1.8E-05**	**1.3[1.2-1.5]**
	Total Chinese	**M**	**242/964**	**0.93**	**0.79**	**7.5E-07**	**3.5[2.0-5.8]**
		F	**2457/1627**	**0.83**	**0.79**	**9.8E-07**	**1.3[1.2-1.5]**
		All	**2696/2591**	**0.84**	**0.79**	**2.9E-09**	**1.4[1.2-1.5]**
Japanese	**Replication**	**M**	**36/390**	**0.89**	**0.69**	**0.01**	**3.5[1.2-10.2]**
		F	**524/523**	**0.75**	**0.71**	**0.04**	**1.2[1.0-1.5]**
		All	**560/913**	**0.75**	**0.70**	**7.0E-03**	**1.3[1.1-1.5]**
Eastern Asian*	**Combined**	**M**	**343/1438**	**0.89**	**0.76**	**4.2E-07**	***2.5[1.7-3.5]***
		F	**3784/3135**	**0.81**	**0.77**	**3.0E-09**	***1.3[1.2-1.4]***
		All	**4127/4573**	**0.81**	**0.77**	**2.4E-12**	***1.3[1.2-1.4]***

*: comprised of subjects of Chinese, Korean or Japanese descent

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ACR Concurrent Abstract Sessions

Vasculitis I

Sunday, October 18, 2009, 4:30 PM - 6:00 PM

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A Cross Sectional Study Comparing the CDA to the VDI for the Assessment of Damage in Vasculitis. R. Suppiah[1], O. Flossmann[2], C. Mukhtyar[1], A. Judge[1], D. Brown[1], B. Baslund[3], D. Jayne[2], Mark A. Little[4], J. Holle[5], N. Hasan[1] and R. Luqmani[1], [1]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [2]Addenbrooke's Hospital, Cambridge, United Kingdom, [3]The National University Hospital, Copenhagen, Denmark, [4]University of Birmingham, Birmingham, United Kingdom, [5]University of Schleswig–Holstein, Bad Bramstedt, Germany

Purpose: The Vasculitis Damage Index (VDI) measures damage related to vasculitis, but it may not capture all relevant damage, especially in ANCA associated vasculitis, compared to a more comprehensive assessment measure: the Combined Disease Assessment index (CDA). The aims of the study are to compare the CDA and VDI to measure damage in vasculitis and to validate the CDA for truth, discrimination and feasibility.

Methods: In a cross sectional study, patients with vasculitis were assessed for disease activity using the Birmingham Vasculitis Activity Score 3 (BVAS) and for damage using the VDI and CDA. Inter and intra-observer differences were measured in a sub group and by using paper cases. Feasibility questionnaires for the VDI and CDA were applied.

Results: We evaluated 288 patients from 11 European centres (disease duration 0-480 months). Wegener's granulomatosis (58%) and microscopic polyangiitis (10.4%) were the most common diagnoses. The CDA has already satisfied face and content validity during initial development. The degree of agreement between the VDI and CDA scores (measured using Spearman's rank correlation coefficient) was 0.89 (95%CI 0.87-0.91) confirming their convergent validity. There was good correlation between individual systems (0.71-0.94) except for skin and mucous membranes which was 0.53 (95%CI 0.45-0.60), mainly attributed to the inclusion of easy bruising (18.5% of patients) and cutaneous scarring (10.2%) in the CDA (items not present in the VDI). Inter observer reliability using Lin's concordance correlation coefficient was 0.90 (95% CI 0.83-0.96) for VDI, and 0.70 (95%CI 0.55-0.85) for CDA. Intra observer reliability was 0.89 (95% CI 0.77-1.0) for VDI and 0.86 (95%CI 0.72-1.0) for CDA. Assessing the use of items in the cohort, 9 items were never recorded in the VDI compared to 26 in the CDA. Neither VDI nor CDA correlated with BVAS, CRP or ANCA. Most observers reported that the CDA covered the full spectrum of damage attributable to vasculitis and that it could be used to record the natural history of vasculitis. Only 66% thought that it was useful for measuring damage in clinical trials compared to 100% for the VDI. The CDA took longer to complete (mean 17mins vs. 8mins); it was difficult to complete (67%); and not practical for routine clinical use (83%). By contrast, VDI was easy to complete (100%) and practical for daily clinical use (83%). Overall, 83% preferred to use the VDI when considering all factors.

Conclusion: The CDA measures damage in more detail but the increased complexities result in inferior intra and inter observer reliability and more redundant items than in VDI; CDA is not feasible for daily clinical practice and therefore does not fulfill the requirements of the OMERACT filter. We propose an improvement in VDI, by removing the 9 redundant items identified and adding easy skin bruising and scarring.

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Risk of Malignancy in Patients Treated for ANCA-Associated Vasculitides: Follow-up Data From Clinical Trials of the European Vasculitis Study Group (EUVAS). Caroline Heijl[1], Lorraine Harper[2], Oliver Flossmann[3], Isabelle Stücker[4], David GI Scott[5], Richard Watts[6], Peter Höglund[7], Kerstin Westman[1] and Alfred Mahr[8], [1]University Hospital MAS, Malmö, Sweden, [2]School of Infection and Immunity, Birmingham, United Kingdom, [3]Royal Berkshire Hospital, Reading, United Kingdom, [4]INSERM U754, Villejuif, France, [5]Norfolk and Norwich University Hospital, Norwich, United Kingdom, [6]University of East Anglia, Ipswich, United Kingdom, [7]Lund University Hospital, Lund, Sweden, [8]Hospital Cochin, Paris, France

Purpose: Standard immunosuppressive treatment for the ANCA-associated vasculitides (AAV), Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), may pose a significant risk for the development of malignancies. Previous studies suggested that WG treatment was associated with higher incidences of bladder cancer, non-Hodgkin lymphoma (NHL), leukemia and/or non-melanoma skin cancer (NMSC). This study assessed the malignancy risk for patients treated for AAV in the framework of 4 EUVAS trials.

Method: This analysis was based on the 535 patients with newly diagnosed WG or MPA from 14 European countries (and Mexico) who had been enrolled between 1995 and 2002 in the NORAM, CYCAZAREM, CYCLOPS and MEPEX trials. The 4 trials covered the wide spectrum of severities in AAV presentation and evaluated distinct severity-adapted treatment regimens. Over the period 2004–2007, study participants' follow-up events, including cancers diagnosed, were updated by a cross-sectional mailing survey. Age-, sex- and area-

standardized incidence ratios (SIR) were calculated by linkage to 5 European cancer registries. Cumulative malignancy rates were computed using the Kaplan–Meier method.

Results: Follow-up data were obtained for 467 (87.3%) patients. The overall cohorts' median time of observation was 5.16 years (range: 0.01–11.46), corresponding to 2648 person-years. During that time, 50 malignancies were diagnosed in 46 patients, including 14 NMSC, 4 bladder cancers, 1 NHL and 2 leukemias. The cumulative 5-year cancer rate was 8.6% (95% CI: 5.7–11.5). SIR were: all-sites malignancies, 1.48 (95% CI: 1.10–1.96); all-sites malignancies excluding NMSC, 1.28 (95% CI: 0.89–1.77); bladder cancer, 2.26 (95% CI: 0.62–5.78); NHL, 1.02 (95% CI: 0.03–5.69); and leukemia, 3.25 (95% CI: 0.39–11.75). Subgroup SIR for all-sites malignancies were 1.79 (95% CI: 1.23–2.53) for WG, 1.14 (95% CI: 0.67–1.80) for MPA, and 1.48 (95% CI: 1.08–1.97) for cyclophosphamide-treated patients.

Conclusion: Cancer rates for AAV patients treated with conventional immunosuppressive therapy exceeded the expected general population numbers. The smaller magnitude of malignancy risk in this patient cohort compared to previous studies might reflect less extensive use of cyclophosphamide in current treatment protocols.

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Proteinase 3 Transcription in Peripheral Blood Mononuclear Cells Predicts Disease Activity in Wegener's Granulomatosis. Chris Cheadle, Alan E. Berger, Felipe Andrade, Regina James, Kristen Johnson, Tonya Watkins, Yu-Chi Chen, Eva Ehrlich, Marissa Mullins, Kathleen C. Barnes and Stuart M. Levine, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Wegener's granulomatosis (WG) is a systemic inflammatory disease that can lead to substantial morbidity. Its immunologic hallmark is the generation of anti-proteinase 3 (PR3) antibodies, although their levels do not reliably correlate with disease activity in the majority of patients. Whether changes in PR3 transcription could be used to assess disease activity in WG is unknown.

Method: Gene expression profiling using Illumina bead arrays was performed using total RNA from the separated PBMC and granulocyte (PMN) fractions from 41 WG patients and 23 healthy controls. Quantitative signature analysis was performed using gene set matrix (GSMA), gene set enrichment (GSEA), and principal component analyses (PCA) to search for candidate WG-associated molecular pathways and disease activity biomarkers. Differentially expressed genes satisfied the significance threshold criteria of: (i) t-test p-values ≤ 0.01 (10^{-2}); (ii) a false discovery rate ≤ 0.1; and (iii) a fold change > 1.5 or $< 1/1.5$. Longitudinal changes in PR3 expression were evaluated in 5 patients using RT-PCR, and clinical outcomes including remission status, persistent disease activity, and flare were determined using BVAS-WG scores.

Results: We identified 86 significantly up-regulated genes in WG PBMCs and 40 in WG PMNS relative to controls. Up-regulated genes in WG PBMCs were largely comprised of genes involved in myeloid differentiation, and included the major WG autoantigen, PR3. The coordinated regulation of myeloid differentiation genes in WG PBMCs was confirmed using gene set analysis. PR3 transcription was highly correlated with the myeloid signature as a whole ($r^2=0.78$), and was significantly up-regulated in the PBMC ($p=1.3 \times 10^{-5}$, FDR=0.0021), and not the PMN (p=0.03, FDR=0.28) fraction of WG patients compared to controls. Increased PR3 transcription was seen in all patients with active disease, and both patients in remission and healthy controls expressed similarly low levels of PR3 in the peripheral blood. Changes to and from remission were associated with corresponding decreases or increases in PR3 RNA levels in all patients, whereas changes in ANCA titer correlated with disease activity status in only one case.

Conclusion: These data suggest that PR3 transcription in the peripheral blood mononuclear cells of WG patients might represent a novel marker for assessing disease activity in WG.

Disclosure: C. Cheadle, None; **A. E. Berger**, Johnson & Johnson, 1 ; **F. Andrade**, None; **R. James**, None; **K. Johnson**, None; **T. Watkins**, None; **Y. C. Chen**, Johns Hopkins University, 3 ; **E. Ehrlich**, None; **M. Mullins**, None; **K. C. Barnes**, None; **S. M. Levine**, None.

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Comparison of Disease Manifestations of ANCA-Associated Vasculitis Based On ANCA Type Among Participants in a Multicenter Clinical Trial. U. Specks[1], P.A. Merkel[2], P. Seo[3], R. Spiera[4], C. A. Langford[5], C.G.M. Kallenberg[6], E. William St. Clair[7], B.J. Fessler[8], N. Tchao[9], L.V. Webber[10], L. Ding[10], W. Wu[11], D. Ikle[12], D. Weitzenkamp[12], F.C. Fervenza[1], K.A. Keogh[1], P. Brunetta[13], E. Y. Kissin[2], K.S. Mieras[1], P.A. Monach[2], T. Peikert[1], L. Seismundo[3], C. Stegeman[6], S.R. Ytterberg[1], J. H. Stone[14] and The RAVE-ITN Research Group[9], [1]Mayo Clinic, Rochester, MN, [2]BU, Boston, MA, [3]Johns Hopkins, Baltimore, MD, [4]HSS, New York, NY, [5]Cleveland Clinic, Cleveland, OH, [6]Med.Univ., Groningen, Netherlands, [7]Duke University Medical Center, Durham, NC, [8]UAB, Birmingham, AL, [9]ITN, San Francisco, CA, [10]NIH, Bethesda, MD, [11]PPD, Wilmington, NC, [12]Rho, Chapel Hill, NC, [13]Genentech, Inc, South San Francisco, CA, [14]MGH, Boston, MA

Purpose: To compare disease phenotypes based on ANCA type (PR3 vs. MPO) among patients with severe ANCA-associated vasculitis (AAV).

Method: Baseline demographic data, AAV history, disease activity, and organ involvement of participants in the Rituximab in ANCA Vasculitis Trial (RAVE) were compared by ANCA type. RAVE is a multicenter, randomized, double-blind, placebo-controlled trial designed to determine whether rituximab is not inferior to cyclophosphamide for remission induction in severe AAV. ANCA were measured by ELISA. Organ involvement and disease activity were recorded using the Birmingham Vasculitis Activity Score for WG (BVAS/WG).

Results: Of the 197 trial participants, 131 (66.5%) had PR3-ANCA and 66 (33.5%) had MPO-ANCA. Ninety-nine trial participants (50.3%) were men, 75 with PR3-ANCA and 24 with MPO-ANCA (P<0.006). Among the 98 women enrolled, 56 had PR3- and 42 MPO-ANCA, respectively. The mean (SD) time from diagnosis to enrollment was 47.4 (61.1) months in patients with PR3-ANCA versus 14.7 (32.2) months with MPO-ANCA (p<0.001).

96 of 197 patients (49%) were newly diagnosed at enrollment. Fifty of these were men; 50 (52%) had PR3-ANCA and 46 (45%) had MPO-ANCA. Subsequent analyses are based on this subset of newly diagnosed patients with major results in the Table. Compared to PR3-positive patients, MPO-positive patients were significantly older, more commonly female, had lower BVAS/WS scores but had more major (severe) manifestations. Major renal disease was more common in patients with MPO-ANCA, but the frequencies of alveolar hemorrhage (27%) and nervous system involvement (24%) did not differ between ANCA types. Joint, mucous membrane, ENT, and granulomatous lung involvement were more common in patients with PR3-ANCA.

Conclusion: The clinical disease phenotype of patients presenting with new-onset severe AAV in a clinical trial differs depending on the ANCA type. These data support the decision to stratify treatment assignment by ANCA type in RAVE and justify use of stratification by ANCA type in future clinical trials.

Table: Clinical manifestations of by ANCA type for patients with new-onset AAV

New-Onset AAV	Age mean (sd)	Male n (%)	PGA (0-100 mm)	BVAS/WG	Minor Items mean (sd)	Major Items mean (sd)
PR3 (n=50)	49 (16)	32 (64%)	57	9.8 (3.0)	5.1 (2.3)	1.6 (1.0)
MPO (n=46)	61 (15)*	18 (39%)*	61	8.3 (3.1)*	2.2 (1.7)*	2.0 (0.9)*

* = p < .05 compared to PR3-positive patients. PGA = Physician Global Assessment

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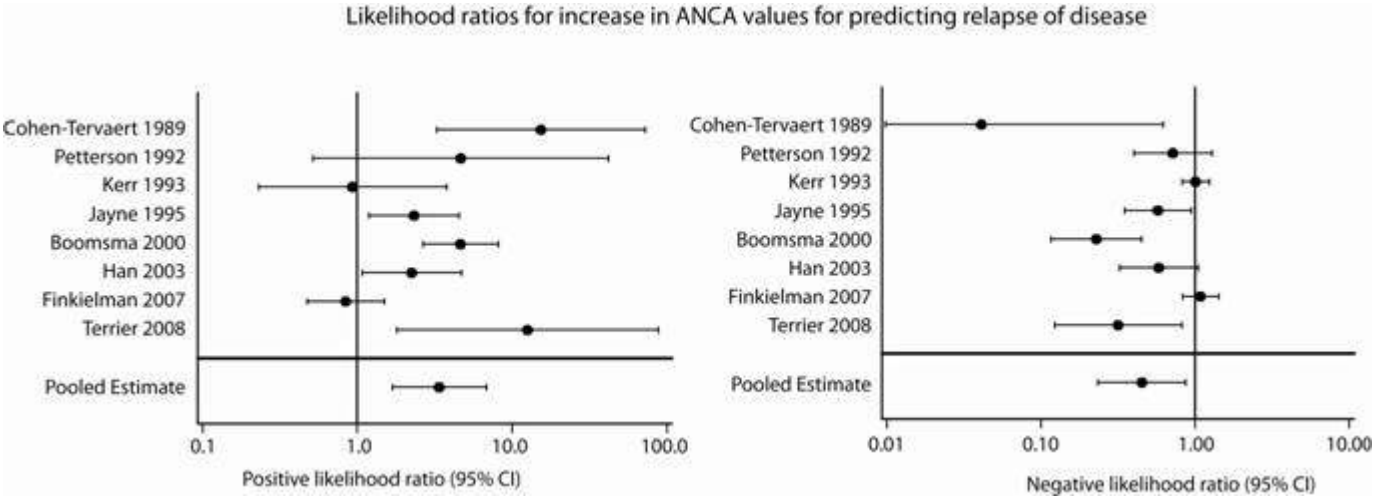
The Value of Rise in Anti-Neutrophil Cytoplasmic Antibody (ANCA) Measurements for Predicting Relapse Among Patients with ANCA-Associated Vasculitis - A Meta-Analysis. Gunnar Tomasson[1], Peter C. Grayson[1], Alfred Mahr[2], Michael P. LaValley[1] and Peter A. Merkel[1], [1]Boston University, Boston, MA, [2]Hospital Cochin, Paris, France

Purpose: Testing for the presence of anti-neutrophil cytoplasmic antibodies (ANCA) has an undisputed role in diagnosing ANCA-associated vasculitis (AAV) but the value of serial ANCA measurements to guide disease management remains controversial. The objective of this study was to perform a meta-analysis to explore whether serial ANCA measurements predict subsequent disease relapse.

Methods: A comprehensive literature review was performed, focused on studies of serial ANCA measurements for prediction of relapse in subjects with established AAV. Articles cited in MEDLINE and conference abstracts were reviewed as were relevant references. Studies were included in the analysis if i) at least 10 participants with established AAV had serial ANCA measurements; ii) data was reported on rises in ANCA values prior to flares or conversions from ANCA-negative to ANCA-positive status during remission; and iii) the number of individuals with ANCA rises and flares could be extracted. For each study, positive- and negative likelihood ratios (LR) were calculated and pooled separately using random-effects models and reported with 95% confidence intervals (CI). To evaluate between-study heterogeneity and publication bias, the arcsine data transformation was used, I^2-value was calculated with 95% CI, a funnel plot was constructed, and the Egger test performed.

Results: 31 articles were identified for full-text review of which 8 studies with a total of 448 subjects were included for the analysis. Frequencies of ANCA measurements ranged from monthly to every 3 months. Follow up for disease relapse ranged from 12 months to 54 months. A rise in ANCA gave a pooled positive likelihood ratio of 3.39 (95% CI: 1.69-6.82) for future flare, absence of a rise in ANCA gave a pooled negative likelihood ratio of 0.45 (95% CI: 0.23-0.87) **(Figure).** If there is a clinically estimated 40% relapse risk, these results indicate a post-test probability for subsequent relapse of 69% in situations of an ANCA measurement rise and a post-test probability for subsequent relapse of 23% in situations of no ANCA measurement rise. There was high heterogeneity among the included studies (I^2 = 0.90 [95% CI: 0.83-0.94]). The funnel plot was asymmetric but Egger's test for publication bias was not statistically significant (p=0.36).

Conclusion: Rise in ANCA values during remission of AAV showed modest predictability for future relapse of disease with some relapses occurring more than one year after the rise in ANCA. Treatment decisions based on a rise in ANCA titer alone would likely result in exposure to unwarranted and potentially harmful therapy in a significant number of situations. In addition, there was considerable heterogeneity in the included studies, along with some suggestion of publication bias.



Disclosure: G. Tomasson, None; **P. C. Grayson**, None; **A. Mahr**, None; **M. P. LaValley**, None; **P. A. Merkel**, None.

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Behçet Syndrome (BS) in the US: Clinical Characteristics, Treatment and Ethnic/Racial Differences in Manifestations in 347 Patients with BS. Yusuf Yazici[1], Elizabeth Schimmel[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: Behçet syndrome (BS) is a systemic vasculitis that is common in the old Silk Route but rare in northern Europe and the US. Previous reports have suggested that there may be ethnic and racial differences in disease presentation and possible clustering of manifestations. We started a dedicated Behçet clinic in 2004 and now report on the disease characteristics of the first 347 patients, we believe representing thus far the largest cohort in the US

Methods: All patients seen at the center have complete a MDHAQ, and a questionnaire about past medical history, medication use, Behçet specific history, ethnic and demographic information. These data are prospectively collected and updated each visit. About 2/3 of patients live within driving distance of NYC while patients from over 30 states have been seen. Patients were analyzed as the whole cohort and then also separated into to 2 groups: Group A= with ethnic background in northern Europe and North America and /or self declared Caucasians without background around the Mediterranean and/or the Far East; Group B= Patients with an ethnic background in the Mediterranean, Middle East, North Africa, and Far East. These groups were compared for disease manifestations, demographic information and medication use.

Results: 347 patients (76% female, mean (SD) disease duration 3.8 (5.4) years, mean (SD) age 53 (13)) of whom 88% fulfilled the International Behçet classification criteria, were analyzed. For the whole cohort most common symptoms were oral ulcers (94%), genital ulcers (76.2%), skin involvement (70.2%), arthritis (54.7%), GI disease (37.9%) and eye disease (27.9%). 15.2% had CNS, 9.7% had vascular/DVT involvement. Less than 10% were positive for pathergy test and 11% had a positive HLA B51. None of the patients were blind. Group A had statistically more significant GI disease (47.5% vs. 27.4%, $p<0.001$). There were also more females in Group A, compared to Group B (Group A: 85%, Group B:69%, $p<0.001$). Most commonly used medication was low dose prednisone (69.6%), in most patients as needed for flares, followed by colchicine (50.9%), TNF inhibitors (23.3%) and azathioprine (22.5%). 17.6% were on methotrexate, the only medication with significantly different frequency of use among the two groups (Group A=26.8%, Group B=8.6%, $p<0.001$).

Conclusion: In this cohort of 347 BS patients, largest cohort in the US to the best of our knowledge, some clinical differences were noted between patients with different ethnic backgrounds. There were significantly more female patients in the non-ethnic groups and GI disease was significantly more among these patients also. Eye disease prevalence for both groups was less than reported from other centers and may be less severe as none of the patients were blind. These finding may have implications regarding the pathogenesis and the effect of nature vs nurture on the presentation of BS in different geographic areas.

Disclosure: Y. Yazici, BMS, Roche, UCB, Centocor, Celgene, 5 ; **E. Schimmel**, None; **C. J. Swearingen**, None.

ACR/ARHP Poster Session B

Animal Models II-Novel Mechanisms and Treatment

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Essential Role of MASP1/3 in Activation of the Complement Alternative Pathway in Collagen Antibody-Induced Arthritis in Mice.

Nirmal K. Banda[1], Brandt Levitt[1], Minoru Takahashi[2], Magdalena J. Glogowska[3], Kazue Takahashi[4], Gregory L. Stahl[5], Teizo Fujita[2], William P. Arend[1] and V. Michael Holers[1], [1]Division of Rheumatology, University of Colorado Denver, Aurora, CO, [2]Department of Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, [3]University of Colorado Denver, Aurora, CO, [4]Developmental Immunology, Massachusetts General Hospital for Children, Boston, MA, [5]Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Boston, MA

Purpose: Sera from mice genetically lacking mannose-binding lectin-associated serine proteases 1/3 *(MASP1/3$^{-/-}$)* unexpectedly have been shown by Takahashi and Fujita to contain only inactive, pro-factor D (pro-Df) and not proteolytically generated active factor D. Active factor D is required for function of the alternative pathway (AP) of complement by promoting formation of the AP C3 and C5 convertases. AP is both necessary and sufficient for mediation of collagen antibody-induced arthritis (CAIA) in mice. The objective of this study was to examine the hypothesis that *MASP1/3$^{-/-}$* mice will be resistant to CAIA due to an impaired AP.

Method: Wild type (WT), *MASP1/3*$^{-/-}$ and *Df*$^{-/-}$ C57BL/6 mice were used. CAIA was induced by injecting 4 anti-type II collagen (CII) mAb intraperitonally (i.p.) on day 0 and LPS i.p. on day 3. Clinical disease activity scores (DAS) were determined daily and histopathology was performed on joint tissues from mice sacrificed on day 10. The absolute levels of C1q, C4, C3, factor B, and factor D in sera from *MASP1/3*$^{-/-}$ and WT mice were measured by ELISA. Sera from *MASP1/3*$^{-/-}$, *C4*$^{-/-}$, *Bf*$^{-/-}$, *Df*$^{-/-}$ were reconstituted with human recombinant Df (hu-rDf), and anti-CII mAb-induced C3 deposition, C3a and C5a generation were measured.

Results: DAS were significantly decreased between days 4 and 10 ($p < 0.05$) both in *MASP1/3*$^{-/-}$ and *Df*$^{-/-}$ mice with a 93% and 88% decrease, respectively, compared to WT mice at day 10. The incidence of disease was 50%, 60% and 100% in *MASP1/3*$^{-/-}$, *Df*$^{-/-}$ and WT mice, respectively. Histopathology scores were consistent with the DAS. C3 deposition in the synovium and cartilage at day 10 was also reduced in *MASP1/3*$^{-/-}$ and *Df*$^{-/-}$ mice with CAIA ($p < 0.05$). There were no differences in the absolute levels of C1q, C4, C3, factor B, and factor D using sera from *MASP1/3*$^{-/-}$ and WT mice. However, the factor D present in the sera of *MASP1/3*$^{-/-}$ mice was entirely in the form of pro-Df, as determined by immunoblot analysis. Anti-CII mAb-induced C3 deposition, C3a and C5a generation in vitro were all absent using sera from *MASP1/3*$^{-/-}$ or *Df*$^{-/-}$ mice under conditions where only the AP was active. However, significant ($p < 0.05$) increases in C3 deposition, and in C3a and C5a levels were observed when sera from *MASP1/3*$^{-/-}$ or *Df*$^{-/-}$ mice were reconstituted with as little as 0.5 ng/ul of hu-rDf. These results indicate that *MASP1/3*$^{-/-}$ mice have an impaired AP of complement due to a lack of active factor D in the serum.

Conclusion: Our studies show that *MASP1/3*$^{-/-}$ mice are resistant to CAIA because of an inability to generate active factor D that is essential to activate the AP in vivo.

Disclosure: N. K. Banda, None; **B. Levitt**, None; **M. Takahashi**, None; **M. J. Glogowska**, None; **K. Takahashi**, None; **G. L. Stahl**, None; **T. Fujita**, None; **W. P. Arend**, None; **V. M. Holers**, Taligen Therapeutics Inc., 4 .

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The Role of MR1-Restricted MAIT Cells in the Pathogenesis of Arthrhtis. Asako Chiba, Ryohsuke Tajima, Yusei Miyazaki, Daiju Ichikawa, Takashi Yamamura and Sachiko Miyake, Natl Institute of Neuroscience, Tokyo, Japan

Purpose: Mucosal associated invariant T (MAIT) cells are a subset of T cells which are restricted MR1, a MHC class Ib molecule, and express an invariant TCRα chain (Vα19-Jα33 in mouse and Vα7.2-Jα33 in human). Previously, we reported the regulatory role of Vα19i T cells in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. However, their role in other autoimmune disease models is still unclear. We sought to understand the role of Vα19i T cells in murine models of arthritis.

Method: Antibody-induced arthritis was induced in C57BL/6 wild-type (WT) and MR1$^{-/-}$ mice by injecting either K/BxN serum i.p. or anti-type II collagen antibody i.v. followed by lipopolysaccharide i.p.. To induce collagen-induced arthritis (CIA), MR1$^{-/-}$ DBA/1J mice or WT littermates were immunized intradermally at the base of the tail with 150μg of bovine type II collagen (CII) emulsified with an equal volume of Freund's complete adjuvant containing 250μg of H37Ra *Mycobacterium tuberculosis*. Mice received booster immunization with 150μg of bovine CII emulsified with incomplete Freund's adjuvant on day 21. To evaluate CII-specific T cell responses, lymph node (LN) cells were isolated and were stimulated with CII. Vα19i T cells were sorted from liver or spleen cells of Vα19iTCR-Transgenic (Vα19iTg) CD1d$^{-/-}$ mice by using anti-TCRVβ and anti-NK1.1 monoclonal antibodies. For adoptive transfer studies, $5x10^5$ NK1.1$^+$ TCRVβ$^+$ Vα19i T cells sorted from Vα19iTg CD1d$^{-/-}$ mice were injected i.v. into naïve WT mice on the day before the induction of arthritis. Cytokines in culture supernatants were measured by ELISA or cytokine bead assay kit.

Results: The severity of clinical and pathological features of K/BxN serum transfer arthritis and anti-CII antibody-induced arthritis were reduced in MR1$^{-/-}$ mice compared to control WT mice. MR1$^{-/-}$ mice reconstituted with sorted Vα19i T cells developed severe forms of arthritis to the similar level of arthritis in WT mice. MR1$^{-/-}$ DBA/1J mice were more resistant to CIA compared to WT littermates, as demonstrated by clinical and histological scores of arthritis. LN cells from CIA-induced MR1$^{-/-}$ DBA/1J mice produced less IL-17 and MCP-1 upon in vitro re-stimulation with CII, compared to littermate controls. The cytokine production by anti-CD3mAb-stimulated Vα19i T cells was augmented in the presence of IL-1 or IL-23.

Conclusion: Vα19i T cells contribute to the pathogenesis of arthritis by augmenting autoimmune T cell responses. Inflammatory cytokines which are abundant in inflammatory conditions including arthritis may activate Vα19i T cells, which in turn amplify autoimmune responses.

Disclosure: A. Chiba, None; **R. Tajima**, Yakulut, 3 ; **Y. Miyazaki**, None; **D. Ichikawa**, None; **T. Yamamura**, None; **S. Miyake**, None.

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Mycobacterium-Derived Heat Shock Protein 70 Induces Anti-Citrullinated Protein/Peptide Antibodies. Hirofumi Shoda[1], Keishi Fujio[2] and Kazuhiko Yamamoto[3], [1]Graduation School of medicine, the University of Tokyo, Tokyo, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

Purpose: Rheumatoid arthritis (RA) is characterized by sustained and destructive joint inflammation, and several autoantibodies appear in the serum of RA patients. Paticularly, anti-citrullinated protein/peptide antibodies (ACPAs) are highly specific for the diagnosis of RA. However, it remains unclear how APCAs develop and what kinds of antigens relate to this process. In this study, we propose *Mycobacterium*-derived heat-shock protein 70 (MycHSP70) as a candidte of ACPA inducible antigen.

Method: We immunized MycHSP70, coupled with CFA, to DBA/1J mice, and serum were obtained after 28 days. To indude collagen-induced arthritis (CIA), bovine type 2 collagen with CFA was immunized 14 days after MycHSP70 immunization, and clinical and histological scores of joint inflammation were measured. Serum ACPAs were measured by ELISA (anti-cyclic citrullinated peptide (CCP) antibody and anti-citrullinated fibrin antibody) and immunostain of rat-esophageal tissues. In RA patients, serum antibodies to MycHSP70 and anti-CCP antibody were measured. To assay T cell response, CD4+ T cells were isolated from peripheral blood mononuclear cells (PBMCs) by MACS system, and were incubated with MycHSP70 for 3 days. Cell proliferation was measured by 3H-thymidine uptake.

Results: MycHSP70 immunized mice developed ACPAs, including anti-CCP antibody, anti-citrullinated fibrin antibody, and anti-citrullinated fillagrin antibody. And CIA got worse in MycHSP70 pre-immunized mice. In RA patients, serum titers of anti-MycHSP70 antibodies and anti-CCP antibodies were significantly collerated. CD4+ T cells from RA patients proliferated in response to MycHSP70.

Conclusion: In RA patients, immune response to MycHSP70 was observed both in B and T cells. In mouse models, immunization of MycHSP70 could induce ACPAs and exacerbate experimental inflammatory arthritis. We suggest that MycHSP70 could be a good candidate antigen for the inducer od ACPAs.

Disclosure: H. Shoda, None; **K. Fujio**, None; **K. Yamamoto**, None.

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Natural IgM Is Required for the Suppression of Arthritis Mediated by Transfer of Apoptotic Cells. Clare Notley and Michael R. Ehrenstein, University College London, London, United Kingdom

Purpose: The clearance of apoptotic cells has been implicated in the maintenance of immune homeostasis. Efficient clearance of apoptotic cells leads to production of IL-10 and TGF-beta, whilst defective apoptotic cell clearance has been linked to the development of autoimmunity. Since natural IgM plays a key role in the clearance of apoptotic cells, we investigated whether the immune modulatory effects of apoptotic cells were altered in mice lacking secretory IgM.

Method: Arthritis was induced using methylated bovine serum albumin (BSA) administered subcutaneously with adjuvant, followed by intra-articular injection 7 days later, in genetically targeted mice deficient in secretory IgM or wild type littermates. Severity of arthritis was assessed by measurement of knee swelling and by histology. Apoptotic cells were generated in vitro using dexamethasone. FACS was used to analyse different cell populations and their cytokine profile, the latter confirmed by ELISA.

Results: Intravenous injection of apoptotic cells at the time of BSA immunisation significantly reduced arthritis severity ($p=0.005$). A profound reduction in joint inflammation and damage, as assessed by histology, was accompanied by suppression of the Th17 response, and increased IL-10 production by both marginal zone (MZ) splenic B cells ($p=0.01$) and T cells ($p=0.01$). No changes in TGF-beta production or the number of Foxp3+ Treg was found following apoptotic cell administration. In contrast, the protective effect of apoptotic cells on the development of inflammatory arthritis was completely abrogated in mice lacking secretory IgM. The marked Th17 response during the course of arthritis were unaltered following injection of apoptotic cells and no induction of IL-10+ MZ B cells or T cells occurred in secretory IgM deficient mice.

Conclusion: Our results indicate that natural IgM is necessary for the protective effects of apoptotic cells in inflammatory arthritis. We propose a model whereby clearance of apoptotic cells by natural IgM drives IL-10 production by MZ B cells and T cells, which in turn can suppress inflammatory arthritis.

Disclosure: C. Notley, None; **M. R. Ehrenstein**, None.

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Disturbed Communication Between the Brain and the Immune System and Adrenal Insufficiency During Collagen Type II Induced Arthritis in Rats. Christine Wolff[1], Johannes Wildmann[2], Anja Hahnel[1], Hugo O. Besedovsky[2], Adriana del Rey[2] and Rainer H. Straub[1], [1]University Hospital Regensburg, Regensburg, Germany, [2]Institute of Physiology, Medical Faculty, Philipps University, Marburg, Germany

Purpose: Disruption of brain-immune system-joint communication (BISJC disruption) has been demonstrated in rheumatoid arthritis. In this study, BISJC was experimentally disrupted in rats before immunization and the influence on collagen type II arthritis (CIA) was studied. It was also part of this project to analyze the behavior of the adrenal cortex because one feature of BISJC disruption is inadequate corticosterone secretion.

Method: Arthritis was induced in rats by injection of collagen type II in incomplete Freund's adjuvant. Noradrenergic and serotonergic neurons in the brain were depleted with 6-hydroxydopamine and 5,7-dihydroxytryptamine fourteen days before immunization. Plasma corticosterone was evaluated by RIA, adrenal cholesterol was quantitatively studied by Sudan-III staining, scavenger receptor class BI (SR-BI) by immunohistochemistry, and joint innervation by immunofluorescenc.

Results: Depletion of hypothalamic noradrenergic neurons had anti-inflammatory effects during a short time window between day 15 and day 24, which is interpreted as a progressive BISJC disruption during this period. Interestingly, serotonin depletion demonstrated a longer lasting anti-inflammatory effect. Both initially increased plasma corticosterone levels and SR-BI expression in the adrenal cortex were reduced to baseline or lower levels in the later phase of arthritis (day 28 onwards). Cholesterol in the adrenal cortex was only slightly increased at the start of overt arthritis and remained stable. Sympathetic nerve fibers in the joint area were rapidly diminished already on day 28.

Conclusion: This study demonstrated that BISJC disruption happens shortly after the manifestation of symptomatic disease between day 15 and day 28. Disruption is visible in form of adrenal insufficiency and loss of sympathetic nerve fibers in the joint.

Disclosure: C. Wolff, None; **J. Wildmann**, None; **A. Hahnel**, None; **H. O. Besedovsky**, None; **A. del Rey**, None; **R. H. Straub**, None.

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Splenic DC Subsets During Collagen-Induced Arthritis in Mice: a Role for Inflammatory Conventional DC? M.C. Lebre[1], L. Bevaart[2], M.I.P. Ramos[1], S. Aarrass[1] and Paul P. Tak[3], [1]Div. of Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Arthrogen BV, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Dendritic cells (DC) play a pivotal role in the orchestration of T cell immunity and tolerance due to their ability to stimulate naive T cells and direct effector cell function. Immunomodulated and tolerogenic DC could be used to ameliorate arthritis. Therefore, in order to gain insight into the characteristics of DC subsets in murine collagen-induced arthritis (CIA) we analyzed the frequencies and phenotype of conventional (c)DC and plasmacytoid (p)DC in a murine C57Bl/6 CIA model during different stages of the arthritis process.

Methods: Arthritis was induced in female C57Bl/6 mice on day 0 (i.d. injection of a chicken collagen/CFA emulsion at the base of the tail) and on day 21 i.d. injection with this emulsion was repeated. Mice were inspected daily from day 20 on for signs of arthritis by two independent observers. Clinical scores were assigned using an established method. At different time points (at days 20, 30, 41 and 63 after CIA induction), mice were sacrificed and spleens were collected. The frequency and phenotype of cDC and pDC was assessed by FACS using specific antibodies: CD11c (total cDC), CD8a (to distinguish 2 cDC populations: $CD8a^+$ and $CD8a^-$) and PDCA-1 together with B220 and Ly-6C (pDC). In addition, isolated cDC and pDC were stimulated for 48h with LPS or CpG, respectively, and cell-free supernatants were analyzed for the contents of inflammatory cytokines using a cytokine-bead assay (CBA).

Results: As expected clinical signs of arthritis started at day 22 (mean±SEM, 0.125±0.125). On days 30, 41 and 63 the mean clinical scores were 1.000±0.555, 2.563±0.922 and 6.500±0.945 respectively. At all the time points studied, the frequencies of splenic cDC (total $CD11c^+$, $CD8a^+$ or $CD8a^-$) exceeded significantly those of pDC ($PDCA\text{-}1^+B220^+Ly\text{-}6C^+$) except $CD8a^-$ at days 20 and 30. Within CIA mice the frequencies of $CD8a^-$ increased significantly (compared to day 20) starting from day 30 while the frequencies of $CD8a^+$ and pDC were

significantly increased on day 63 only. When all the DC subsets from CIA mice were compared to those present in mice without CIA the frequencies of total CD11c, $CD8a^+$, $CD8a^-$ and pDC were significantly increased on day 63. Interestingly, within CIA mice activated cDC produced significantly higher levels of IL-6 on days 41 and 63 while TNF-a was increased only on day 63 (compared to day 20). In contrast, IL-6 and TNF-a-derived from pDC decreased on day 63.

Conclusion: The observation that cDC subsets and their inflammatory cytokines are significantly increased during the development of CIA and that pDC-derived inflammatory cytokines are decreased suggests an inflammatory role for cDC and an regulatory role for pDC in the arthritic process. Thus, cDC rather than pDC may represent an important therapeutic target in arthritis.

Disclosure: M. C. Lebre, None; **L. Bevaart**, None; **M. I. P. Ramos**, None; **S. Aarrass**, None; **P. P. Tak**, None.

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Chromosome 15 Carries Sex-Specific Loci Controlling the Effector Inflammatory Phase of Arthritis. Elena Kudryavtseva[1], Toni Forde[2] and Vyacheslav A. Adarichev[3], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Albert Einstein Collage of Med, New York, NY, [3]Albert Einstein College of Med, Bronx, NY

Purpose: Gender differences in susceptibility to autoimmune diseases including rheumatoid arthritis (RA) are well recognized. Mouse chromosome 15 (chr15) harbors two loci, Pgia8 and Pgia9, that regulate proteoglycan-induced arthritis (PGIA) in a sex-dependent manner. These two loci cluster with arthritides induced with collagen type II, pristane and *Borrelia burgdorferi*. The present study was undertaken to dissect mechanisms of chr15 loci sex-specificity and clustering with diverse types of arthritides.

Method: Congenic strains C.D2-Pgia8 and C.D2-Pgia9 were generated using genetic transfer of DBA/2 loci into BALB/c genetic background in a series of back-crosses. Collagen antibody-induced arthritis (CAIA) was induced in male and female congenic mice by intravenous injection of a cocktail containing four monoclonal antibodies to type II collagen followed by LPS stimulation. Mice were scored for paw inflammation on a daily basis. Paws were collected for differential gene expression analysis at the end of the observation period.

Results: Congenic strains were susceptible to CAIA, however, the significant strain differences were found in arthritis severity. C.D2-Pgia8 congenic mice showed significant sex-related suppression of arthritis. Severity of inflammation in C.D2-Pgia8 males was 30% lower ($p < 0.005$) than in wild-type BALB/c males. Arthritis suppression was significant from day 8 and persisted until the end of observation. No genetic effect of the Pgia8 locus upon CAIA was observed in congenic females. On the contrary, C.D2-Pgia9 congenic mice did not show any sex-related differences in CAIA severity when they were compared to wild-type BALB/c of the same sex. Pgia9 locus promoted CAIA inflammation in both males (12% up-regulation, $p < 0.05$) and females (24% up-regulation, $p < 0.02$).

Conclusion: Our data indicate that two separate regions of chr15 are involved in the effector stage of arthritis (CAIA). These two chromosome intervals are similar to Pgia8 and Pgia9 loci by their locations and sex-related effects, which might provide an explanation for clustering of diverse RA animal models loci on chr15.

Disclosure: E. Kudryavtseva, None; **T. Forde**, None; **V. A. Adarichev**, None.

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TNFalpha-Induced Adipose-Related Protein (TIARP) in Experimental Autoimmune Arthritis. Asuka Inoue[1], Isao Matsumoto[1], Yoko Tanaka[1], Reiko Minami[2], Kayo Yamamoto[1], Naoto Umeda[1], Taichi Hayashi[1], Daisuke Goto[1], Satoshi Ito[1] and Takayuki Sumida[1], [1]University of Tsukuba, Graduate School of Comprehensive Human Sciences, Tsukuba, Japan, [2]University of Tsukuba, Tsukuba, Japan

Purpose: TNFα is a pivotal factor of the inflammatory and tissue destructive pathways in rheumatoid arthritis (RA). Therapeutic effectiveness of anti-TNFα mAb was denoted in glucose-6-phosphate isomerase (GPI) -induced arthritis, suggesting the similar etiology to RA. We recently demonstrated that TNFα-induced- adipose related protein (TIARP) was highly expressed in spleens and joints from GPI-induced arthritis. In this study, to elucidate the role of TIARP in arthritis, we used two experimental models of arthritis such as GPI-Induced arthritis and collagen type II-induced arthritis (CIA).

Method: (1) DBA/1 mice were immunized with 300ug recombinant human GPI emulsified in complete freund's adjuvant (CFA). The expression of TIARP mRNA and proteins in spleens, lymph nodes (LNs) and joints were evaluated in GPI-induced arthritis (on day0, 7, 14,

28) by RT-PCR and immunoblotting methods. (2) Splenocytes (on day 0,7) from GPI-induced arthritis were separated into four groups (CD4+, CD19+, CD11b+, CD11c+) by MACS and the expression of TIARP mRNA was compared by quantitative PCR. (3) Anti-TIARP polyclonal Abs were prepared and administrated to GPI-induced arthritis on day8, and the clinical score of arthritis was monitored. In vitro, splenocytes (on day 8) were cultured for 24h with GPI plus anti-TIARP Abs or control Abs, and TNFα, IL-6 and MCP-1 in their culture supernatant were measured by ELISA. (4) CIA was induced by immunization with 100ug of bovine type□ collagen and CFA to DBA/1 mice, followed by boost immunization after 21days of primary immunization. In the same way, the fluctuation of TIARP mRNA in spleens and joints were monitored in CIA (on day 14, 23, 28, 40). We also evaluated TIARP-dominant cells of splenocyte in CIA by the method (2) on day 23.

Results: (1) The TIARP mRNA and proteins were dominantly expressed in splenocytes on day 7. On the other hand, the expression of TIARP in joints was accompanied with the joint swelling, especially elevated on day 14 and 28. (2) The splenic CD11b+ cells were mainly expressed TIARP mRNA on day 7. (3) Arthritis was exacerbated in mice administrated with anti-TIARP Abs comparing to control Abs. The amount of TNFα and IL-6 increased twice by the addition of anti-TIARP Abs in vitro, although the amount of MCP-1 was comparable. (4) In CIA model, the expression of TIARP mRNA in splenocytes was the highest in early phase of arthritis (on day23), the expression in joints was accompanied with the joint swelling as well as GPI-induced arthritis. Splenic CD11b+ cells were also mainly expressed TIARP mRNA in CIA.

Conclusion: TIARP expression in spleens and joints are fluctuated in the same manner within two different arthritis models. The administration of anti-TIARP Abs exacerbates arthritis as well as induces the high expression of TNFα and IL-6, suggesting TIARP might be a new regulatory molecule against arthritis by controlling the production of inflammatory cytokines.

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NOD2 and TLR2 Function Independently in Arthritis Triggered by Intra-Articular Peptidoglycan. Holly L. Rosenzweig[1], Monica J. Jann[2], Emily E. Vance[1], Stephen R. Planck[1], James T. Rosenbaum[1] and Michael P. Davey[3], [1]Oregon Health & Science University, Portland, OR, [2]VA Medical Center, Portland, OR, [3]VA Medical Center/Oregon Heath & Science University, Portland, OR

Purpose: NOD2 is linked with joint pathology as mutations in *NOD2* cause Blau syndrome, an autoinflammatory disease affecting joints. In the bowel, NOD2 functions as a negative regulator of inflammation and different polymorphisms in *NOD2* predispose to Crohn's disease. Here, we investigated the role of NOD2 in an experimental model of arthritis and the potential interplay between NOD2 and TLR2.

Methods: Mice deficient for TLR2, MyD88, or NOD2 and their wild-type controls were administered an intraarticular injection of peptidoglycan (PGN), muramyl dipeptide (MDP) (a ligand for NOD2 and a derivative of PGN), or Pam_3CSK4 (a synthetic TLR2 agonist). Neutrophil depletion was performed using an anti-Ly6G antibody. Joint inflammation was assessed by near-infrared fluorescence imaging and histopathology.

Results: PGN results in arthritis, which depended on TLR2 and its signaling mediator MyD88. As opposed to what is reported in bowel inflammation, NOD2 is essential in promoting joint inflammation because NOD2 deficiency significantly diminished PGN-induced arthritis. TLR2 and NOD2 are capable of eliciting inflammation independently as deficiency in either TLR2 or MyD88 did not influence arthritis induced by the NOD2 agonist, MDP. Conversely, NOD2 deficiency did not alter TLR2-dependent joint inflammation elicited by Pam_3CSK4. Neutrophils are present in the joint; however they are not necessary mediators of PGN-induced arthritis as measured by fluorescence imaging.

Conclusion: Whereas NOD2 and TLR2 are both critical for the development of arthritis, they appear to elicit inflammation independently of each other. Our data support an inflammatory role for NOD2 in arthritis in contrast to what is reported for colitis.

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Studies of Combination of IMO-3100, An Antagonist of TLR7 and TLR9, and Etanercept, a TNF-α Inhibitor, in a Mouse Model of Collagen-Induced Arthritis (CIA). Fu-Gang Zhu, Dong Yu, Ekambar R. Kandimalla and Sudhir Agrawal, Idera Pharmaceuticals, Inc., Cambridge, MA

Purpose: IMO-3100 is an antagonist of Toll-like receptors (TLRs) 7 and 9 and has potent activity in preclinical studies of prevention as well as treatment models of collagen-induced arthritis (CIA) in mice. We have studied the efficacy of the combination of IMO-3100 and etanercept, a TNF-a inhibitor, which have complementary and distinct mechanisms of action, for the treatment of CIA in a DBA/1 mouse model.

Method: Arthritis was induced in DBA/1 mice by intradermal administration of bovine collagen type II (BCII) with complete Freund's adjuvant (CFA) on day 0 and with incomplete Freund's adjuvant (IFA) on day 21. Mice were divided into six groups (n=8). Mice received IMO-3100 (s.c.) at 100 or 300 µg/mouse, or etanercept (i.p.) at 100 or 300 µg/mouse, or the combination of IMO-3100 (100 µg/mouse) and etanercept (100 µg/mouse), or PBS on days 28, 31, 34, 37, 40, 43, and 46. Mice were monitored for arthritic symptoms in the paws from day 21 until the last day of the study (day 58). Following termination of the study, serum levels of anti-BCII antibodies and spleen cell cytokines were determined, and paw joint tissues were examined for histopathological changes.

Results: Mice treated with IMO-3100 or etanercept had lower arthritic scores than did untreated (PBS) mice; the effect was dose-dependent. Mice treated with the combination of IMO-3100 and etanercept had lower arthritic scores than did mice treated with either agent alone at the highest dose. Mice treated with IMO-3100 or the combination of IMO-3100 and etanercept had lower serum anti-BCII IgG1 and IgG2a antibodies and lower IFN-g levels in spleen cell cultures; the IMO-3100 effect was dose-dependent. Histological examination of foot joint tissues of mice in IMO-3100 and etanercept treatment groups showed a dose-dependent reduction in inflammation and bone destruction. Lower levels of inflammation and bone destruction were observed in the foot joint tissues of mice treated with the combination of IMO-3100 and etanercept than in mice treated with either agent alone.

Conclusion: These results suggest that the combination of IMO-3100 and etanercept, which have complementary and distinct mechanisms of action, is effective in this model of CIA in mice. This study provides a rationale for combination therapy with IMO-3100 and etanercept for potential treatment of rheumatoid arthritis in humans.

Disclosure: F. G. Zhu, Idera Pharmaceuticals, Inc., 3 ; **D. Yu**, Idera Pharmaceuticals, Inc., 3 ; **E. R. Kandimalla**, Idera Pharmaceuticals, Inc., 3 ; **S. Agrawal**, Idera Pharmaceuticals, Inc., 3 .

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Pten Deficiency in Myeloid Cells Protects From Collagen Induced Arthritis. Stephan Blüml[1], Gernot Schabbauer[2], Michael Bonelli[1], J. S. Smolen[1] and Kurt Redlich[1], [1]Medical University Vienna, Dpt. of Rheumatology, Vienna, Austria, [2]Dpt. of Vascular Biology, Vienna, Austria

Purpose: Pten is a lipid phosphatase, whose substrate is phosphatidylinositol 3,4,5-trisphosphate. Therefore, pten is one of the main antagonists of the PI3-kinase, which plays a major role in many important cellular functions, such as proliferation, migration or response to inflammatory stimuli.

Here we investigated the role of pten in collagen induced arthritis.

Methods and **Results:** We show that conditional deletion of pten under the LysM promoter (LysMCrePten$^{flox/-}$) leads to a significant reduction in clinical severity of collagen induced arthritis. Histological analysis of CIA, LysMCrePten$^{flox/-}$ mice displayed significantly reduced joint inflammation as well as erosive bone destruction. Total anti-collagen antibodies, however, as well as anti-collagen IgGs were identical in both groups. Upon analysis of inflammatory cytokines in serum after immunisation we found a significant reduction of IL-6 as well as IL-8 levels. Furthermore, pten deficient macrophages and dendritic cells showed reduced induction of IL-6 as well as IL-12 and IL-23 upon stimulation with various TLR-ligands. Since these cytokines play an important role in the induction of pathogenic Th-17 T cells, we measured Th-17 cytokines in lymph nodes after immunisation with collagen. Although dendritic cell and macrophage recruitment to the draining lymph node was comparable in both groups, there was a slight reduction of IL-17 and a strong reduction of IL-22 in the draining lymph node of immunized LysMCrePten$^{flox/-}$ compared to wild-type mice, whereas the levels of IL-4 as well as the numbers of regulatory T cells were increased.

Conclusion: These data point to a potent regulatory role of pten in antigen presenting cells in the development of CIA by skewing T cells polarisation away from pathogenic Th17, favouring Th2/ regulatory T cell development instead.

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Overexpression of Tristetraprolin Regulates Collagen Induced Arthritis. Takashi Jingu[1], Takeshi Suzuki[1], Makoto Sugihara[1], Eiji Suzuki[2], Yuya Kondo[1], Isao Matsumoto[1], Taichi Hayashi[1], Daisuke Goto[1], Satoshi Ito[1], Satoru Takahashi[1], Akito Tsutsumi[3] and Takayuki Sumida[1], [1]University of Tsukuba, Tsukuba, Japan, [2]Ohta-Nishinouchi Hospital, Koriyama, Japan, [3]Takikawa city hospital, Takikawa, Japan

Purpose: Tristetraprolin (TTP) is a widely expressed protein with two zinc finger domains that act as active RNA-binding sites. TTP is an immediate early response gene expressed in fibroblasts and other cells upon induction by a variety of stimuli. TTP is posttranscriptional regulation molecule that downregulates tumor necrosis factor-α (TNF-α) production by binding to AU-rich element on TNF-α mRNA, and promoting TNF-α mRNA degradation. TTP-knockout mice display an inflammatory phenotype characterized by inflammatory arthritis, dermatitis, cachexia, autoimmunity, and myeloid hyperplasia and this phenotype can be prevented by administration of anti-TNF-α antibodies. We developed transgenic mice overexpressing zinc finger (ZF-Tg DBA/1 mice), a part of TTP, and investigated TTP mRNA expression in several organs, TNF-α mRNA stability, and production by lipopolysaccharide (LPS) stimulation in vitro. Furthermore, we examined the development of collagen induced arthritis (CIA) in vivo.

Method: (1) We investigated TTP mRNA distribution in joint, muscle, heart, thymus, lung, liver, small intestine, colon, spleen, and inguinal lymph nodes of ZF-Tg DBA/1 mice by RT-PCR. (2) We investigated TTP mRNA stability in the splenocytes of ZF-Tg DBA/1 mice. (3) We investigated TNF-α production in splenocytes of ZF-Tg DBA/1 mice after LPS stimulation by ELISA. (4) We induced CIA by immunization of type II collagen to DBA/1 mice and ZF-Tg DBA/1 mice at twice (day 0 and day 21), and monitored the clinical score of arthritis.

Results: (1) TTP-ZF transgene mRNA was expressed in these all tissues. (2) TNF-α mRNA in ZF-Tg DBA/1 mice was more instable than DBA/1 mice. (3) TNF-α production in ZF-Tg DBA/1 mice was more decreased than DBA/1 mice. (4) The clinical score of arthritis in ZF-Tg DBA/1 mice was significantly suppressed.

Conclusion: We identified that the overexpression of zinc finger part of TTP caused the instability of TNF-α mRNA and the downregulation of TNF-α production, and resulting in the suppression of CIA. These findings open a new strategy for the regulation of autoimmune arthritis through TTP induction.

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Active Immunization against VEGF Improves Joint Inflammation and Destruction in Collagen-Induced Arthritis. Eric Assier[1], Luca Semerano[2], Laure Delavallée[1], Géraldine Grouard-Vogel[3], Emilie Bernier[3], Daniel Zagury[3] and Marie-Christophe Boissier[2], [1]EA 4222 Paris 13 University, Bobigny, France, [2]AP-HP, Avicenne hospital, Bobigny, France, [3]NéoVacs, Paris, France

Purpose: Cytokines play a key role in the development of rheumatoid arthritis (RA), allowing hypertrophy of the pannus by neovascularisation, articular inflammation and destruction. We recently demonstrated in experimental models the efficacy of vaccination against cytokines, using a heterocomplex of keyhole limpet hemocyanin (KLH) and human TNF, called TNF kinoid (K). VEGF is a potential target in RA, since it plays a major role in angiogenesis and pannus formation. We aimed at demonstrating an inhibitory effect of a sustained inhibition of VEGF by an anti-VEGF vaccine in collagen-induced-arthritis (CIA).

Method: Anti-murine VEGF immunization was performed by injecting intra-muscularly VEGF-K formulated in incomplete Freund adjuvant (IFA) in DBA/1 mice. Control groups received KLH or PBS at the same dates. A fourth group received a chemical angiogenesis inhibitor in drinking water from D28 to sacrifice (Ammonium Tetrathiomolybdate, TM, 0.03mg/ml). Arthritides were induced by two subcutaneous injections of bovine type II collagen, the first at Day 40 in complete Freund adjuvant, the second at Day 61 in IFA. Clinical scores of arthritis were evaluated twice per week. Histological scores of the paws were quantified after sacrifice and Hematoxylin/Eosin staining. Anti-VEGF and anti-KLH antibody (Ab) levels were assessed by ELISA, and the anti-VEGF neutralizing capacity (NC) of sera by HUVEC bioassay.

Results: VEGF-K and TM groups showed lower arthritic scores as compared to KLH and PBS groups ($p<0.005$). At histological analysis, inflammation and destruction scores of the paws were lower in VEGF-K group versus KLH ($p<0.005$) and PBS group ($p<0.001$). VEGF-K group was the only one to show anti-VEGF Ab production as assessed by ELISA at Day 60 and sacrifice. The neutralizing activity of anti-VEGF Ab was confirmed by HUVEC at sacrifice.

Conclusion: These data show that VEGF-K improves arthritis in a murine RA model.

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HGF Antagonist, NK4, Inhibits Th1 Immune Response, RANKL Expression On Synovial Fibroblasts and Enhances Osteoblast Generation. Sachi Tsunemi[1], Tsuyoshi Iwasaki[2], Sachie Kitano[1], Kunio Matsumoto[3] and Hajime Sano[1], [1]Hyogo College of Medicine, Nishinomiya, Japan, [2]Hyogo University of Health Sciences, Kobe, Japan, [3]Kanazawa University, Kanazawa, Japan

Purpose: Hepatocyte growth factor (HGF) is a potent pro-angiogenic molecule that induces neovascularization. The HGF antagonist, NK4, encodes the NH_2terminal hairpin and four kringle domains of the HGF subunit. NK4 competitively antagonizes HGF binding to its receptor and also abrogates angiogenesis promoted by other angiogenic inducers, including basic fibroblast growth factor and vascular endothelial growth factor. Previously (ACR/ARHP Scientific Meeting 2007, 2008), we reported that NK4 can inhibit arthritis and bone destructions in joints of rheumatoid arthritis (RA) model mice. In the present study we investigated the mechanisms by which NK4 inhibited arthritis and bone destructions in affected joints.

Method: SKG mice spontaneously develop T cell-mediated chronic autoimmune arthritis as a consequence of impairment of negative selection of autoimmune $CD4^+$ T cells in the thymus. Arthritis was induced by a single intraperitoneal injection of the ß-glucan laminarin (45 mg). Recombinant adenovirus containing NK4 cDNA (AdCMV.NK4) (1×10^9 pfu) was also injected intravenously at the time of laminarin injection. Joint swelling was monitored by inspection and through assessment of paw volume. The ankles bone destructions were examined radiographically. Histopathology of joints were examined by hematoxylin and eosin and immunohistochemical staining. Prostaglandin E2 (PGE_2) production by synovial fibroblast cell line (MH7A) and IFN-γ production by $CD4^+$ T cells stimulated by allogeneic spleen cells were determined by ELISA. RANKL expression on MH7A cells was examined by RT-PCR analysis. Osteoblast generation was examined using murine myoid cell line (C2C12) stimulated with BMP-2 and was analyzed by ALP staining of the cells and osteocalucin production in the culture supernatant.

Results: Intravenous injection of AdCMV.NK4 into SKG mice suppressed the progression of laminarin-induced clinical arthritis, as demonstrated by both paw volume and arthritis score. Bone destructions were also inhibited by NK4 treatment. Histopathological findings of the foot joints revealed that infiltration of Th17 cells and RANKL expressions on synovial cells were significantly suppressed by NK4 treatment. NK4 gene transfection into MH7A cells inhibited PGE2 production and TNF-α-induced RANKL expression by these cells. NK4 gene transfection into C2C12 cells enhanced BMP-2 induced osteoblast generations. Furthermore, NK4 suppressed IFN-γ production by $CD4^+$ T cells stimulated by allogeneic spleen cells.

Conclusion: These results indicate that NK4 can inhibit PGE2 production by synovial cells and IFN-γ production by $CD4^+$ T cells. NK4 can also enhance osteoblast generation and inhibit osteoclastogenesis by inhibiting TNF-α-induced RANKL expressions on synovial cells. Molecular targeting of HGF by NK4 can therefore be potentially applied as a novel therapeutic approach for the treatment of RA.

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Multiple Effects of FTY On the Immune System, Inflammation, and Bone Remodeling in Rheumatoid Arthritis. Tsuyoshi Iwasaki[1], Sachi Tsunemi[2], Sachie Kitano[2], Chieri Kanda[2] and Hajime Sano[2], [1]Hyogo University of Health Sciences, Kobe, Japan, [2]Hyogo College of Medicine, Nishinomiya, Japan

Purpose: SKG mice spontaneously develop T cell-mediated chronic autoimmune arthritis as a consequence of impairment of negative selection of autoimmune $CD4^+$ T cells in the thymus. FTY720 (FTY) is a new immunomodulatory agent that decreases peripheral blood

lymphocytes by sequestration of lymphocytes in secondary lymphoid tissues and the thymus. Previously (ACR/ARHP Scientific Meeting 2007), we reported that FTY can inhibit arthritis and bone destructions in joints via sequestration of autoimmune $CD4^+$ T cells in the thymus in SKG mice. In the present study, we investigated the effects of FTY on immune system, inflammation, and bone remodeling in rheumatoid arthritis (RA).

Method: Arthritis was induced by a single intraperitoneal injection of laminarin (45 mg). FTY (1 mg/kg/day) was administered orally from the time of laminarin injection. The numbers of $CD4^+$/$CD8^+$ T cells and $B220^+$ B cells were examined by flow cytometry. RANKL expression on $CD4^+$ T cells in the spleen or on human $CD4^+$ T cells were analyzed by either flow cytometry or RT-PCR analysis, respectively. Hematoxylin and eosin staining and immunoperoxidase staining for IL-6, TNF-α was performed on formalin fixed paw sections. Prostaglandin E2 (PGE_2) production by synovial fibroblast cell line (MH7A) and cytokine production by spleen $CD4^+$ T cells were determined by ELISA.

Results: FTY administration suppressed the progression of laminarin-induced arthritis in SKG mice, as demonstrated by both paw volume and arthritis score. Expression of IL-6 and TNF-α in synovial fibroblast cells and inflammatory cells was significantly decreased after FTY administration. Bone destructions were also suppressed by FTY administration. The numbers of $CD4^+$ and $CD8^+$ T cells were significantly increased in the thymus and decreased in the spleen after FTY administration. Interestingly, RANKL expression on $CD4^+$ T cells in the spleen was increased after FTY administration. In vitro FTY treatment also augmented RANKL expression on human CD4+ T cells. In vitro FTY treatment enhanced IL-4 production but not IFN-γ productions from $CD4^+$ T cells stimulated by allogeneic spleen cells. In vitro FTY treatment also inhibited PGE2 production by TNF-α stimulated MH7A cells.

Conclusion: These results indicate that that this greater anti-arthritis potency of FTY may be due to its multiple effects on the immune system and inflammation in SKG mice that we observed in this study including sequestration of autoimmune $CD4^+$ T cells in the thymus, enhancement of Th2 immune responses, and inhibition of PGE2 production by synoviocytes. FTY can therefore be potentially applied as a novel therapeutic approach for the treatment of RA. However, FTY may have an adverse effect on bone remodeling by the enhancement of RANKL expression on $CD4^+$ T cells infiltrated in synivial tissues.

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Treatment with Cl-Amidine, A Peptidyl Arginine Deiminase (PAD) Inhibitor, Significantly Reduces the Severity of Collagen Induced Arthritis (CIA). Van Willis[1], Alison Gizinski[2], Bryan Knuckley[3], Nirmal K. Banda[1], Kristen Cordova[1], Yuan Luo[3], Corey Causey[3], Brandt Levitt[1], Magdalena Glogowska[1], Piyanka Chandra[4], Maya BenBarak[4], Liudmila Kulik[1], William P. Arend[1], William Robinson[4], Paul R. Thompson[3] and V. Michael Holers[1], [1]UCDenver, Aurora, CO, [2]Univ of Michigan, Ann Arbor, MI, [3]Univ of S Carolina, Columbia, SC, [4]Stanford School of Med, Stanford, CA

Purpose: Antibodies to citrullinated self proteins are present in the sera of patients with rheumatoid arthritis (RA). The epitopes recognized by antibodies to citrullinated protein antigens (ACPA) are created when proteins undergo a post-translational conversion of arginine to citrulline, a process dependent upon enzymes designated PADs. We and others have shown that ACPA develop in the murine CIA model and contribute to joint damage. The purpose of this study was to determine the effect of a specific inhibitor of all five PAD enzymes, Cl-amidine, on the development of arthritis in the CIA model.

Method: Male DBA/1j mice were immunized with bovine type II collagen (CII) in Complete Freund's Adjuvant at days 0 and 21 to induce CIA. For collagen antibody-induced arthritis (CAIA), male DBA/1j mice received 4 mg Arthrogen IP followed by 50 µg LPS IP 3 days later. Five groups of immunized mice were studied: no drug treatment, vehicle alone by IP injection or 1,10, or 50 mg/kg/day Cl-amidine in PBS IP. Clinical disease activity (CDA), histologic injury and complement C3 deposition were scored in a blinded fashion on a standard scale. CIA and CAIA mice were sacrificed on days 35 and 10 respectively.

Results: Preliminary results by Western blot analysis of splenocyte extracts with the Senshu antibody show inhibition of PAD enzymes *in vivo* by Cl-amidine. Treatment with Cl-amidine reduced the CDA scores in CIA by 55%, 53% and 42% in the 50, 10 and 1 mg/kg/day groups, respectively. Histologic severity and complement C3 deposition scores paralleled the decreases in CDA. No differences were observed in anti-bovine CII antibody titer between treatment groups. However, a significantly lower IgG1 anti-mouse CII antibody titer was observed in the 50 and 10mg/kg/day groups and significantly lower IgG2a anti-mouse CII antibody titer in the 10mg/kg/day groups, compared to controls. Mice receiving Cl-amidine showed reduced epitope spreading by peptide microarray, especially to citrullinated joint

antigens. No changes in the percentages of T cell, B cell or monocyte populations were observed by flow cytometry analysis in treated mice compared to controls. In contrast to the effect in CIA, no change in CDA scores was observed in the CAIA model.

Conclusion: Cl-amidine treatment in mice inhibits PAD activity *in vivo* and substantially decreases CDA scores in CIA without major effects on immune cell populations. In contrast, Cl-amidine treatment has no effect on CDA scores in CAIA, indicating that inhibition of PADs does not alter the effector phase of the immune response. These results suggest that PADs are obligate, rate-limiting participants in the autoimmune process and the loss of tolerance to citrullinated self antigens. In addition, Cl-amidine may represent a novel class of therapeutics for RA that targets citrullination and perhaps other processes necessary for the development of inflammatory arthritis.

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Neutralization of Angiopoietin 2 Reduces Disease in Murine Arthritis and Augments Efficacy of Anti-TNF Treatment. Brian Naiman[1], Martyn Foster[2], Chris Stannard[2], ChingChing Leow[1], Steven Coats[1], William Dall'Acqua[1], Nancy Kohut[1], Wendy Trigona[1], Anthony J. Coyle[1], Bahija Jallal[3] and Jane Connor[1], [1]MedImmune, LLC, Gaithersburg, MD, [2]Astra Zeneca, Charnwood, United Kingdom, [3]MedImmune, Gaithersburg, MD

Purpose: In the past 20 years, the development of TNFa-neutralizing biologics has revolutionized the treatment of rheumatoid arthritis (RA). However, in spite of the growing number of anti-TNF treatment options, over 30% of patients receive incomplete or no benefit from anti-TNF therapy. In recent years, RA has become recognized as a disease with an angiogenic as well as an inflammatory drive. Pathological blood and lymphatic vessel growth in the synovium provide nutrients for the hyperproliferative synovium as well as routes of entry for infiltrating inflammatory cells. In this way, angiogenesis is an attractive target for augmenting the anti-inflammatory activity of anti-TNF therapy. Angiopoietin-2 (Ang2) is an important regulator of angiogenesis, blood vessel maturation and integrity of the vascular endothelium. Ang2 and its receptor, Tie2, are localized in the vasculature of joints of RA patients and may contribute to disease maintenance and progression.

Method: To assess the therapeutic potential of neutralizing Ang2 in RA, an anti-Ang2 IgG2 monoclonal antibody with cross-reactivity to mouse was evaluated in the mouse collagen-induced arthritis (mCIA) model of RA. Subsequently, a human anti-Ang2 IgG1 with cross reactivity to mouse, MEDI3617, which has been characterized for its anti-angiogenic activity in a number of angiogenesis and tumor growth models, was evaluated in another model of mouse RA, the glucose-6-phosphate isomerase (G6PI) model.

Results: In mCIA, treatment with anti-Ang2 antibody inhibited clinical signs of disease as well as histopathological changes in the joints in a dose-dependent manner. Importantly, anti-Ang2 treatment inhibited vessel density in the synovium, providing direct evidence of the anti-angiogenic effect of treatment. In G6PI, MEDI3617 partially inhibited the development of clinical signs of joint disease and combination treatment with etanercept, the soluble TNF receptor, provided increased efficacy compared to either agent administered alone. In a model designed to evaluate efficacy in established joint disease, neither MEDI3617 nor etanercept were significantly efficacious, but treatment with the two agents in combination resulted in a measurable inhibition of clinical scores of the joint. In addition, the combined treatment did not result in any observable adverse effects.

Conclusion: These data support the continued development of anti-Ang2 antibody with anti-TNF agents as a possible therapeutic improvement in the treatment of RA.

Disclosure: B. Naiman, Medimmune, LLC, 3 ; **M. Foster**, Astra Zeneca, 3 ; **C. Stannard**, Astra Zeneca, 3 ; **C. Leow**, MedImmune, LLC, 3 ; **S. Coats**, MedImmune, LLC, 3 ; **W. Dall'Acqua**, MedImmune, LLC, 3 ; **N. Kohut**, MedImmune, 3 ; **W. Trigona**, MedImmune, 3 ; **A. J. Coyle**, MedImmune, LLC, 3 ; **B. Jallal**, MedImmune, LLC, 3 ; **J. Connor**, Medimmune LLC, 3 .

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Treatment of Arthritis by Anti-Inflammatory Effect of E3 Ubiquitin Ligase, c-Mir. Masayasu Toyomoto[1], Satoshi Ishido[2], Nobuyuki Miyasaka[3] and Hitoshi Kohsaka[4], [1]Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan, [2]RIKEN Research Center for Allergy and Immunology, Yokohama City, Japan, [3]Tokyo Medical and Dental University, Tokyo, Japan, [4]Tokyo Med and Dent Univ, Tokyo

Purpose: c-MIR is a newly defined E3 ubiquitin ligase that ubiquitinates membrane-bound molecules associated with antigen presentation. Its targets include MHC class II and CD86. The ubiquitination results in their endocytosis and down modulation of their expression. Assuming that c-MIR overexpression suppresses antigen presentation and following activation of acquired immunity in the inflammatory synovial tissues, we examined whether forced expression of c-MIR in the synovial tissues suppresses an animal model of rheumatoid arthritis (RA).

Method: DBA/1J mice were immunized with bovine type II collagen (CII) for development of collagen-induced arthritis (CIA). Recombinant adenoviruses expressing c-MIR or LacZ as a control were prepared. After booster immunization on day 21, the mice were subjected to intraarticular adenovirus gene transfer to bilateral hind legs at the ankles, the knees, and the tarsal joints on day 24, 28 and 35. Mice were examined visually for arthritis scoring. The joints were examined histologically. Serum levels of anti-CII antibodies and proliferative responses of the splenocytes to CII were studied. In vitro, fibroblast-like synoviocytes (FLS) were isolated from the joint tissues of the CIA mice and infected with the c-MIR adenoviruses. They were then stimulated with TNF-α or IL-1β. Bone marrow macrophages (BMM) expressing c-MIR derived from c-MIR transgenic mice were stimulated with LPS. The amounts of IL-6 in the culture supernatants and the levels of IL-6 mRNA of the c-MIR expressing cells were quantified with ELISA and real-time PCR, respectively.

Results: The intraarticular c-MIR gene transfer exerted therapeutic effects on CIA. The arthritis score and histological changes were both suppressed. Unexpectedly, the therapeutic effect was not observed in the joints in the forelegs. In accordance with this fact, no difference in the serum anti-CII antibody levels or thereactivity of the splenocytes to CII was observed between the c-MIR gene-treated and control mice. The expression of c-MIR gene suppressed production of IL-6 and level of IL-6 mRNA in the activated FLS and BMM.

Conclusion: The intraarticular c-MIR gene transfer failed to inhibit acquired immunity against CII. Instead, the local treatment exerted local therapeutic effects. Because expression of c-MIR suppressed inflammatory cytokine production, this should have contributed to inhibition of the arthritis. Molecular pathways of this inhibition are now under investigation. c-MIR induction in the synovial tissues may provide an new approach to the effective treatment of RA.

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Bim-BH3 Mimetic Therapy Is Effective at Suppressing Inflammatory Arthritis through the Activation Myeloid Cell Apoptosis. John C. Scatizzi[1], Jack Hutcheson[2], Richard M. Pope[3], Gary S. Firestein[4], Alisa E. Koch[5], Melissa Mavers[6], G. Kenneth Haines III[7] and Harris R. Perlman[8], [1]The Scripps Research Institute, La Jolla, CA, [2]UT Southwestern, Dallas, TX, [3]Northwestern University, Chicago, IL, [4]UCSD School of Medicine, La Jolla, CA, [5]Veteran's Affairs and University of Michigan, Ann Arbor, MI, [6]Saint Louis University School of Medicine, St. Louis, MO, [7]Yale University, New Haven, CT, [8]Northwestern University Feinberg School of Medicine, Chicago, IL

Purpose: Rheumatoid arthritis (RA) is a destructive autoimmune disease associated with increased morbidity and mortality and characterized by an increase in inflammatory cells within the joint. It is clear that therapies which directly activate the apoptotic cascade may have potential as a future therapy for RA, however to date few therapeutics fit this category. Recently, therapies that mimic the action of Bcl-2 homology 3 (BH3) domain-only proteins have shown success in preclinical studies of cancer but their potential for controlling the fate of inflammatory cells, especially in autoimmune disease is unknown.

Method: Synovial tissue from RA and osteoarthritis (OA) patients were analyzed for expression of Bim and CD68 using immunohistochemistry. Macrophages from mice lacking (Bim-/-) were examined for response to lipopolysaccride using flow cytometry, real time PCR, ELISA, and immunoblot analysis. Bim-/- mice were stimulated with thioglycollate or LPS and examined for macrophage activation by flow cytometry and for IL-1b production by ELISA. Experimental arthritis was induced using the serum transfer model. Systemic delivery of a mimetic peptide corresponding to the BH3 domain of Bim (TAT-BH3) were administered as a prophylactic and as a

therapeutic. Edema of the ankles and histopathogical analysis of ankle sections were used to determine severity of arthritis, cellular composition of the joint, and apoptosis.

Results: n RA synovial tissue, the expression of the BH3-only pro-apoptotic protein Bim is reduced, particularly in macrophages. Bim-/- macrophages display elevated expression of markers of inflammation and secrete more IL-1beta following stimulation with LPS or thioglycollate. Analysis of peritoneal cells harvested at 6 hours following injection of K/BxN serum reveal that TAT-BH3 peptide induces apoptosis primarily in the myeloid cell population. In addition, TAT-BH3 peptide treated mice exhibited an increased numbers of TUNEL positive cells in the joints. Further, the reduction of circulating myeloid cells and increased apoptosis corresponded with fewer myeloid cells in the joint of TAT-BH3 peptide treated mice.

Conclusion: These data demonstrate that BH3 mimetic therapy is efficacious in RA-like disease model and suggest that this therapy may have significant potential for RA treatment.

Disclosure: J. C. Scatizzi, None; **J. Hutcheson**, None; **R. M. Pope**, None; **G. S. Firestein**, None; **A. E. Koch**, None; **M. Mavers**, None; **G. K. Haines**, None; **H. R. Perlman**, None.

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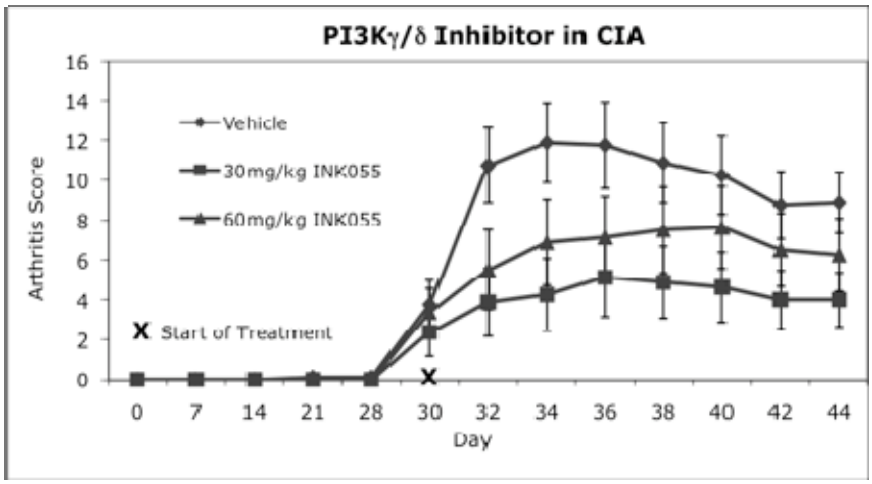
A Novel PI3Kinase γ/δ Inhibitor Suppresses Collagen-Induced Arthritis. David L. Boyle[1], Christian Rommel[2], Katharyn Topolewski[1] and Gary S. Firestein[1], [1]UCSD School of Medicine, La Jolla, CA, [2]Intellikine, La Jolla, CA

Purpose: The four members (α, β, γ, and delta [d]) of the phosphoinositide 3-kinases (PI3K) family transduce a variety of receptor-mediated signals. However, the gamma and delta PI3K isoforms are primarily restricted to leukocytes and act independently to regulate cytokine, chemokine and immunoglobulin responses. The delta isoform is associated with many cell surface receptors while the gamma isoform exclusively associates with G-protein coupled receptors, such as chemokine receptors. While selective γ and d inhibitors have potential for diseases like rheumatoid arthritis (RA), we hypothesized that combined inhibition would be especially effective. Therefore, we evaluated the effect of a dual PI3Kγ/d (INK055) inhibitor on murine collagen induced arthritis.

Method: DBA1/J mice (n=8/group) were immunized with bovine type II collagen in complete Freund's adjuvant and again on day 21 with type II collagen in PBS. On day 28, 5 μg of LPS in PBS was injected intraperitoneally. Paws were scored using a 0-4 scale, maximum 16 per animal. Animals were treated by gavage daily starting day 20 or 30 with vehicle, 30, or 60 mg/kg with a novel dual specific PI3K γ/d inhibitor, INK055 (IC50: PI3Kd: 3.2nM, PI3Kγ: 5.7nM, >600 for PI3Kα and PI3Kβ). ELISA was performed to assess anti-type II collagen levels in serum. Quantitative PCR was used to determine the effect on ankle joints gene expression.

Results: Initiating treatment with INK055 on day 20 in CIA significantly decreased disease severity by day 32 in both treatment groups (peak difference on day 36, vehicle 5.6±1.9, 30mg/kg 2.4±1.0, 60mg/kg 2.6±1.5; $p<0.05$). Serum anti-type II collagen antibody levels were unchanged in the low dose group and only modestly decreased in high dose group (Vehicle 200±3, 30mg/mg 180±20, 60mg/kg 143±12 μg/ml). MMP3 and MMP13 expression was significantly reduced in the ankles after treatment (MMP3 77±41, 46±12, 38±16 relative expression units in vehicle, 30mg/kg, 60mg/kg respectively). Treatment of established disease beginning on day 30 significantly decreased severity compared with vehicle with the peak effect on day 34 (see Figure) (vehicle 11.9±2, 30mg/kg 4.3±1.8, 60mg/kg 6.9±2.2; $p<0.05$). Anti type II collagen antibody levels were not affected in the delayed treatment study despite improved clinical arthritis (vehicle 151±17, 30mg/kg 125±19, 60mg/kg 152±18).



Conclusion: The dual PI3Kγ/d inhibitor INK055 was effective as prophylactic therapy as well as in established arthritis. The modest effect on autoantibody production and benefit observed in established disease suggests that the mechanism is through an effect on innate immunity rather than antibody production. A dual specific PI3Kγ/d inhibitor might be effective in rheumatoid arthritis while limiting systemic toxicity of α and β inhibitors.

Disclosure: D. L. Boyle, Intellikine, 2 ; **C. Rommel**, Intellikine, 3 ; **K. Topolewski**, None; **G. S. Firestein**, Intellikine, Intellikine, 2 .

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Increased Lymphatic Flow Reduces the Severity of Joint Tissue Damage in a Murine Model of Chronic Inflammatory Arthritis. Q. Zhou, R. Guo, R. Wood, B. Boyce, E.M. Schwarz and L. Xing, University of Rochester, Rochester, NY

Purpose: We have demonstrated previously that the blockage of lymphatic flow from joint tissues to the local draining lymph nodes (DLNs) increases the severity of joint inflammation and tissue damage in TNF transgenic (TNF-Tg) arthritic mice, indicating that efficient lymphatic flow is required for controlling the joint lesions of rheumatoid arthritis (RA). In this study, we test the hypothesis that increasing joint lymphatic flow attenuates the progression of arthritis by removing macrophages from inflamed synovium to local DLNs through local lymphatic circulation.

Methods: Human VEGF-C, a potent lymphatic growth factor, was cloned into an AAV expression vector. AAV-hVEGF-C or AAV-Luc control virus (N=5 mice/treatment) was injected intra-articularilly into knee joints of 1.5 month-old TNF-Tg mice before the onset of RA. Three months later, a clinical arthritic assessment was performed and the lymphatic draining function was measured by our newly developed near infrared-indocyanine green (NIR-ICG) lymphatic imaging method in which ICG, a NIR tracer, was intra-dermally injected into footpads and the movement of ICG from foot to the DLN was imaged and recorded. The expression of hVEGF-C in vivo was confirmed by RT-PCR using specific human VEGF-C primers. The joint inflammation, bone erosion, cartilage loss and lymphatic and blood vasculature were examined by histomorphometric analysis.

Results: VEGF-C treatment significantly decreased the arthritic deformation score (1.0+0.5 vs Luc 1.9+0.4) and increased the joint range of motion (110+15o vs Luc 167.5+/2.7o). Lymphatic flow from foot to DLNs was remarkably increased in legs which received VEGF-C virus. ICG signal intensity in DLNs was 8-fold higher in VEGF-C injected legs (58.4+37.3 vs Luc 6.7+7.1) and the clearance of ICG from the footpad was 6-fold faster (77.7+12.5% vs Luc 27.6+16.5%). VEGF-C administration significantly increased LYVE-1+ lymphatic vessels in the synovium (vessel area/synovial area: 0.25+0.12mm2 vs Luc 0.09+0.04mm2), had no effect on CD31+ blood vessels (blood vessel area/synovial area: 0.19+0.04mm2 vs Luc 0.23+0.12mm2), and decreased joint tissue damage including reduced inflammation area (0.099+0.04 mm2 vs Luc 0.171+0.03 mm2), eroded surface (0.34+0.11% vs Luc 0.88+0.11%), and cartilage loss (12+10 % vs Luc 38+18%). In contrast to joints, in DLNs of VEGF-C injected legs, both area of lymphatic vessels and the size of lymphatic sinuses were decreased (area: 0.34+0.08 mm2 vs Luc 0.45+0.05 mm2; size: 0.03+0.017mm2 vs Luc 0.19+0.11mm2).

Conclusion: Intra-articular administration of lymphatic growth factor VEGF-C decreases the severity of joint inflammation, bone erosion, and cartilage loss in TNF-Tg arthritic mice, which is associated with increased local lymphatic drainage from foot to DLNs and reduced inflammtion-induced DLN lymphangiogenesis. Thus, increasing joint lymphangiogenesis and lymphatic flow may represent a novel therapy for RA pathology.

Disclosure: Q. Zhou, None; **R. Guo**, None; **R. Wood**, None; **B. Boyce**, None; **E. M. Schwarz**, None; **L. Xing**, None.

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Jun N-Terminal Kinase 1 Is Required for Mast Cell Degranulation and IL-1b Production in Inflammatory Arthritis. Monica Guma[1], Maripat Corr[2], Gary S. Firestein[2] and Michael Karin[1], [1]UCSD, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA

Purpose: Jun N-terminal kinases (JNK) are activated in RA synovium and play a major role in cytokine production and extracellular matrix regulation through the production of metalloproteinases (MMP). We aimed to further analyze the mechanisms through which JNK promotes disease development and to test the ability of a specific JNK inhibitor that targets both JNK1 and JNK2 to improve the arthritis.

Methods: Wildtype (WT), *Jnk1*$^{-/-}$, bone marrow chimeras and mast cell reconstituted mice were injected with K/BxN sera on day 0 to induce arthritis. Ankle thickness and clinical arthritis scores were serially assessed. Joints were evaluated histologically for inflammation and joint damage using a semi-quantitative scoring system. Joint extracts were evaluated by ELISA and quantitative real-time PCR. Joint sections were mounted on slides stained with touluidine blue and scanned using the iCys laser scanning cytometer (CompuCyte) to quantify mast cells. In vitro mast cell cultures were stimulated with IgG and IL-1 release quantified by ELISA. A cell permeable peptide (D-JNKi) JNK inhibitor was injected i.p. on day 0 or day 4 after induction of passive K/BxN arthritis.

Results: *Jnk1*$^{-/-}$ mice had significantly lower clinical scores (peak score: 9.17 ± 0.7 and 5.5 ± 0.3; $p<0.01$ for WT and *Jnk1*$^{-/-}$ mice respectively) and histological changes on day 10 compared to WT mice. IL-1b protein levels, and IL-6, VEGF, MMP3 and MMP13 mRNA expression levels were significantly lower in inflamed *Jnk1*$^{-/-}$ joints compared with WT joints. Bone marrow chimeras and mast cell reconstitution showed JNK1 in bone marrow derived cells and mast cells were critical for passive K/BxN serum transfer arthritis. Histologic analysis showed a decrease in the number of degranulated mast cells (70% ± 8.5% and 40% ± 5.7%; $p<0.01$ for WT and *Jnk1*$^{-/-}$ mice respectively). Moreover, IL-1b secretion through FcgR in vitro was impaired in *Jnk1*$^{-/-}$ mast cells. Finally, D-JNKi successfully prevented arthritis in pre-treatment protocols and effectively decreased joint swelling in established disease.

Conclusion: JNK1 deficiency attenuated arthritis induction and joint destruction in the passive K/BxN model. JNK1 dependence was mediated by bone marrow derived cells, particularly mast cells. In the absence of JNK1, mast cells did not degranulate efficiently after stimulation with through their Fcg receptors, and released diminished amounts of IL-1b. Pharmacologic inhibition of JNK1 in this model effectively prevented arthritis onset and abrogated joint swelling in established disease. Hence, selective JNK1 blockade might prove an effective anti-inflammatory strategy for arthritis or other mast-cell mediated diseases.

Disclosure: M. Guma, None; **M. Corr**, None; **G. S. Firestein**, None; **M. Karin**, None.

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Absence of Integrin α2β1 Alters MMP Expression and TNF-Dependent Inflammatory Cartilage Destruction. Marvin A. Peters[1], Simon Strietholt[1], Doreen Wendholt[1], Svetlana Frank[1], Adelheid Korb[1], George Kollias[2], Beate Eckes[3] and Thomas Pap[4], [1]University Hospital Muenster, Muenster, Germany, [2]Biomedical Sciences Research Center Alexander Fleming, Vari, Greece, [3]University of Cologne, Cologne, Germany, [4]Univ Hosp, Muenster, Germany

Purpose: Integrins are main receptors for cell-matrix interactions, and integrin signaling is critical for a variety of cellular functions such as adhesion, cell spreading and inflammatory responses. α2β1 integrin functions as a major receptor for type I collagen on a number of different cells, including fibroblasts and inflammatory cells. Although α2 integrin deficient mice appear normal apart from mild platelet dysfunction and abnormal angiogenesis, it was shown that α2 integrin contributes to the induction of MMPs in tissue remodeling. Based on the hypothesis that under stress conditions such as chronic inflammation, α2 integrin may be involved in the activation of synovial cells, we investigated the role of α2 integrin in inflammatory arthritis.

Method: To determine the role of α2 in TNF-mediated joint disease, we crossed α2-deficient mice with arthritic human TNFalpha transgenic (hTNFtg) mice. Clinical signs of arthritis and weight as well as the histological degree of synovitis and cartilage destruction in hind paws were investigated using standard clinical evaluation and histomorphometric analysis. In addition, we analyzed levels of cytokines and MMPs using serum and synovial fibroblasts from all genotypes. In addition, we used an established in vitro assay to investigate the role of the α2-subunit in the attachment of mouse synovial fibroblasts to healthy and IL-1 damaged articular cartilage.

Results: We found that loss of α2 integrin in hTNFtg mice resulted in improved clinical signs and symptoms as compared to hTNFtg mice arthritis score. hTNFtg/α2(-/-) mice had less paw swelling (1.87 vs. 2.66), increased grip strength (-1.83 vs. -2.66) and a less pronounced weight loss. Histological analysis of these mice revealed that loss of α2 integrin lead to a decrease in synovial inflammation as compared to hTNFtg mice. To evaluate the role of α2 for MMPs we analyzed serum levels of α2-deficient and wt mice and found no significant difference in MMP3 or MMP9. However in α2(-/-) synovial fibroblasts MMP3 expression was downregulated, compared to wt synovial fibroblasts (127.5 vs. 170.5 ng/ml). This downregulation was similar in synovial fibroblasts from hTNFtg/α2(-/-) mice compared to fibroblasts from hTNFtg animals. In addition, we found a diminished attachment of α2-deficient mouse synovial fibroblasts particularly after induction of proteoglycan loss in IL-1 treated cartilage pieces in vitro.

Conclusion: Our findings suggest that although α2 integrin appears to be dispensable for normal development, the loss of α2 leads to a decrease in inflammation and bone destruction in an animal model of inflammatory arthritis.

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R-Spondin1 Protects against Bone Loss During Murine Arthritis by Modulating the Wnt Pathway. Gerhard Krönke[1], Stefan Uderhardt[1], Kyung-Ah Kim[2], Georg Schett[1] and Arie Abo[2], [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Nuvelo Inc., San Carlos, CA

Purpose: To test the efficiacy of the secreted Wnt modulator R-Spondin-1 (RSpo-1) in the preservation of joint integrity in a murine model of arthritis

Method: RSpo-1 was applied to isolated osteoblasts and osteoclast/osteoblast co-cultures to evaluate its effect on the differentiation of these celltypes *in vitro*. To test the potency of RSpo-1 as a joint preserving agent *in vivo*, arthritic TNF-transgenic mice were treated with recombinant RSpo-1 by daily subcutaneous injection.

Results: RSpo1 was highly effective in preserving structural integrity of joints in the TNF transgenic mouse model of rheumatoid arthritis by protecting bone and cartilage from inflammatory damage. RSpo1 antagonized the Wnt inhibitor Dkk1 and modulates Wnt signaling in mesenchymal cells. In osteoblasts RSpo1 induced differentiation and expression of OPG thereby inhibiting osteoclastogenesis *in vitro*. In joints, RSpo1 blocked osteoclast development and globally modulated the homeostasis of anabolic and catabolic gene expression. We observed induction of genes involved in both chondrogenesis and osteogenesis, which contributed to the integrity of cartilage and bone during joint inflammation.

Conclusion: Our results demonstrate the therapeutic potential of RSpo1 as an anabolic agent for the preservation of joint architecture.

Disclosure: G. Krönke, None; **S. Uderhardt**, None; **K. A. Kim**, Nuvelo, 3 ; **G. Schett**, None; **A. Abo**, Nuvelo, 3 .

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PLX FK1, A Novel Dual Inhibitor of Kit and Fms Receptor Tyrosine Kinases Reverses Clinical and Histological Disease Parameters in Multiple Autoimmune Disease models. Gaston Habets, Jiazhong Zhang, Betsy Burton, Chao Zhang, Prabha Ibrahim, Bernice Wong, Marika Nespi, Ben Powell, Brian West, Paul Lin, Gideon Bollag and Peter Hirth, Plexxikon Inc, Berkeley, CA

Purpose: PLX FK1 is a potent and highly selective inhibitor of the tyrosine kinase activities of the Kit (K_I = 0.9nM) and Fms (K_I = 1nM) receptors. Kit is a key regulator of mast cells and dendritic cells, and Fms is a key regulator of macrophages, dendritic cells, and osteoclasts. Together, the cellular targets of these receptors control autoimmune processes involved in many diseases, including rheumatoid

arthritis (RA), multiple sclerosis (MS), lupus and inflammatory bowel disease. Knockout studies suggest roles for both Fms and Kit kinases in models of arthritis, through their direction of macrophages and mast cells, respectively. Therefore, PLX-FK1 is a valuable compound to test the role of Fms and Kit target cells in autoimmune diseases.

Methods: and **Results:** In an acute MOG-induced EAE mouse MS-model, a 50 mg/kg q.d. oral dose of PLX FK1 resulted in rapid and substantial regression of disease over a 6 week period, with most mice showing no evidence of disease at study end. In a MLR/lpr mouse lupus-model, treatment with a 50 mg/kg q.d. oral dose of PLX FK1 significantly decreased proteinurea levels from 100 mg/dL: following 8 weeks of treatment proteinurea in PLX FK1-treated mice decreased to 30-50 mg/dl, while proteinurea in vehicle-treated mice increased to 250-300 mg/dl. In addition, auto-antibodies against dsDNA and paw and joint swelling were decreased by PLX FK1 treatment. Based on these data, the same dose of PLX FK1 was chosen to examine its efficacy in an aggressive model of RA: in a rendition of murine collagen-induced arthritis, DBA/1 mice were immunized with Bovine Collagen II in CFA on day 0 and given a Collagen boost ip on day 21. By day 19, disease had progressed to a mean score of 4 (out of 16), and treatment was initiated. Dexamethasone 0.5 mg/kg ip was included as the active control. Within the first week of treatment, the 50 mg/kg q.d. oral dose of PLX FK1 resulted in significant stabilization of disease that continued through the course of treatment. Following three weeks of treatment, the mean disease score of the PLX FK1-treated animals was 5.2, while progressive disease in the vehicle-treated animals reached a mean score of 13.3. Upon histopathological examination of wrist, paw and ankle joints, the disease scores for inflammation, pannus formation, cartilage damage and bone resorption were all significantly lower in the PLX FK1 treated animals versus vehicle treated animals. Also, macrophage and mast cell counts were lower in the PLX FK1 treatment group.

Conclusion: Dual inhibition of Kit and Fms kinase activities by the potent and highly selective inhibitor PLX-FK1 results in substantial efficacy in aggressive models of MS, lupus and RA and warrants further development in clinical studies.

Disclosure: G. Habets, Plexxikon, 1, Plexxikon, 3 ; **J. Zhang**, Plexxikon, 1, Plexxikon, 3 ; **B. Burton**, Plexxikon, 1, Plexxikon, 3 ; **C. Zhang**, Plexxikon, 1, Plexxikon, 3 ; **P. Ibrahim**, Plexxikon, 1, Plexxikon, 3 ; **B. Wong**, Plexxikon, 1, Plexxikon, 3 ; **M. Nespi**, Plexxikon, 1, Plexxikon, 3 ; **B. Powell**, Plexxikon, 1, Plexxikon, 3 ; **B. West**, Plexxikon, 1, Plexxikon, 3 ; **P. Lin**, Plexxikon, 1, Plexxikon, 3 ; **G. Bollag**, Plexxikon, 1, Plexxikon, 3 ; **P. Hirth**, Plexxikon, 1, Plexxikon, 9 .

ACR/ARHP Poster Session B

B-Cell Biology and Targets in Autoimmune Disease

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Suppression of Primary SLE B Cells by XmAb®5871, An Anti-CD19 Monoclonal Antibody (mAb) That Co-Engages the B Cell Antigen Receptor (BCR) and the FcγRIIb Inhibitory Receptor. Seung Y. Chu[1], Elizabeth C. Ortiz[2], Erik Pong[1], Holly M. Horton[1], Noam Jacob[2], William Stohl[2] and David E. Szymkowski[1], [1]Xencor, Inc., Monrovia, CA, [2]Univ Southern California, Los Angeles, CA

Purpose: XmAb®5871 is a genetically-engineered humanized anti-CD19 mAb that mimics the immunosuppressive effects of immune complexes through its high-affinity binding (0.2 nM) of CD19 (a component of the BCR complex) and simultaneous high-affinity (4 nM) engagement of the B cell inhibitory receptor FcγRIIb (normally a low-affinity receptor for native IgG Fc). Such co-engagement of BCR and FcγRIIb on human B cells potently suppresses activation responses such as intracellular calcium flux, cell proliferation, and class switching. Since FcγRIIb-mediated inhibition may be perturbed in SLE patients, it is critical to determine whether FcγRIIb is a pharmacologically tractable target in SLE. Therefore, we assessed the ability of XmAb5871 to suppress activation of primary SLE and normal B cells.

Method: SLE patients with elevated circulating levels of at least one SLE-associated autoantibody (anti-dsDNA, anti-Sm, anti-RNP, anti-SS-A, anti-SS-B, anti-cardiolipin) were recruited. B cells were purified from the venous blood of these SLE patients and healthy normal control donors, and cultures containing either XmAb5871 or control mAb were established. In vitro responses of SLE and normal B cells were assessed by suppression of BCR-induced proliferation, intracellular calcium flux, and surface expression of costimulatory molecules. FcγRIIb expression on B cells was measured by flow cytometry and was correlated with the in vitro potency of XmAb5871.

Results: In vitro studies indicated that the FcγRIIb pathway in SLE B cells can be amplified pharmacologically by XmAb5871. Intracellular calcium signaling was suppressed by XmAb5871 in SLE B cells as well as in normal B cells. Inhibition was critically dependent on amplified FcγRIIb engagement, because control anti-CD19 mAb containing native IgG1 or knocked-out Fc domains were inactive.

Conclusion: The normal physiological role of immune complexes in suppressing B cell activation can be mimicked by a novel engineered mAb that co-engages FcγRIIb and BCR with high affinity. This inhibitory pathway is functional in SLE B cells, suggesting that a mAb that amplifies FcγRIIb signaling may represent a new therapeutic strategy to suppress autoreactive B cell populations in SLE and related autoimmune diseases.

Disclosure: S. Y. Chu, Xencor, Inc., 1, Xencor, Inc., 3 ; **E. C. Ortiz**, None; **E. Pong**, Xencor, Inc., 1, Xencor, Inc., 3 ; **H. M. Horton**, Xencor, Inc., 1, Xencor, Inc., 3 ; **N. Jacob**, None; **W. Stohl**, Xencor, Inc., 2, Xencor, Inc., 5 ; **D. E. Szymkowski**, Xencor, Inc., 1, Xencor, Inc., 3 .

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Peripheral Blood B Cells Subsets in Patients with Systemic Lupus Erythematosus: Correlation with Disease Activity and Organ Involvement. Elisa Gremese[1], Barbara Tolusso[1], Alessandro Michelutti[1], Marcin Nowik[1], Antonella Laria[1], Graziella D'Antona[1] and Gianfranco Ferraccioli[2], [1]Division of Rheumatology – Catholic University of the Sacred Heart, Rome, Italy, [2]Division of Rheumatology, Catholic University, Rome, Italy

Purpose: Disturbance in peripheral blood (PB) B cells subpopulation have been observed in patients with SLE, but have not been fully delineated in relation to disease phenotype.

The aim of the study was to analyze the frequency and distribution of B cells subsets in a cohort of patients with SLE with different organ involvement and the possible correlation with the disease activity.

Method: 47 SLE patients (41 females; mean age 37.1±10.9 years; 25 with renal, 15 with articular, 3 with SNC, 3 with vascular and 1 with cutaneous involvement; 25 with an active disease-SLEDAI>10) and 15 healthy controls were analyzed for the delineation of circulating PB B cell subpopulations by staining for CD19, CD38, and IgD in combination with the B cell memory marker CD27, by flow cytometry.

Results: Subjects with SLE had a significantly lower frequency of Bm5 cells defined by the expression of IgD and CD38 (12.2±8.1%) than healthy controls (17.2±6.3%, p=0.01).

In SLE patients, disease activity index (SLEDAI) correlated negatively with the absolute number of lymphocytes (r= -0.36, p=0.03), instead positively with the percentage of CD19+ cells (r=0.43, p=0.004).

SLE patients with an active disease had an higher percentage of CD19+ cells compared with patients with inactive disease (12.2±7.6% vs 6.5±7.7% respectively, p=0.001). Patients with active disease had an higher absolute number of memory cells (eBm5+Bm5 42±43/ul, CD27+ 24±33, CD27+/IgD- 19±22) and of the CD19+/CD27+CD38+ (13±16) compared with patients with inactive disease (eBm5+Bm5 15±13, p=0.01, CD27+ 7±7, p=0.01, CD27+/IgD- 5±5, p=0.002, CD19+/CD27+CD38+ 3±3, respectively, p=0.004). The distribution of Bm1-Bm5 subsets was similar in patients with renal and articular involvement, even if considering only the subgroup with active disease, patients with renal involvement showed an higher percentage of memory B cells (eBm5+Bm5 37.5 ± 22.7%) compared with patients with articular involvement (16.4±6.9%, p=0.02). This difference was also confirmed by the ratio Bm2+Bm2'/eBm5+Bm5 in active renal disease (1.4±0.9) compared to 4.7±2.4 in active articular disease (p=0.01).

Conclusion: SLE patients showed a significant reduction of memory B cells compared with controls, regardless of the organ involvement. An increase of memory B cells appeared, however, in patients with renal active engagement, while an higher percentage of active cells was present in patients with active articular involvement.

Disclosure: E. Gremese, None; **B. Tolusso**, None; **A. Michelutti**, None; **M. Nowik**, None; **A. Laria**, None; **G. D'Antona**, None; **G. Ferraccioli**, None.

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Prolonged but Variable Effects of B Cell Depletion Therapy in Murine Lupus Nephritis. Kai Bekar[1], Teresa Owen[1], Robert Dunn[2], Travis Ichikawa[1], Jennifer Barnard Hossler[1], Sarah Nevarez[1], Sean Brady[1], Bruce Goldman[1], Marilyn R. Kehry[2] and Jennifer H. Anolik[3], [1]University of Rochester Medical Center, Rochester, NY, [2]Biogen Idec, San Diego, CA, [3]University of Rochester, Rochester, NY

Purpose: The pathogenic significance of B cells in systemic lupus (SLE) has been highlighted by the abrogation of disease in B cell deficient mice. However, the benefit of B cell depletion therapy (BCDT) in human SLE has recently been questioned by lack of clinical efficacy observed in the Explorer and Lunar studies. Development of a murine lupus model of BCD would be helpful to better understand the mechanisms and effects on disease outcomes.

Methods: Young NZB/NZWF1 female (8-12 weeks), early disease (18 weeks), and established nephritis (24-30 weeks with durable proteinuria > 2+ or 100 mg/dl) animals were dosed with anti-CD20 antibody (IgG2a), BR3-Fc, or control antibody (10 mg/kg) i.v. Additionally, normal BALB/c were dosed with anti-CD20, CpG1826, and/or anti-CD40. Peripheral blood (PB), lymph node (LN), bone marrow (BM), spleen and peritoneal cells were harvested and analyzed by flow cytometry. Nephritis was monitored by proteinuria (Uristix) and kidney IHC. Serum IgG anti-dsDNA levels were measured by ELISA.

Results: A single injection of anti-CD20 in normal mice caused rapid depletion of B cell subsets although with a gradation of sensitivity (%depletion): PB>spleen>LN>peritoneum>BM. Germinal center (GC) B cells in immunized mice were relatively resistant to depletion, an effect potentiated by anti-CD40 and a B cell stimulatory TLR9 CpG agonist. B cell reconstitution began ~6 weeks after initial treatment. Administration of a CpG agonist resulted in significantly earlier B cell reconstitution. In young NZB/NZWF1 mice BCD was incomplete with early reconstitution at 3 weeks. A sequential weekly dosing x 4 was subsequently utilized and improved depletion of more resistant subsets, including splenic marginal zone (30% depletion at 1 week to 97% depletion at 4 weeks). Treatment of older mice with established nephritis (2+) resulted in a significant decrease in the %B220+ cells compared to control antibody treated animals (12.19±3.69 vs. 44.40±3.69, $p<0.001$). However, there was significant variability among animals ranging from 7% to 91% depletion in the spleen, with relative resistance of the MZ and GC B cells. Depletion was improved by combination with BAFF blockade (BR3-Fc). BCDT prevented the progression of nephritis, with a significant difference in protein free survival that was maintained 20 weeks beyond completion of treatment ($p<0.01$). Serum anti-dsDNA antibodies were not different between the two groups, but activated and memory T cells were decreased with BCD ($p<0.05$). In a prevention study, treatment of 18 wk mice with 4 wks of anti-CD20 significantly delayed the onset of disease by over 20 wks ($p=0.0007$), a prolonged benefit that extended well after B cell reconstitution.

Conclusion: The lasting benefit of a short course of BCDT in NZB/NZWF1 mice supports a critical role of B cells in this disease model. Resistance of B cell populations to depletion may explain some heterogeneity in clinical response but could be overcome by combination therapeutic approaches. Supported by a Lupus Research Institute grant

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Plasmin Cleavage of Beta2-Glycoprotein I Promotes Maternal Anti-Ro60 IgG Opsonisation of Apoptotic Cells: A Permissive Factor in Congenital Heart Block? Joanne H. Reed[1], Bill Giannakopoulos[2], Kenneth M. Kaufman[3], Steven A. Krilis[2] and Thomas P. Gordon[1], [1]Flinders Medical Centre, Bedford Park, Australia, [2]University of New South Wales, Sydney, Australia, [3]Oklahoma Medical Research Foundation, OK, OK

Purpose: Maternal anti-Ro60 autoantibodies are thought to initiate tissue damage in congenital heart block (CHB) by binding to apoptotic fetal cardiocytes. The plasma protein beta2-glycoprotein I (β2GPI) binds to Ro60 (amino acid residues 82-244) on the surface of apoptotic cells via its fifth domain and prevents the formation of pathogenic anti-Ro60 IgG-apoptotic cell immune complexes. The current study was initiated to define the precise Ro60-β2GPI binding sites and determine whether plasmin mediated cleavage of β2GPI influences immune complex formation.

Method: The β2GPI binding site on Ro60 was mapped by ELISA using overlapping soluble recombinant Ro60 subfragments spanning amino acids (aa) 82-244. The Ro60 binding on β2GPI was studied by apoptotic cell flow cytometry inhibition experiments using β2GPI peptides and plasmin-cleaved β2GPI. Binding of anti-Ro60 IgG from mothers of infants with CHB to apoptotic cells was determined by flow cytometry in the presence or absence of plasmin-cleaved β2GPI.

Results: The Ro60 β2GPI-binding site was mapped to a 64 aa region within the middle third of the Ro60 protein. A peptide representing a charged region within domain V (CKNKEKKC) of β2GPI partially inhibited binding to Ro60 on apoptotic cells. Plasmin cleavage of the β2GPI hydrophobic loop (Lys317-Thr318) abrogated binding of β2GPI to both recombinant and apoptotic cell membrane-bound Ro60 by

flow cytometry. Maternal anti-Ro60 IgG opsonised apoptotic cells in the presence of plasmin cleaved β2GPI under conditions where an equivalent concentration of native β2GPI completely inhibited immune complex formation.

Conclusion: β2GPI interacts with a 64 aa region of Ro60 via its hydrophobic loop and adjacent positively charged lysine rich region in domain V. Stimulation of plasmin production by infection or inflammation in the fetal heart may eliminate the protective effect of β2GPI and open the way for maternal anti-Ro60 autoantibody-mediated tissue damage.

Disclosure: J. H. Reed, None; **B. Giannakopoulos**, None; **K. M. Kaufman**, None; **S. A. Krilis**, None; **T. P. Gordon**, None.

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Novel Autoantibody Markers for Early and Seronegative Rheumatoid Arthritis. Klaartje Somers[1], Piet P.M.M. Geusens[2], Marieke JH Coenen[3], Marlies Blom[3], Piet Stinissen[1] and Veerle Somers[1], [1]Hasselt University, Biomedical Research Institute, Diepenbeek, Belgium, [2]Maastricht University Medical Center and Hasselt University, Biomedical Research Institute, Diepenbeek, Belgium, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose: Approximately one-third of rheumatoid arthritis (RA) patients are seronegative for the 2 serological RA markers, rheumatoid factor (RF) and antibodies directed against cyclic citrullinated peptides (anti-CCP antibodies). The sensitivities of both markers in early RA are even lower. The aim of this study was to identify novel markers for early RA and for RA patients that are seronegative for RF (RF-) and anti-CCP antibodies (ACPA-).

Method: We applied an autoantibody profiling procedure which entailed the screening of a RA cDNA phage display library, for antigen-reactivity with pooled serum from 10 early RA patients (symptoms of less than 1 year) and 10 RF- ACPA- RA patients.

Results: This approach resulted in the identification of 11 RA-specific and 3 RA-associated novel autoantibody targets for which no immunoreactivity was detected in the HC group (n=38). Antibodies against the panel of 11 RA-specific clones were demonstrated in 37% (34/92) of tested RA patients, with 100% specificity for the disease. By adding 2 RA-associated clones to the panel, 53% (49/92) of RA patients were antibody-positive with an associated specificity of 90% (reactivity in 7/30 rheumatic control patients). Antibody-reactivity against the panel was demonstrated to be associated with early disease (P=0.0087). In addition, as antibodies against the panel were detected in RA patients that were serologically negative for RF and/or ACPA, the detection of these novel antibody markers was of added value to the diagnostic testing for RF and ACPA; testing for the presence of antibodies against the panel increased the sensitivity of serological tests for RA by 25%. Moreover, several of the identified antigens demonstrated exclusive immunoreactivity in ACPA- RA patients, indicating their potential relevance as markers for this RA subtype. Furthermore, the presence of antibodies against our panel was shown to be associated with higher inflammatory disease activity (C-reactive protein levels) (P=0.0146). These findings clearly demonstrate the diagnostic and prognostic potential of the panel. Besides the marker potential of these antigens, the demonstration of increased expression of several of the identified antigens in RA synovial tissue supported a biological rationale for these novel RA antibody targets.

Conclusion: In conclusion, we identified a panel of 13 novel antibody markers for RA and illustrated the usefulness of these markers for improved RA diagnostics and prognostics. Moreover, we provided evidence for a biological relevance of several of the identified novel RA antigens in the RA disease process, providing more insight into the autoimmune processes occurring in RA.

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Comparision of Clinical Outcome in Rheumatoid Arthritis Patients Treated with a Fixed or On-Demand Regime of Rituximab: Two Year Follow Up. Janneke Tekstra[1], Onno Y. K. Teng[2], Paco M.J. Welsing[1], Jaap M. van Laar[3], Floris P.J.G. Lafeber[1] and Johannes W. J. Bijlsma[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Newcastle University, Newcastle, United Kingdom

Purpose: Rituximab has proven to be an effective and safe treatment for rheumatoid arthritis (RA). However, the preferred timing and dosage of repeated treatment of Rituximab is still a matter of debate. Our objective was to compare the clinical outcome of two treatment regimes with Rituximab in refractory RA patients.

Method: In a two-center prospective open-label study over 2 years, patients with refractory RA were treated with two different regimes of rituximab. All patients received initial treatment with 2x1gr intravenously, and retreatment with 1gr intravenously. In one center, 26 patients received retreatment every 24 weeks, while 20 patients in another center received retreatment only when disease relapsed (DAS28 >3.2 and decrease of DAS28<1). Clinical response was defined according to the European League Against Rheumatism (EULAR) criteria and the average DAS28 and HAQ over time were calculated and compared. The difference in average DAS28 and HAQ were corrected for baseline prognostic differences between groups using regression analysis. The number of serious adverse events (SAE), aberrant values for leukocytes and total immunoglobulins, and number of rituximab doses were also compared between the groups.

Results: At baseline, both treatment groups differed significantly in DAS28 (5,1 for the fixed retreatment group vs 6,1 for the on-demand group, P=0.01), indicating that the on-demand group had more severe RA. This is further reflected by a significantly higher number of previous anti-TNF medication used (1,54 vs 2,05, P=0.33). EULAR responses at 24 months were not significantly different in the fixed retreatment group resp in the on-demand group: 38.5% resp 21.4% (good responders) and 38.5% resp 35.7% (moderate responders).

The mean DAS28 over time was 0,5 points higher in the on-demand group corrected for baseline DAS28 (p=0.069). No difference in HAQ score between regimes was found. In the fixed retreatment group, a trend toward more SAE's as a reason for study discontinuation was observed (26,9% vs 10%, P=0.054) as well as a significantly higher incidence of (transient) leukopenia (34,6% vs 10%, P=0.044). No differences between the groups were found for total immunoglobulin levels. On average 1.15 fewer rituximab retreatments were used in the on-demand group (p=0.001).

Conclusion: The fixed retreatment regime with rituximab compared to an on-demand retreatment regime in RA patients seemed to result in a modestly lower mean DAS28. It also seemed to result in an increased number of SAE and cases of leukopenia, although transient. Moreover, significantly more doses of rituximab were needed to achieve this difference in DAS28. In practice, these factors must be weighed against the clinical benefit.

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Response to Rituximab in Rheumatoid Arthritis Patients: Association with B-Cell Markers. Athina Pyrpasopoulou, Stella Douma, Areti Triantafyllou, Sofia Chatzimichailidou, Magda Samara, Efthymia Parapanisiou and Spyros Aslanidis, Hippokration General Hospital, Thessaloniki, Greece

Purpose: Rituximab is used to deplete B cells, and control disease activity in, mainly, anti-TNF failing RA patients. Response rates and time to relapse vary significantly among treated individuals. The objective of this study was to monitor response of seropositive and seronegative RA patients to rituximab and correlate relapse with B cell markers in the two groups.

Methods: Seventeen patients with RA (8 seropositive and 9 seronegative, aged 25-77 years), with 2-30 years disease duration, received 2 cycles of rituximab. There was no statistically significant difference in the baseline characteristics of the two groups. Rituximab was readministered when disease relapse was confirmed by clinical-laboratory measures (DAS28). CD20(+) cells and CD20 receptor expression were estimated at initiation, relapse, and reevaluation timepoints.

Results: Mean time to relapse after the 1st cycle of rituximab was 337.5+127 for seropositive vs 233.3+59.6 days for seronegative patients (p=0.043), table I. The mean DAS28 score decrease 3 months post treatment respectively was 1.695±1.076 vs 0.94±1.620. At relapse, CD20 receptor quantitative expression was higher in Rf(+) patients compared to the Rf(-) group (122,085.6±86,147.7 molecules/ cell vs 2,450 molecules/ cell [1,100-189,140], despite lower % of CD20+ cells (5.36±4.66 vs 8.62±7.20, p=0.043).

Conclusion: Rituximab treatment is efficient both in seropositive and seronegative RA. However, Rf(+) RA patients tend to exhibit a favorable and more sustained response compared to Rf(-) ones. The differential CD20 receptor expression in the two groups at relapse potentially suggests a different pathogenetic mechanism of relapse and merits further investigation.

Table I. Disease activity measurements in the total sample, in seropositive and in seronegative rheumatoid arthritis patients

	Total n=17		**Seropositive n=8**		**Seronegative n=9**	
	1st	**2nd**	**1st**	**2nd**	**1st**	**2nd**
TJC	13.4 ±7.22	11.2 ±6.1	13.0 ±7.3	10.7 ±5.1	13.8 ±7.6	11.6 ±7.2
SJC	8.8 ±6.6	4(0-22)	9.3 ±7.8	10.0 ±7.8	8.6 ±5,7	4(0-16)
CRP (mg/L)	22.51(2.93-132)	6.24(3.02-89.9)	12.35(2.93-81.2)	7.31(3.08-14.8)	7.53(3.13-132)	5.07(3.02-89.9)
ESR	44.0(6-122)	26(12-16)	45.38 ±22.89^	35.86 ±21.3^	30(18-122)	26(12-116)
DAS28	6.08 ±1.19**	5.28 ±0.94**	5.81 ±1.27	5.37 ±1.09	5.79(5.52-8.64)*	5.19 ±0.85*
Mean time to relapse (days) between 1st &2nd cycle	270(150-540)		337.5 ±127.0+		233.3 ±59.6+	
CD20%	8.96 ±3.16	7.10 ±6.18	9.86 ±2.19	5.36 ±4.66+	8.19 ±3.80	8.62 ±7.20+
CD20 receptor molecules/cell	127,824.9 ±43,314.3	87,317. ±86,860.8	142932.6 ±36,883.2	122,085.6 ±86,147.7	114,605.7 ±46,457.5	2,450.0(1100-189,140)

**p<0.05 between 1st and 2nd cycle, ** p<0.01 between 1st and 2nd cycle, ^p=0.051 between 1st and 2nd cycle*

+p<0.05 between seropositive and seronegative group

Disclosure: A. Pyrpasopoulou, None; **S. Douma**, None; **A. Triantafyllou**, None; **S. Chatzimichailidou**, None; **M. Samara**, None; **E. Parapanisiou**, None; **S. Aslanidis**, None.

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Inhibition of Immunoglobulin Light Chains by Rituximab Correlates with Inhibition of Clinical Activity in Patients with RA.

Janneke Tekstra[1], Tom Groot Kormelink[2], Rogier M. Thurlings[3], Maartje J. H. Boumans[3], Koen Vos[3], Paul P. Tak[3], Johannes W. J. Bijlsma[1], Frank A.M. Redegeld[2], Floris P.J.G. Lafeber[1] and Joel A.G. van Roon[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Utrecht Institute for Pharmaceutical Sciences, Fac. Science, Utrecht, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Immunoglobulin kappa and lambda free light chains (FLCs) are produced physiologically and levels are increased in several inflammatory diseases like asthma, inflammatory bowel disease and rheumatoid arthritis (RA). FLCs are short-lived products of B lymphocytes and have been shown to promote inflammation by activation of mast cells. Our purpose was to investigate how FLC concentrations correlate with disease activity and whether FLC changes upon B cell targeted therapy in RA patients correlate with changes in disease activity.

Method: 50 RA patients with active disease were treated with rituximab. Clinical response was defined according to the European League Against Rheumatism (EULAR) criteria. FLC kappa and lambda concentrations were measured using a sensitive ELISA. FLCs were measured at baseline and 3 and 6 months after treatment. At these time points, total immunoglobulin concentrations, rheumatic factor (RF) and anti-CCP were also measured.

Results: At baseline FLC concentrations significantly correlated with DAS 28 (p=0.006 for kappa and p=0.04 for lambda) and ESR and CRP (all p<0.01). Over time, kappa and lambda FLC concentrations decreased significantly after rituximab treatment (p<0.001 for baseline vs 3 months and p<0.01 for baseline vs 6 months after treatment for both kappa and lambda FLC). Patients without clinical response to rituximab showed no significant reduction of FLC concentrations, whereas patients who responded clinically did show a significant decrease in FLCs. Changes in FLC concentrations (kappa and lambda), 3 and 6 months after treatment, showed a highly significant (P<0.001) correlation with the changes in ESR. As described previously, RF levels and, to a lesser extent, anti-CCP antibody levels decreased after rituximab treatment (45% and 26%, resp). In contrast to FLC concentrations, RF levels decreased significantly in clinical responders as well as in non-responders. Total IgG, IgA and IgM concentrations remained within normal limits.

Conclusion: Rituximab significantly decreases FLCs in RA patients. Changes in FLC concentrations significantly correlate with the clinical response. In contrast, RF levels decrease after treatment in patients with and without clinical response. Our study suggests that inhibition of FLCs may represent a novel anti-inflammatory mechanism of Rituximab treatment.

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The FMS-Like Tyrosine Kinase 3 Ligand Is Associated with the Abnormal Blood B-Cell Distribution in Sjögren's Syndrome.
Jacques-Olivier Pers[1], Gabriel Tobon[1], Valérie Devauchelle[2] and Pierre Youinou[1], [1]Brest University Medical School Hospital, Brest, France, [2]CHU Brest, Brest, France

Purpose: Sjögren's syndrome (SS) is a chronic autoimmune epithelitis. The relevance of B-cell in the physio-pathology of SS has been emphasized over the past five years. Recently we demonstrated that the distribution of mature B-cell subsets from Bm1 through Bm5 in peripheral blood of patients with SS is different from other autoimmune diseases and controls, characterized by an increase in Bm2 and Bm2' B cell-subsets. FMS-like tyrosine kinase 3 ligand (FL), a cytokine implicated in the B-cell ontogenesis and malignant hematological proliferation, might be responsible for this abnormal blood B-cell distribution in SS.

Method: Serum levels of FL were evaluated in sixty-four SS patients and 20 matched healthy controls. FL and its receptor Flt3 were quantified in circulating B cells by real time-PCR and fluorescence-activated cell-sorter, but also in salivary gland biopsies by immunofluorescence. The impact of FL on circulating B lymphocytes was then evaluated by co-culture experiments using the human salivary gland cell line HSG.

Results: Serum levels of FL were increased in SS patients compared to controls (135.8 pg/mL ± 43.9 vs. 64.4 pg/mL ± 19.5 ; p < 0,001). Higher serum levels of FL were significantly associated with the abnormal B-cell profile in SS patients (r=0,459; p<0,0006). We found a selective expression of Flt3 in Bm2 and Bm2' B cells, which are also the main cells expanded in SS. B cell culture experiments showed that FL alone is not able to generate an effect on B cell proliferation, but potentiates the proliferative effect of an anti-IgM stimulation. In salivary glands, we have found that infiltrating B cells express Flt3 whereas epithelial cells produce FL. This cytokine was shown to be functional in that survival of co-cultured B cells with HSG cells was abrogated by anti-FL or anti-Flt3 antibodies.

Conclusion: FL is elevated in SS patients which is correlated with an abnormal B-cell profile in the blood. Flt-3 is express by Bm2 and Bm2' (subsets of B cells altered in the disease). The role of FL over the B cell proliferation may explain the clinical evolution to B cell lymphoma observed in some patients. Targeting FL may open new strategies in SS patients therapy.

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RNA Recognition Motif (RRM) of La/SSB: The Bridge for Inter-Particle Spreading of Autoimmune Response to RNP.
John G. Routsias, Nikolaos Kyriakidis, Michael Latreille, Haralampos M. Moutsopoulos and Athanasios G. Tzioufas, School of Medicine, National University of Athens, Athens, Greece

The hallmark of SLE is the production of grouped sets of autoantibodies targeting mainly the U1-RNP and/or Ro/La ribonucleoprotein particles. Intra-particle diversification of the autoimmune response is believed to occur via epitope spreading. So far, it remains unsolved how the autoimmune response "jumps" from one particle to another. To the extent that the majority of nuclear autoantigens in lupus are RNA binding proteins and major epitopes were previously mapped within their RRM (RNA recognition motifs), conserved sequences within RRM could be involved in the intermolecular and inter-particle diversification process of autoimmune response.

Purpose: To investigate the potential of RRM of the La autoantigen to induce antibodies that cross-recognize components of U1-RNP particle and therefore its capacity to produce inter-particle epitope spreading.

Method: New Zealand white rabbits were immunized with a peptide corresponding to the epitope 145-164 of La/SSB (belongs to RRM of La/SB), attached in four copies on a scaffold carrier. Sera were drawn from twenty sera of patients with SLE and anti-U1RNP antibodies and 26 sera of SS patients with anti-La antibodies. All sera were evaluated for reactivity against the major epitope of La/SSB (pep349-364), the RNP antigen and the RRM related epitope of La (pep145-164). Specific antibodies against the pep145-164 were purified with immunoaffinity columns from selected sera.

Results: After the immunization of the animals with pep145-164, a specific, IgG, antibody response was detected, directed against the La autoantigen (weeks #3-#7) the immunizing peptide (weeks #3-#27) and the RNP autoantigen (weeks #7-#20). This response gradually decreased to low levels between post immunization weeks #27-#42. Purified antibodies against pep145-164 recognized La/SSB and a 70kD autoantigen in western blot and exhibited significant reactivity in anti-RNP ELISA. In addition, pep145-164 was recognized to a greater extent by autoimmune sera with anti-RNP reactivity as compared to anti-La/SSB positive sera, in contrast to pep349-364 of La/SSB, which was recognized almost exclusively by sera with anti-La/SSB reactivity.

Conclusion: Our data suggest that the RRM region of La can trigger inter-particle B cell diversification to U1-RNP-70 autoantigen via molecular mimicry. Identification of "key sequences" that trigger and perpetuate the autoimmune process is particularly important for understanding pathogenetic mechanisms in autoimmunity.

Disclosure: J. G. Routsias, None; **N. Kyriakidis**, None; **M. Latreille**, None; **H. M. Moutsopoulos**, None; **A. G. Tzioufas**, None.

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The Sympathetic Nervous System Promotes the Development of B Cells That Show Regulatory Potential in Collagen-Induced Arthritis. Georg Pongratz, Madlen Melzer and Rainer H. Straub, University Hospital Regensburg, Regensburg, Germany

Purpose: The cells recent success in the treatment of some autoimmune disease, such as rheumatoid arthritis (RA), with depleting anti-CD20 antibodies, led to a revival of the concept that B play a role in the pathogenesis of these disease. However, a complete depletion of CD20+ B cells, no matter if autoreactive or not, is a rather unspecific method and has the potential to cause complicating side effects such as severe infection. To avoid this problem it is important to understand how B cells might be regulated to influence the course of disease more specifically. A known regulator of B cell function is the sympathetic nervous system (SNS), but recent studies also showed a clear influence of the SNS on the development and severity of experimental arthritis.

Therefore, it was hypothesized that the SNS acts via regulating B cell function to modulate the development and severity of arthritis.

Method: Collagen type II-induced arthritis, adoptive transfer of isolated splenic B cells, splenectomy, *in vitro* B cell culture.

Results: We show that the SNS has the potential to support the generation of B cells that possess regulatory potential in collagen induced arthritis (CIA):

1) We activated B cells with anti-CD40 (1mg/ml) / IL-4 (1ng/ml) in the presence or absence of norepinephrine (10^{-6}M), and adoptively transferred 3 Mio. of these cells in arthritic DBA1J mice. Compared to arthritic mice that received PBS, mice that received B cells developed a less severe arthritis *per se*, however, this effect was significantly more pronounced when B cells activated in the presence of norepinephrine were used for treatment.

2) We induced arthritis in sympathectomized mice and control mice. At day 28 after induction of arthritis, we exchanged splenic B cells between the groups by adoptive transfer. *Per se*, sympathectomized mice developed more severe arthritis after splenectomy than control mice. However, transferring B cells from the sympathectomized mice into control mice, and *vice versa*, also changed the course of disease, respectively.

Conclusion: Both findings point to a role of the sympathetic nervous system in generating B cells that possess regulatory potential in the collagen induced arthritis model.

Disclosure: G. Pongratz, None; **M. Melzer**, None; **R. H. Straub**, None.

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Fine Specificity of the ACPA Response in Arthralgia Patients. L.A. van de Stadt[1], W.H. Bos[1], G.J. Wolbink[1], B. A. C. Dijkmans[2], Dirkjan van Schaardenburg[1] and D. Hamann[3], [1]Jan van Breemen Institute, Amsterdam, Netherlands, [2]M.D., PhD, Amsterdam, Netherlands, [3]Sanquin Diagnostics, Amsterdam, Netherlands

Purpose: Anti-citrullinated peptide antibodies (ACPA) are probably involved in the pathogenesis of RA. Environmental and genetic factors predispose to the formation of ACPA. During the course of disease epitope spreading might occur and the antibody response may expand. Finding the immunodominant epitope in established RA is therefore troublesome. In this study, the ACPA repertoire of arthralgia patients and the association with arthritis development were studied.

Methods: 221 anti-CCP and/or IgM-RF positive arthralgia patients were included. Absence of clinical arthritis at baseline was confirmed by an experienced rheumatologist. Arthritis was defined as development of one or more swollen joints at clinical examination during twice-yearly follow-up. Minimum follow-up was 8 months. Sera were tested at baseline for reactivity to 5 citrullinated peptides derived from fibrinogen (3), vimentin (1) and alpha-enolase (1) and the 5 corresponding arginine peptides in an ELISA. Reactivity was expressed as Δ optical density (OD) between citrullinated and arginine peptides. Sera with ΔOD more than the mean plus 2SD of 40 healthy control sera were considered positive.

Results: 59 patients (27%) developed arthritis in a median of 3 joints after a median follow up of 8 (IQR: 4-18) months. Nine (11%) anti-CCP negative patients and 126 (88%) anti-CCP positive patients showed reactivity to one or more citrullinated peptides. Reactivity to each peptide was significantly associated with arthritis development ($p < 0.002$). However, reactivity patterns did not differ between patients who did or did not develop arthritis (Figure1). Nevertheless, within anti-CCP positive patients, a trend was seen towards more arthritis development in patients who recognized two or more peptides (Figure 2). Furthermore, the number of recognized peptides was positively associated with the anti-CCP level ($p < 0.001$).

Conclusion: The ACPA response in arthralgia patients is already expanded and resembles that of patients with arthritis. This could indicate cross-reactivity between peptides or genuine epitope spreading, a process that might be initiated before onset of arthralgia. The trend towards more arthritis development in patients that recognize more peptides, would fit with the latter. Studying the ACPA response earlier in the course of arthritis development, i.e. before onset of joint complaints, is therefore necessary.

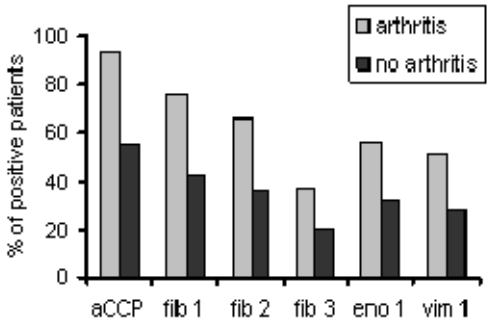

Figure 1 ACPA reactivity pattern of arthralgia patients who did and who did not develop arthritis

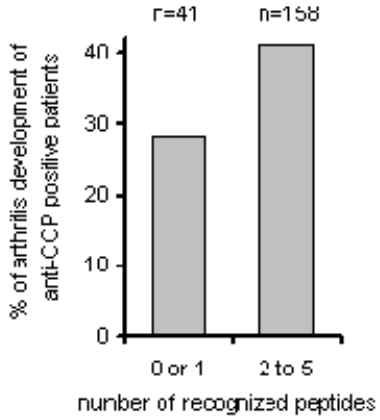

Figure 2 Association between number of recognized peptides and arthritis development

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TNF-Induced Expansion of CD23+/CD21hi B Cells in Draining Lymph Nodes Are Associated with the Onset of Inflammatory-Erosive Arthritis in Proximal Joints and Are Targets of Anti-CD20 Therapy. J. Li[1], I. Kuzin[1], S. Moshkani[1], Christopher Ritchlin[2], Jennifer H. Anolik[1], I. Sanz[1], R. J. Looney[1], L. Xing[1], E.M. Schwarz[1] and A. Bottaro[1], [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY

Purpose: B cell depletion therapy (BCDT) with anti-CD20 is an effective treatment for some RA patients. However, the role of B cells in arthritis and the primary target of BCDT are unknown. Previously we utilized the TNF-Tg mouse model of RA and longitudinal contrast enhanced (CE) MRI to evaluate their arthritis, which initiates in distal joints of the ankle and progresses proximally with age. We also noticed that the popliteal lymph nodes (PLN) become enlarged following ankle synovitis, but prior to knee arthritis. Flow cytometry (FC) revealed that PLN enlargement was due to a 4 to 7-fold increase in B cell numbers, accounting for the expansion in cellularity. We proposed that these B cells in inflamed nodes (B-in) could be the primary target of anti-CD20 BCDT. To test the hypothesis we performed a formal phenotypic characterization of B-in and their response to anti-CD20 therapy.

Methods: Multicolor FC with probes for B220, IgM, IgD, CD1d, CD5, CD19, CD21, CD23, CD24, CD25α, CD69, CD80, CD86, CD93 (AA4.1), CD138 and GL7, was performed on cells from spleen, PLN, mesenteric (M)LN and axillary (A)LN from young (<2-months), adult (3-6 months) and old (>8 months) TNF-Tg and wt mice (N= 4 to 13), which were untreated or received anti-CD20 (10mg/kg/i.v. every 2 weeks for 6 weeks). Luminex was performed on B-in and follicular B cells from TNF-Tg PLN, as well as pooled LN follicular B cells and peritoneal B cells from WT mice. 105 cells/well were cultured with CpG, PMA, and ionomycyn for 48 hrs, and the supernatants were assayed for the cytokines IL1β, IL2, IL4, IL6, IL10, IL12p70, IFNγ, RANTES, and muTNF.

Results: TNF-Tg PLN had significantly ($p<0.001$) more IgMhi, IgD+, CD21hi, CD23+, CD1d+, CD24hi, CD93 lo B-in, which increase from 10% to >30% of PLN B cells and localize to the medullary/paracortical areas in mice with overt knee arthritis. No other differences in wt vs. TNF-Tg were detected. PLN of young TNF-Tg with ankle synovitis showed an expansion of B-in before CE-MRI detected changes in PLN or the knee. No increases in B-in were detected in spleen (wt: 12%; TNF-tg: 11-15%), MLN (wt: 10%; TNF-tg: 8-14%) or ALN of TNF-Tg mice <8 months of age (wt: 9%; TNF-Tg: 4-11%), while B-in were significantly increased in ALN of old arthritic TNF-Tg with forelimb arthritis (wt: 9%; TNF-tg: 24%; $p<0.01$). Anti-CD20 treatment resulted in a >90% decrease in PLN B-in. Luminex, confirmed by qPCR, revealed an increase in secretion of IL6, but not other cytokines, by stimulated PLN B cells from arthritic mice.

Conclusion: A unique B cell population – B-in - accumulates in efferent LN that drain inflamed joints in TNF-Tg mice, and is efficiently depleted by BCDT. B-in surface phenotype, but not cytokine profiles, resembles that of B-regs in the spleen of mice with remission-phase collagen-induced arthritis. Based on the cytokine data, a model for B-in derived IL-6 in arthritic progression is proposed.

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TNF Alpha Impairs Humoral T Cell Dependent Antibody Responses. Gabriela Franco Salinas[1], Leen De Rycke[1], Tineke Cantaert[1], Mirjam van der Burg[2], Philip Remans[1], Barbara Barendregt[2], Paul P. Tak[3] and Dominique Baeten[1], [1]Academic Medical Centrum, Amsterdam, Netherlands, [2]Rotterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: TNF blockade in spondyloarthritis (SpA) induces antibodies specific for double stranded DNA, which is a T cell independent (TI) antigen. As these antibodies were restricted to the IgM isotype and no antibodies to T cell dependent (TD) antigens were induced, we investigated here if TNF blockade impairs the induction and maturation of TD humoral responses.

Method: 30 SpA patients (20 treated with TNF blockade, 10 untreated controls) were vaccinated with a TD vaccine to Hepatitis B and a TI vaccine to S. pneumoniae. Another 10 SpA patients treated with infliximab were vaccinated with a TD vaccine to S. pneumoniae. Serum and

PBMCs were collected before and after vaccination. Vaccine-specific antibody titers were measured by ELISA. B and T cell populations were evaluated by flow cytometry. Somatic hypermutation was determined by the Igκ REHMA assay (Anderson, Blood 2005).

Results: IgM and IgG responses against TI antigens were moderately decreased in anti-TNF treated patients compared to controls but were still robust. In contrast, IgG responses against TD antigens were almost completely absent in anti-TNF treated patients. The greater suppression of TD versus TI responses by TNF blockade was confirmed by lower anti-S. pneumoniae IgG titers with TD versus TI vaccines. Phenotypic analysis showed a normal number of B cells but a decrease in naïve and memory CD4+ T cells upon TNF blockade. Within the B cell population, TNF blockade significantly increased the frequency of memory B cells, which displayed an activated phenotype with increased expression of CD40 and HLA-DR. In parallel, however, TNF blockade decreased the frequency of CD138+ plasmablasts, suggesting a defective maturation towards antibody-producing cells. Confirming this hypothesis, TNF blockade significantly decreased the degree of somatic hypermutation as evidenced by Igκ REHMA analysis of peripheral blood B cells before and after treatment.

Conclusion: TNF blockade severely impairs TD humoral responses by interfering with the affinity maturation and differentiation of activated B cells towards antibody producing cells. * Both authors contributed equally to this work

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Phenotypical and Functional Aberrations of B Cells in Patients Treated with Anti-Tnfa Agents. Maria Karampetsou, Fotini Paliogianni, Andrew P. Andonopoulos and Stamatis Nick C. Liossis, University of Patras Medical School, Patras, Greece

Purpose: To dissect the mechanisms of autoimmunity in anti-TNFa (a-TNFa) treated pts, we analyzed a-TNFa-induced alterations in B cell phenotype and function. We also examined a-TNFa therapy effects on the percentages of B1 B cells, a source of natural autoAb.

Method: PBMCs were isolated from 22 pts (9 with RA, 13 with SpA; 13 men, 9 women; mean age, 48 ±13; range, 24-71 yr) on day 0 and wk 30 following a-TNFa treatment, and from 10 healthy donors using standard Ficoll-Hypaque overlays. MACS isolated B cells were stained with mAbs against CD20,CD21 and CD5 and evaluated using 3-color flow cytometry. Levels of protein tyrosine phosphorylation (P-Y) and expression of Lyn, Syk and SHP-1 were evaluated in whole B-cell lysates[treated with 10μg/1x10^6 cells of F(ab)2 fragment of anti-human IgM or medium at 37 C for 1 min], using Western immunoblots. GAPDH was used as a loading control. Data are expressed as densitometric ratios of Lyn, Syk or SHP-1 O.D. over GAPDH.

Results: Expression of B- cell surface CD20 increased in 14 out of 22 pts following a-TNFa treatment (mean MFI ± SD: 3.312 ±1.611 vs 4.263 ± 2.093 at day 0 and wk 30 respectively, p=0.012) and ANA emerged in 9 out of these 14 pts. Induction of CD20 characterized pts with RA (mean MFI ± SD: 3.148±2.231 vs 4.624 ± 2.306 at day 0 and wk 30 respectively, p=0.039), but not pts with AS (mean MFI ± SD: 3.803 ± 1.187 vs 4.000 ± 1.444 at day 0 and wk30 respectively, p=NS) and was unrelated to disease activity. Expression of CD21 remained unchanged (mean MFI ±SD: 2.286±0.699 vs 2.411±0.644 at day 0 and wk 30 respectively, p=NS).

In 5 out of 9 patients with SpA B cells showed increased levels of protein P-Y without any BCR-initiated activation. Anti-sIgM stimulation further enhanced protein P-Y, suggesting that these B cells were functionally intact. 2 out of these 5 patients developed ANA following a-TNFa treatment.

In 9 out of 10 pts with SpA B-cell Lyn was significantly induced following a-TNFa (mean O.D. ratio Lyn/GAPDH: 0.381± 0.148 vs 0.639 ± 0.182 at day 0 and wk 30 respectively, p=0.003). Expression of Syk and SHP-1 was not altered (Syk/GAPDH: 0.701 ± 0.214 vs 0.729 ± 0.135 at day 0 and wk 30 respectively, p=0.7, and SHP-1/GAPDH: 0.488 ± 0.146 vs 0.485 ± 0.115, p=0.9). Five out of 9 pts developed ANA.

Circulating B1 B cells expanded in 5 out of 6 pts after a-TNFa (mean MFI ± SD: 6.5 ± 4.3 vs. 10.2 ± 6.4 at day 0 and wk 30 respectively, p=0.028) and 3 out of those developed ANA by wk 30.

Conclusion: We report that surface CD20 and cytoplasmic Lyn are induced in B cells from patients receiving a-TNFa agents. Additionally, early signaling events (protein P-Y) are enhanced in such B cells in the resting state and B1 B cells become overexpanded. Such changes may underlie, at least in part, a-TNFa-induced autoimmunity.

Disclosure: M. Karampetsou, None; **F. Paliogianni**, None; **A. P. Andonopoulos**, None; **S. N. C. Liossis**, None.

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Proximal B Cell Receptor Signaling and Tolerance in Autoreactive IgM+CD27+ B Cells. Scott A. Jenks and Iñaki Sanz, University of Rochester School of Medicine and Dentistry, Rochester, NY

Purpose: To understand whether active regulatory mechanisms contribute to censor autoreactive B cells within the unswitched (marginal-zone-like) memory compartment. Unswitched IgM+CD27+ B cells (IgM+CD27+) make up a substantial portion of healthy donor PBL and have been postulated to represent recirculating marginal zone (MZ) cells. In the mouse, the MZ may play a protective role by sequestering low-affinity autoreactive B cells away from the pathogenic germinal center pathway on the basis of low intensity BCR signaling. We postulated that in humans, active inhibitory mechanisms would also contribute to censoring this pathogenic potential. In this study we tested whether the decreased BCR signaling responses we have observed in autoreactive 9G4+ naïve cells and characteristic of anergic follicular B cells would also be present in MZ B cells.

Methods: PBL were stimulated with anti-human IgM, IgD, or control anti-IgG for either 2 minutes or varying time points. Following stimulation cells were fixed with 1.6% paraformaldehyde and permeabilized with 100% ice-cold methanol. Cells were later stained to differentiate the naïve and IgM+CD27+ populations. To determine the degree of phosphorylation cells were stained with phosphorylation specific antibodies against BLNK (pY84,), pSYK (pY348) and pPLC-γ2 (pY759). In some experiments cells were stained with the rat anti-human idiotype 9G4.

Results: 3 fold more phosphorylation was observed after anti-IgM stimulation in IgM+CD27+ as compared to naïve cells while anti-IgD stimulation was decreased. Under basal conditions IgM+CD27+ had slightly higher levels of phosphorylation. Despite having increased phosphorylation after IgM stimulation, the IgM+CD27+ kinetics of phosphorylation was comparable to naïve B cells, with rapid phosphorylation followed by a quick loss and a return to nearly basal levels at 30 minutes. Interestingly, 9G4+ IgM+CD27+ B cell phosphorylation was significantly decreased after stimulation as compared to 9G4- IgM+CD27+ cells.

Conclusion: IgM+CD27+ cells respond more to anti-IgM and less to anti-IgD than naïve cells. This likely reflects the relative level of expression of the corresponding isotypes on the cell surface. The degree of BCR-induced phosphorylation is dependent on the balance between kinase and phosphatase activity as the phosphatase activity quickly diminishes phosphorylation in naïve cells. The similar signaling kinetics of IgM+CD27+ and naïve cells compared to switched memory cells suggests that this is an inherent property of the IgM receptor and associated signaling molecules rather than the differentiation state of the cell. The decreased signaling observed in the 9G4+ fraction of the IgM+CD27+ population strongly suggests that, as in the naïve compartment, these autoreactive B cells are rendered hyporesponsive by chronic self-antigen stimulation. These findings are the first to indicate that B cell anergy may also be operative in the MZ and contribute to the maintenance of B cell tolerance beyond naïve cells.

Disclosure: S. A. Jenks, None; **I. Sanz**, None.

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Unique Tolerance Mechanism Permitting Autoreactivity by Human CD5+ Pre-Naïve B Cells. Jisoo Lee[1], You-Hyun Lee[1], Nancy Longo[2], Colleen Satorius[2] and Peter E. Lipsky[3], [1]Ewha Woman's Univ Schl of Med, Seoul, South Korea, [2]NIAMS, N.I.H, Bethesda, MD, [3]National Institutes of Health, Bethesda, MD

Purpose: $CD5^+$ pre-naïve B cell population is a newly identified unique intermediate between transitional and naïve B cells during human peripheral B cell development. Although developmentally immature, $CD5^+$ pre-naive B cells, at the same time, have capacities of the mature naïve B cells to differentiate and present antigen. Because of functional immaturity, most of $CD5^+$ pre-naïve B cells are predicted to be removed by negative selection at peripheral tolerance checkpoint. However, because they possess functions of mature naïve B cells, inefficient tolerance checkpoint regulation at $CD5^+$ pre-naïve B cell stage, may result in systemic autoimmunity.

The study was performed to determine the tolerance mechanisms operating at $CD5^+$ pre-naïve B cell stage that may contribute to development of autoimmunity.

Method: Comprehensive comparative analysis of Ig H gene repertoire at transitional, $CD5^+$ pre-naïve, and naïve B cell human peripheral B cell developmental check point was performed. V_H rearrangements were amplified from genomic DNA of individual B cells by polymerase

chain reaction. Analysis included 133 V_H rearrangements from the transitional B cells, 371 from the $CD5^+$ pre-naïve B cells, and 185 from the naïve B cells. To predict the autoreactivity of a B cell receptor, presence of long IgH CDR3, and highly positively charged amino acids were analyzed.

Results: By comparing the distribution between the productive and the nonproductive repertoires of transitional, pre-naïve, and the naïve B cells, we found that negative selection for long and highly positive charged $CDR3_H$ occur at all human peripheral B cell developmental stages. However, analysis of the productive repertoires revealed that $CDR3_H$ length of pre-naïve B cells (52.5±12.5bp) was significantly longer compared to that of the transitional (48.9±12.6bp) and the naïve (49.0±10.5bp) B cells ($p<0.01$). This skewing for longer $CDR3_H$ length in pre-naïve B cells was due to maintenance of significantly longer germline D segment. Notably, an increased proportion of $CD5^+$ pre-naïve B cells were found in peripheral blood of patients with systemic lupus erythematosus (SLE).

Conclusion: Distinctive feature of longer $CDR3_H$ in the expressed repertoire of $CD5^+$ pre-naïve B cells suggests auto/poly-reactivity of these cells which may perform beneficial functions in normal immune regulation. However, ineffective tolerance checkpoint regulation at $CD5^+$pre-naïve B cells may contribute to autoimmune pathology in patients with SLE.

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A Nonfucosylated Human Antibody to CD19 with Potent B-Cell Depletive Activity for Treatment of Autoimmune Diseases. Pina M. Cardarelli[1], Diann Blanset[2], Chetana Rao-Naik[1], Alison Witte[1], Ben Preston[1], Sharline Chen[1] and Michael J. Yellin[2], [1]Medarex, Sunnyvale, CA, [2]Medarex, Bloomsbury, NJ

Purpose: CD19 represents an attractive B-cell target for the treatment of autoimmune diseases with a number of potential advantages over CD20-directed therapies. Studies to characterize the in vitro and in vivo activities of a novel anti-CD19 antibody, MDX-1342, have been undertaken.

Method: A human anti-CD19 antibody was expressed in fucosyltransferase-deficient CHO cells to generate nonfucosylated MDX-1342. Assays measuring antibody binding to CD19-expressing cells and FcgRIIIa (CD16) transfectants as well as antibody-dependent cell-mediated cytotoxicity (ADCC) were conducted. In vivo B-cell depletion was monitored in cynomolgus monkeys following a single intravenous dose of MDX-1342. Flow cytometry was carried out by standard methods.

Results: Binding of MDX-1342 to human CD19-expressing cells was similar to its fucosylated counterpart. However, nonfucosylated MDX-1342 exhibited increased affinity for FcγRIIIa-Phe158 and FcγRIIIa-Val158 receptors and enhanced effector cell function, as demonstrated by increased potency and efficacy in antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis assays. MDX-1342 displayed low nanomolar binding to cynomolgus monkey CD19 and demonstrated increased affinity for cynomolgus monkey FcγRIIIa. Administration of MDX-1342 at 1 mg/kg in cynomolgus monkeys resulted in a 90% depletion of circulating B cells while parental anti-CD19 antibody induced approximately 50% depletion of B cells. Furthermore, the duration of B-cell depletion was longer for MDX-1342 compared to parental mAb. The ability of MDX-1342 to deplete cynomolgus monkey B cells was compared to rituximab. The extent and duration of B-cell depletion was similar for MDX-1342 and rituximab, despite higher levels of CD20 antigen on B cells, although the kinetics of depletion appeared to be initially more rapid with rituximab. B-cell repletion was documented in animals treated with both B cell-specific antibodies and there was no effect of treatment on serum IgG or IgM levels. Preliminary data available from an ongoing Phase 1 study of MDX-1342 in subjects with active rheumatoid arthritis (RA) despite treatment with methotrexate demonstrates potent B-cell depletion with single-dose (10 or 30 mg) administration of MDX-1342. Flow cytometric analysis showed that the $CD20^-CD27^+CD38^+$ plasmablasts, a cell population implicated in the pathogenesis of RA and systemic lupus erythematosus and known to be unaffected by anti-CD20-directed monoclonal antibodies, were also depleted in these human subjects.

Conclusion: MDX-1342 is a promising anti-CD19 antibody with enhanced effector function. Clinical studies of MDX-1342 in patients with RA are ongoing.

Disclosure: P. M. Cardarelli, Medarex, 3 ; **D. Blanset**, Medarex, 3 ; **C. Rao-Naik**, Medarex, 3, Medarex, 1 ; **A. Witte**, Medarex, 1, Medarex, 3 ; **B. Preston**, Medarex Inc, 1, Medarex Inc, 3 ; **S. Chen**, Medarex, 3 ; **M. J. Yellin**, Medarex, 3 .

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Characterization of LY2127399, A Neutralizing Antibody for BAFF. Kristy Kikly, Joe Manetta, Holly Smith, Dan Wierda and Derrick Witcher, Eli Lilly and Co., Indianapolis, IN

Purpose: LY2127399 is a fully human IgG4 monoclonal antibody with neutralizing activity against both membrane-bound and soluble BAFF. Dysregulated BAFF expression may contribute to autoimmune diseases via effects on abnormal B lymphocyte activation, proliferation, survival, and immunoglobulin secretion. Therefore, LY2127399 may be of potential therapeutic benefit in these diseases.

Method: Monoclonal antibodies were generated against human BAFF and screened for the ability to neutralize both membrane-bound and soluble BAFF and then characterized for species specificity and affinity. LY2127399 was tested for the ability to affect circulating B cells and a primary antibody response in cynomolgus monkeys.

Results: The affinity of LY2127399 for BAFF from various species was determined and the data indicate that LY2127399 has a very high affinity for human, cynomolgus monkey, and rabbit BAFF. No binding to mouse BAFF was detected. LY2127399 was able to neutralize soluble human, cynomolgus monkey, or rabbit BAFF with equal potency.

BAFF can exist in both a membrane-bound and soluble form, therefore, studies were undertaken to determine the relative potency of each form of BAFF. Our data demonstrate that membrane-bound BAFF is a more potent stimuli for B cells than soluble BAFF. In addition, LY2127399 was able to neutralize both human and cynomolgus monkey membrane-bound BAFF.

A study was conducted in cynomolgus monkeys to determine the effect of treatment with LY2127399 on the immune system, particularly on the proportion of B lymphocytes in the peripheral blood. To test the effect of LY2127399 on an immune response to a novel T-dependent antigen, tetanus toxoid was administered at the same time antibody treatment was started. LY2127399 had no statistically significant effect on tetanus-specific or total IgG levels following immunization with tetanus.

Serial blood samples were evaluated for flow cytometric assessment of the proportions of CD20, CD3, CD4, CD8, and CD14 cells through Day 171. Changes from baseline (Day 0) in the proportions of these cells were evaluated separately for each animal over the course of the study. The results showed that administration of LY2127399 was able to decrease the number of circulating CD20+ cells.

Conclusion: BAFF can exist in both a membrane-bound and soluble form. Our data demonstrate that membrane-bound BAFF is a more potent stimuli for B cells than soluble BAFF, therefore neutralization of both forms of BAFF is important for full therapeutic effect. LY2127399 is a high-affinity human antibody with neutralizing activity against membrane-bound and soluble BAFF. Administration of LY2127399 to cynomolgus monkeys results in a decrease in the number of circulating CD20+ cells but has no effect on the generation of an antibody response to a novel antigen.

Disclosure: K. Kikly, Eli Lilly and Company, 3, Eli Lilly and Company, 1 ; **J. Manetta**, Eli Lilly and Company, 3, Eli Lilly and Company, 1 ; **H. Smith**, Eli Lilly and Company, 3, Eli Lilly and Company, 1 ; **D. Wierda**, Eli Lilly and Company, 3, Eli Lilly and Company, 1 ; **D. Witcher**, Eli Lilly and Company, 3, Eli Lilly and Company, 1 .

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Human Autoreactive Naïve B Cells Are Impaired in Their Response to Activation through the BCR and TLR9 Stimulation. Scott A. Jenks, Nataly Manjarrez-Orduño, Elise M. Palmer, Tam D. Quách and Iñaki Sanz, University of Rochester School of Medicine and Dentistry, Rochester, NY

Purpose: The maintenance of B cell tolerance remains poorly understood in humans. 9G4+ cells represent autoreactive B cells censored at least in part by anergic responses defined by poor Ca++ flux in response to BCR stimulation that renders them unable to form productive germinal centers. Here, we describe the biochemical and cellular responses of naïve 9G4+ cells in response to BCR and TLR9 stimulation.

Methods: Naïve B cells purified from healthy donors were used for CFSE dilution analysis after stimulation with α-IgM plus CpG ODN 2006. Naïve B cells were also stimulated for 18 hours to measure cell death and the induction of apoptosis. Proximal BCR signaling in 9G4 B cells was measured after anti-IgM stimulation for 2 minutes followed by intracellular staining with anti-phosphotyrosine specific antibodies.

Results: Stimulated human naïve 9G4+ cells proliferate significantly less than their 9G4- counterparts as estimated by the fraction of cells undergoing division ($p<0.05$) and the time between consecutive cell divisions (9G4+ cells take on average 22% longer to complete a cell

cycle; $p<0.02$). In addition, 9G4+ cells exhibit higher sensitivity towards activation-induced cell death (AICD), with a three-fold increase in the number of apoptotic cells and four times more total cell death. Moreover, the degree of AICD was dose-dependent for naïve 9G4+ cells but not for 9G4- naïve B cells. To understand the hyporesponsiveness of 9G4+ cells, we analyzed the phosphorylation of Syk, BLNK and PLCγ and found that BCR signaling is significantly attenuated 10%-20% in each of these signaling components. Signaling differences between the two populations were highlighted by a substantial decrease in phopsho-bright Syk/BLNK (64% reduction) and phospho-bright PLCγ (36% reduction) populations observed in 9G4+ versus 9G4- naïve B cells. Of significant interest, an even larger impairment in the response to BCR crosslinking was observed in 9G4+ in the transitional compartment (CD24/CD38 bright) relative to transitional 9G4- B.

Conclusion: Consistent with previous calcium flux studies and their *in vivo* behavior, healthy autoreactive 9G4+ cells display attenuated phosphorylation of BCR-associated signaling molecules. Such attenuation translates into poorer proliferation that cannot be rescued by TLR9 co-stimulation, mechanism known to trigger pathogenic autoreactive B cells in animal models. Enhanced spontaneous apoptotic propensity and increased AICD also contribute to the censoring of 9G4 cells. This report is the first demonstration of attenuated signaling in autoreactive transitional B cells which represent the target of critical tolerance checkpoints enforced at least in part by competition for limited BAFF supplies. Additional studies are underway to understand the ability of BAFF to enhance 9G4 survival and proliferation in the naïve and transitional compartments and to analyze the response of SLE 9G4 cells to similar stimulation conditions.

Disclosure: S. A. Jenks, None; **N. Manjarrez-Orduño**, None; **E. M. Palmer**, None; **T. D. Quách**, None; **I. Sanz**, None.

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Identification of Human Anergic Naive B Cells. Tam D. Quách[1], Nataly Manjarrez-Orduño[2], Hongmei Yang[3] and Iñaki Sanz[1], [1]University of Rochester School of Medicine and Dentistry., Rochester, NY, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY, [3]University of Rochester

Purpose: B cell anergy represents an important mechanism of peripheral immunological tolerance that ensures functional censoring of mature autoreactive B cells that escape central tolerance checkpoints enforced by receptor editing and clonal deletion. While this mechanism has been well documented in transgenic and wild-type mouse B cells, the extent of its participation in human B cell tolerance remains to be fully established. However, it is well established that a significant fraction of human naïve B cells express low levels of surface IgM, a featured shared by anergic and acutely activated mouse B cells. In this study, we aimed to identify the functional behavior of strictly defined human naïve B cells (CD27-neg, ABCB1-neg, IgD-pos) using IgM expression levels to discriminate different naïve populations.

Method: Naïve B cells were strictly identified in peripheral blood and tonsils using multicolor flow cytometry as CD19+IgD+CD27-Mitotracker+. IgM staining was added to quantify and purify naïve fractions with either low expression of IgM (lower 30% of all naïve cells) or higher expression levels. Proliferation (CFSE dilution), activation and Ca++ flux was measured after BCR stimulation with anti-IgM or IgD antibodies. Autoreactivity was determined using a newly developed ANA-ELISPOT assay.

Results: the ability of naïve B cells to flux calcium in response BCR cross-linking is diminished in a dose-response manner in cells expressing low IgM levels (IgM^{lo}) whether they are stimulated through their IgM or IgD surface receptors. In addition, sorted IgMlo cells consistently display a phenotype characterized by the absence of activation markers (in contrast to SLE IgMlo naïve B cells) and poor response to in vitro stimulation as demonstrated by reduced CD69 upregulation, significantly weaker proliferation (determined by CFSE dilution to measure % of dividing cells and time between consecutive divisions) and poor antibody production. Moreover, the frequency of autoreactive IgM^{lo} cells was significantly increased as compared to similarly defined naïve B cells with higher levels of surface IgM.

Conclusion: BCR hypo-responsiveness due to sIgM downregulation is present in a much larger fraction of all human naïve B cells than previously reported and is likely to reflect a state of anergy induced by chronic autoantigen stimulation. Our results also provide preliminary evidence to suggest that in SLE a much larger fraction of naïve IgMlo cells represent activated cells as compared to the same phenotypic population in healthy controls. Combined, this work establishes anergy as a mechanism of tolerance that impacts a large fraction of all human naïve B cells and is likely to be defective in SLE

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Titration of CD45 Expression Reveals Differential Regulation of Antigen Receptor Signaling in T and B Cells and Defines a BCR Signaling Threshold for B Cell Negative Selection. Julie Zikherman[1], Kristin Doan[1], Craig Jenne[1], Susan Watson[1], Christopher Goodnow[2], William Raschke[3] and Arthur Weiss[1], [1]UCSF, San Francisco, CA, [2]ANU, Canberra, Australia, [3]Sidney Kimmel Cancer Center, San Diego, CA

Purpose: Negative selection during lymphocyte development is required to establish a self-tolerant antigen receptor (AgR) repertoire. Here we take advantage of a novel allelic series of CD45 expression in mice which permits precise titration of BCR signal intensity and reveals a BCR signaling threshold for negative selection during splenic B cell development.

The receptor-like tyrosine phosphatase CD45 positively regulates AgR signaling by dephosphorylating the inhibitory tyrosine of the src family kinases (SFKs). It has been previously shown that CD45 is required for normal T and B cell development. Paradoxically, very low levels of CD45 are sufficient to fully rescue T cell but not B cell development. We show here that a negative regulatory role for CD45 that is unique to T cells accounts for this phenomenon.

Method: We have identified a novel allele of CD45, lightning, in which a single residue mutation produces low protein expression levels but normal isoform splicing. We additionally used previously described 'HE' mice that have supraphysiologic levels of CD45 expression. By crossing these two alleles to either wild type or null CD45 alleles, we have generated a series of mice in which CD45 expression levels are titrated across a broad range (0-180% of wildtype).

Results and **Conclusion:** Supraphysiologic doses of CD45 enhance Erk phosphorylation and calcium flux following BCR stimulation, while the opposite is true for T cells. Conversely, low CD45 expression enhances TCR signaling but impairs BCR signaling. We conclude that CD45 plays a negative regulatory role in TCR but not BCR signaling.

Increasing CD45 expression in both T and B cells results in progressive dephosphorylation of the inhibitory tyrosine of the SFKs. However, only in T cells is the activation loop tyrosine of SFKs dephosphorylated with increasing CD45 level. We propose that this provides a biochemical basis for differential regulation of T and B cell signaling by CD45 and, in turn, accounts for the differential capacity of low CD45 expression to rescue T and B cell development.

In mice with increasing CD45 expression and concurrently enhanced BCR signaling, we observe gradual reduction in the MZ B cell compartment, while B1 cell development is preserved. Although splenic T1 B cell numbers are similar across the allelic series, supraphysiologic CD45 expression produces sharp reductions in T2 and in mature (FO) B cell numbers relative to wild type. In contrast, B cell numbers are relatively preserved in CD45 deficient mice, with only a modest decline between T2 and FO B cell compartments. We conclude that the CD45 allelic series reveals a signaling threshold for negative selection at the splenic transitional stages of B cell development. This has important implications for the establishment of a self-tolerant B cell repertoire.

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IL-17 and IL-23 Enhanced Il23r Expression in Germinal Center B Cells and Promoted IL-23-Induced Secretion of Plasma B Cells. Hao Li, University of Alabama at Birmingham, Birmingham, AL

Purpose: Interleukin-17 (IL-17) and IL-23 have both been shown to have a role in the development of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and psoriasis. We have shown that IL-17 can promote the development of autoreactive germinal centers (GCs) by upregulating the expression of regulator of G-protein signaling (*Rgs*) genes. This enhances T-B cell interaction and development of spontaneous GCs in autoimmune BXD2 mice. Here, we investigated the role of IL-23 and IL-23R on B cells of BXD2 mice

Method: FACS analysis was carried out to determine the cell type that produces IL-23 and to detect $PNA^{+}Fas^{+}$ B cells which represent the germinal center B cells. Confocal imaging analysis was carried out to determine the location of IL-23 secreting cells. Immunohistochemistry staining was carried out to detect released IgM plasma cells in the spleen. B cells were purified using a CD19 MACS column method. Subpopulations of B cells were sorted by a FACS sorter for RT-PCR assay to determine the expression of *Il23r*. *In vivo* enhancement of the

levels of IL-23 and IL-17 was achieved by injection of mice with AdIL-23 and AdIL-17 (2 x 10^9 pfu/mouse, tail IV)**.** B-cell migration response to CXCL12 was determined using a transwell migration assay

Results: IL-23 was highly expressed by follicular dendritic cells (FDCs) that are located in the GCs in BXD2 spleens. The expression of *Il23r* was low in naïve B cells but was highly upregulated in PNA^+Fas^+ B cells in BXD2 mice. *In vivo* administration of AdIL-23 alone to BXD2 mice was enough to lead to a 100-fold increase in *Il23r* on B cells. *In vitro* stimulation of B cells with IL-17 (20 ng/ml) or IL-23 (20 ng/ml) separately resulted in a 1.5 fold increase in *Il23r*. Co-stimulation of B cells with IL-17 plus IL-23 resulted in a furthermore enhancement on the expression of *Il23r* (10 ± 5 fold) in a synergetic fashion. Consistent with this, *in vivo* administration of AdIL-17 plus AdIL-23 to C57BL/6 mice synergistically upregulated the expression of *Il23r* on B cells. Interestingly, IL-23 down-regulated the IL-17-induced *Rgs13* expression and abrogated the IL-17-induced B-cell migration arrest in response to CXCL12. AdIL-23 injection to BXD2 mice lead to increased IgM^+CD138^+ plasma B cells in the spleens and peripheral blood mononuclear cells and decreased PNA^+Fas^+ GC B cells in the spleens on day 14 after infection

Conclusion: The increased expression of *Il23r* on GC B cells of BXD2 mice may be a result of increased local production of IL-17 and IL-23. However, unlike IL-17 which is important for GC formation, IL-23 appears to promote the release of plasma B cells and thereby reduces the number of GC B cells. Suppression of IL-17 or IL-23 may both be beneficial to prevent either the development or the release of autoantibody forming B cells

This work was supported by American College of Rheumatology – Within-Our-Reach program (J.D.M.), the Alliance for Lupus Research – Target Identification in Lupus program (J.D.M.), VA Merit Review Grants (J.D.M.), Daiichi-Sankyo Co., Ltd. (J.D.M.), NIH (1AI 071110-01A1) (J.D.M.), and by the Arthritis Foundation (H.-C.H.)

Disclosure: H. Li, None.

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The Application of Protein Microarrays for Autoantibody Profiling in Morphea Patients. Noori Kim[1], Quan-Zhein Li[2] and Heidi Jacobe[3], [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Dallas, TX, [3]Department of Dermatology, Dallas, TX

The Application of Protein Microarrays for the Autoantibody Profiling of Morphea Patients

UTSW Medical Center, Dept. of Dermatology, Dept. of Medicine Division of Rheumatology, Dallas, USA

Purpose: This study utilized protein microarray technology for large-scale analysis of autoantibodies in morphea to: (a) detect multiple autoantibodies in microliter volumes of serum, (b) identify autoantibody profiles specific to morphea, (c) and provide an efficient means to uncover novel antigens by testing the reactivity of morphea sera to candidate antigens.

Method: Sera was utilized from 24 patients enrolled in the UTSW Medical Center Morphea Registry. All subjects had active disease and had not initiated therapy other than topical steroids. We compared the protein microarray signatures of morphea sera with non-immunologic and lupus erythematosus controls, matched for age, sex, and race. 16 new autoantigens were added to the previously published glomerular proteome array used for the evaluation of SLE activity. The added antigen specificities were incorporated based on literature searches linking the antigens to autoimmune sclerosing skin conditions. Manufacture, hybridization, and scanning of autoantigen microarrays and subsequent data analysis were performed according to the protocol previously published. (*Clinical and Experimental Immunology*. 147(2006):60-70.)

Results: Diagrams with row and column clustering were created with the Cluster and Treeview software (http://rana.lbl.gov/EisenSoftware.htm) and found that among the morphea sera, there was a tendency to group according to morphea subtypes, notably linear versus plaque type, for IgG, IgM, and IgA autoantibody profiling. When comparing morphea against SLE, the non-linear types, including plaque, generalized, and mixed, grouped with the SLE while linear morphea exhibited a distinct profile. Of the 92 autoantigens tested, contrary to previous reports, no significant increases were found in all subtypes of morphea of anti-singled stranded, anti-histone, and anti-topoisomerase antibodies. There was a trend toward an autoantibody reactivity pattern for the PDGFR alpha and beta autoantigen in morphea although not statistically significant ($p>0.06$). There was decreased IgG reactivity to aggrecan antibodies in morphea versus both normal and SLE controls ($p=0.0052$).

Conclusion: This study implies morphea subtypes display different autoimmune reactivity profiles across Ig subtypes, suggesting a disease specific signature. The reactivity intensities were greater for the IgG subclass than for IgM and IgA, providing insight into the pathogenesis of morphea on a molecular basis. Previously published data that suggested increased frequency of autoantibodies to single-stranded DNA, histones, and topoisomerase II-alpha in morphea were not duplicated in this larger cohort, while novel antigens like PDGF receptor had notable reactivity intensities in morphea. Protein microarrays for autoantibody profiling in morphea may allow for further characterization of this difficult disorder on a molecular level beyond the cutaneous lesions.

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ACR/ARHP Poster Session B

Epidemiology and Health Services Research II

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Ethnicity and Gender Differences in the Prevalence of Rheumatic Disease Associated Autoantibodies: The Multi-Ethnic Study of Atherosclerosis (MESA). Darcy S. Majka[1], Thanh Huyen T. Vu[1], Marius C. Teodorescu[2], Pamela J. Schreiner[3], Richard M. Pope[1], Kiang Liu[1] and Rowland W. Chang[1], [1]Northwestern University, Chicago, IL, [2]TheraTest Laboratories Inc, Lombard, IL, [3]University of Minnesota, Minneapolis, MN

Purpose: While ethnicity and gender influences on the prevalence of connective tissue diseases (CTDs) have been examined, the association between ethnicity and gender and CTD-related antibodies in subjects without CTDs has not been established. This study was performed to measure the relationship between ethnicity and gender and presence of CTD-related autoantibodies in a population-based sample from the Multi-Ethnic Study of Atherosclerosis (MESA).

Method: MESA is a multicenter prospective study initiated in 2000 to study subclinical and clinical cardiovascular disease in 6,500 Caucasian, African-American (AA), Hispanic, and Asian men and women aged 45-84.

We included all of the Caucasian (N = 555) and AA (N = 302) participants (47% women) from one MESA study site. We measured antinuclear antibodies (ANA), anti-cardiolipin antibodies (aCL IgM, IgG, IgA), anti-β2 glycoprotein I antibodies (anti-β2-GPI IgM, IgG, IgA), rheumatoid factor (RF IgM, IgA) and anti-cyclic citrullinated peptide antibodies (anti-CCP-2) by ELISA. The Connective Tissue Disease Screening Questionnaire (CSQ), a validated screening instrument with high negative predictive value for CTDs, was administered to identify subjects who might have a CTD. Multivariate logistic regression models measured associations between ethnicity and gender and antibody positivity.

Results: ANA, aCL (any isotype), anti-β2-GPI (any isotype), RF (any isotype) and anti-CCP were positive in 29%, 25%, 21%, 17% and 2% of participants respectively (Table 1 shows frequency by ethnicity/gender). After adjustment for age, education and smoking, AA ethnicity was significantly associated with ANA (OR 1.5 [95% CI 1.1, 2.1]) and RF (OR 1.5 [95% CI 1.0, 2.2]), and marginally associated with anti-CCP (OR 2.7 [95% CI 0.9-8.0]) compared with Caucasian ethnicity. AA ethnicity was also inversely associated with anti-β2-GPI (OR 0.5 [95% CI 0.4, 0.8]). Female gender was associated with ANA (OR 1.8 [95% CI 1.3, 2.5]) independent of the association between ethnicity and ANA. aCL was not associated with ethnicity or gender. The results did not change after excluding 118 participants with CSQ results indicating the possible presence of CTDs.

Conclusion: ANA, RF, anti-CCP and anti-β2-GPI positivity differ by ethnicity, and ANA by gender, in population-based participants without clinical CTDs. Because serum autoantibodies have been shown to predict the subsequent development of clinical CTDs, associations of ethnicity and gender with pre-clinical autoantibody positivity may have relevance for future studies on CTD development.

Table 1. Distribution of CTD-Related Autoantibodies by Gender and Ethnicity

	ANA	**aCL**	**anti-β2-GPI**	**RF**	**anti-CCP**
N*	855	857	847	840	838

Caucasian Men	23%	27%	23%	15%	0.8%
Caucasian Women	30%	27%	24%	14%	1.4%
AA Men	24%	21%	15%	18%	4.3%
AA Women	45%	21%	14%	24%	2.0%

* Analysis samples differ for each antibody after excluding missing values.

Disclosure: D. S. Majka, None; **T. H. T. Vu**, None; **M. C. Teodorescu**, TheraTest Laboratories Inc, 1, TheraTest Laboratories Inc, 3 ; **P. J. Schreiner**, None; **R. M. Pope**, None; **K. Liu**, None; **R. W. Chang**, None.

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Factors Influencing Time Span Between Onset of Symptoms to First Consultation in Outpatient Rheumatologic Care Facilities in Germany. Gisela Westhoff[1], Edmund Edelmann[2], Joern Kekow[3], T. Meng[4], S. Simianer[4] and Angela Zink[5], [1]German Rheumatism Research Center Berlin, Berlin, Germany, [2]Rheumatological Office Bad Aibling, 83043 Bad Aibling, Germany, [3]Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany, [4]Wyeth BioPharma, Münster, Germany, [5]German Rheumatism Research Center, Berlin, Germany

Purpose: There is evidence that indicates a critical period of time for early arthritis during which disease processes can be markedly slowed or even halted. This knowledge has evoked multiple efforts to refer patients to rheumatological care as early as possible. We aimed at investigating what influences the time span from onset of symptoms to first rheumatologic consultation in Germany.

Method: 198 German rheumatologists reported in standardised manner information on disease duration, diagnoses, disease severity, and education of patients ≥18 years at their first consultation, as well as the specialisation of the referring physician. They also reported the average time span between making the appointment and the first consultation in their practice. Multivariate logistic regression analysis was performed to investigate the odds ratios for a first consultation within 6 months after symptom onset.

Results: Of the 11,045 patients at initial consultation, 4,973 (45%) were diagnosed with inflammatory rheumatic diseases such as RA (44.7%), PsA (21.1%), PMR (13.7%), AS (5.7%) or SLE (2.6%). Their mean age was 54.9 ±16 years and 67% of them were women. About half of the patients with inflammatory rheumatic diseases had their first rheumatologic consultation within 6 months after symptom onset (49.3%), whereas 31.2% attended only after 12 months (mean disease duration 21 ±47 months; median 6.1). The majority of the patients were referred to rheumatological care by general practitioners (78.5%); the rest by orthopaedic surgeons (12.1%), internists (5.5%) or other physicians (4%).

Factors such as older age, male sex, moderate or severe disease, and being referred to rheumatologic care facilities offering immediate appointments (<2 weeks) for new patients were significantly associated with having the first consultation within 6 months after symptom onset. There was no apparent association with the patients' formal education or the specialisation of the referring physician.

Adjusted odds ratios of being seen by a rheumatologist within 6 months after symptom onset

	adjusted OR	95% CI	P
male vs female	1.14	1.01 – 1.29	0.036
>75 vs <35 years	1.30	1.01 – 1.67	0.042
moderate vs mild activity	1.22	1.07 – 1.40	0.004
severe vs mild activity	1.28	1.08 – 1.52	0.005
average appointment <2 vs >12 weeks	1.93	1.50 – 2.49	<0.001

Conclusion: Neither the patient's educational level nor the specialisation of the referring physician had any influence on the time span until the patients' first visit at a rheumatologist. Consequently, the main focus should be on the appointment regulations of rheumatologists in order to increase their possibilities to see newly referred patients within the 'window of opportunity'.

Disclosure: G. Westhoff, None; **E. Edelmann**, None; **J. Kekow**, None; **T. Meng**, Wyeth BioPharma, 3 ; **S. Simianer**, Wyeth BioPharma, 3 ; **A. Zink**, None.

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Burden On Society From Low Back Pain- Less Than Previously Shown? A Population-Based Register Study. Anna Jöud[1], Martin Englund[2], Thor Lithman[1] and Ingemar F. Petersson[1], [1]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, [2]Lund University, Lund, Sweden

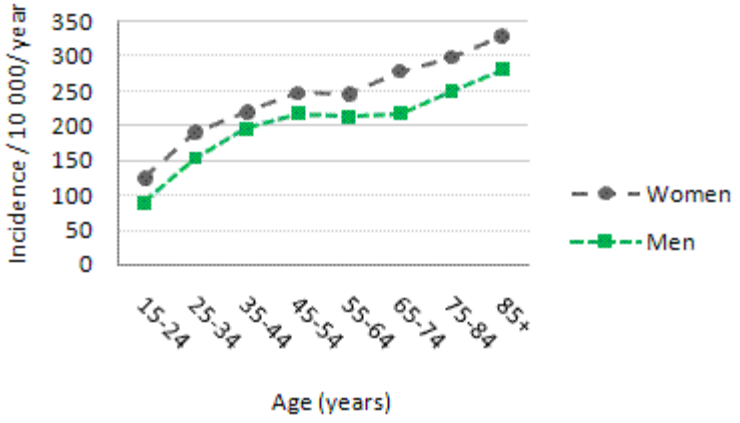
Purpose: Previous data on the occurrence of LBP focus on self assessed complaint. However, less is known about societal consequences of LBP through actual health care consumption. A focus more emphasizing actual health care utilization and costs, will give reliable and more profound figures on the impact of LBP on individual and society. The objective of this study was to study the annual incidence of LBP leading to actual health care seeking and the health care costs associated to this diagnosis.

Methods: Through the population-based Skåne Health Care Register (SHCR) covering nearly 1.3 million inhabitants in a well defined geographic region of Sweden we have access to individual data on e.g., age, sex, health care provider, and ICD-10 codes that are continuously registered for in- and outpatient care (ICD-10 codes for private care not included ~32% of all outpatient care). We identified all individuals who had at least one visit to a physician during 2007 with a primary ICD-10 diagnosis of LBP (M54.3, M54.4, M54.5, M54.8, M54.9) and no health care consultation with a physician due to low back pain 2004 through 2006. We calculated health care seeking incidence estimates for LBP, adjusted for the loss to private care.

Results: We identified 13885 individuals diagnosed with LBP 2007 but not 2004-2006 (56% women). The 2007 crude incidence estimate per 10,000 individuals was 228 (95% CI 227-229) and 186 (95% CI 185-187) for women and men respectively with increasing incidence with age (Figure 1). The overall peak incidence of 315 (95% CI 313-317) per 10,000 was seen in the ages over 85 years. The one year period prevalence of individuals receiving health care by a physician due to LBP was 2.8%.

The costs of all health care consumed in 2007 by patients diagnosed with LBP was €32 000 000, 12 percent of which were directly connected to a LBP diagnosis. The health care consumption and thus the costs of all health care consumed by patients diagnosed with LBP in 2007 was three times higher in the year of diagnosis than three years before with costs gradually increasing up until the year of diagnosis.

Figure 1. Annual incidence of LBP leading to health care seeking



Conclusion: Health care seeking incidence and prevalence of LBP was found markedly lower than previous self assessed estimates of LBP occurrence. Increasing health care seeking incidence with increasing age has not previously been shown suggesting that older people are

more affected by LBP and seek and/or seek health care due to LBP more frequent than young patients do. The health care consumption and the associated costs gradually increased up until first diagnosis of LBP.

Disclosure: A. Jöud, None; **M. Englund**, None; **T. Lithman**, None; **I. F. Petersson**, Wyeth Pharmaceuticals, 9, The Swedish National Insurance Agency, 9 .

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Renal Impairment and Poor Outcomes of Allopurinol Therapy in US Gout Patients. B. J. Pandya[1], A. A. Riedel[2], L. K. Becker[2] and E. Krishnan[3], [1]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [2]i3 Innovus, Eden Prairie, MN, [3]Stanford University School of Medicine, Palo Alto, CA

Purpose: Allopurinol has been utilized in the treatment of hyperuricemia and gout for decades. The dose-limiting factor for allopurinol is renal function. The purpose of this study was to examine rates of renal impairment among gout patients and serum uric acid (sUA) management.

Methods: This was a retrospective analysis using pharmacy, medical, and laboratory data from January 2002-April 2008 for commercial enrollees identified with gout in a large US health plan. Patients had 1-year baseline and minimum 1-year (maximum 6-year) follow-up. Case definition of gout was based on at least two claims evidencing gout (medical claim with ICD9 274.x, prescription claims for gout medication, at least one of which was for allopurinol). Chronic kidney disease (CKD) stage was defined based on National Kidney Foundation standards. Patients on dialysis, kidney transplant, stage 5 (severe) CKD, or cancer were excluded. Multivariate logistic regression was used to identify the association between achievement of sUA goal (<6 mg/dL) and patient demographic and clinical factors.

Results: The study sample included 3,363 gout patients (88% male; mean age: 50 yrs; 38% with stage 2-4 CKD; mean follow-up time: 32 months). Prevalence of CKD was 26% (stage 2), 10% (stage 3), and 2% (stage 4). Significant associations between CKD stage, initial allopurinol dose, and sUA level were identified in this population. In unadjusted analysis, average initiation dose for patients whose sUA was successfully controlled was greater than for those whose sUA was not controlled (262 mg/day vs 222 mg/day, $P<0.001$). Average initial prescribed dose of allopurinol declined significantly with increasing CKD, from an average of 245 mg/day among those with no or stage 1 CKD, to 200 mg/day among those with stage 4 CKD ($P<0.001$). Only 28% of subjects with CKD achieved sUA goal ($P<0.001$) vs 37% without CKD, with rates of goal attainment decreasing with increasing CKD stage ($P=0.066$). Fewer than 7% of patients received allopurinol doses greater than 300 mg/day. Patients with stage 2, 3, and 4 CKD had 39%, 54%, and 74% lower odds of achieving goal compared to those without CKD ($P<0.01$), respectively, controlling for patient covariates.

Conclusion: In this population, increasing severity of CKD was associated with decreased allopurinol dosing and decreased likelihood of achieving sUA goal. Serum uric acid control is poor among gout patients in general and worse among those with renal impairment. A novel therapeutic agent to treat gout that does not require dose adjustment may be helpful in improving sUA control.

Disclosure: B. J. Pandya, Takeda, 3 ; **A. A. Riedel**, None; **L. K. Becker**, None; **E. Krishnan**, Savient, 1, Takeda, 2 .

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Pharmacotherapy Trends in a Large Cohort of Patients with Rheumatoid Arthritis. Jason Cooper[1], Lakevia Hall[1], Andrew Krueger[1] and S. Sam Lim[2], [1]Accordant Health Services, a CVS Caremark Company, Greensboro, NC, [2]Emory University, Atlanta, GA

Purpose: Rheumatoid arthritis (RA) is an inflammatory disease, triggered by the body's immune system. Approximately 1.3 million Americans currently have RA. The treatment goal for RA is to minimize joint damage early in clinical management with the use of appropriate disease-modifying antirheumatic drugs (DMARDs), which can be classified into two categories: biologic (BDMARD) and non-biologic (NBDMARD) therapies. This study aims to describe pharmacotherapy trends in these two therapeutic categories from a large cohort of patients with RA.

Method:

A disease management database containing comprehensive claims data from health plans and employer groups nationwide representing approximately 23 million covered lives was utilized for analyses. The RA cohort consisted of 16,175 patients in 2006 and 17,389 in 2008.Each patient was first identified as having RA via a claims algorithm utilizing diagnostic, procedural, medication, and revenue codes.

All patients confirmed their diagnosis and care by a rheumatologist and an introductory kit was sent to each patient's provider allowing them to refute the diagnosis.

RA therapies reviewed included BDMARDs, NBDMARDs and corticosteroids. Three years of medical and pharmacy claims data (service dates between January 1, 2006 to December 31, 2008) were analyzed. Health plan paid amounts were used for cost analyses.

Results:

The table below shows separate BDMARD, NBDMARD and corticosteroid utilization rates and average costs per person, 2006 vs. 2008.

	Utilization (% using therapy)		Costs (per person per year)	
	2006	2008	2006	2008
BDMARDs	32%	37%	$4,293	$5,161
NBDMARDs	60%	74%	$161	$155
Corticosteroids	46%	61%	$25	$19

Each patient's treatment regimen was also analyzed to understand which RA therapies were being employed in tandem. The most common combination utilized was a NBDMARD with a corticosteroid. A BDMARD coupled with a NBDMARD was the next most common regimen.

Conclusion: Pharmacotherapy trends from a large RA cohort derived from health plans and employers across the United States reveal a rise in utilization of BDMARDS, NBDMARDS and corticosteroids. However, BDMARDS are the largest driver of RA pharmacotherapy costs which continue to rise, while costs for the other therapies have dropped. If BDMARD use continues to increase along with costs, the burden on patients and healthcare systems may not be sustainable. Future studies examining cost effective use of biologic vs. non-biologic therapies are needed in this climate of health care utilization and cost containment.

Disclosure: J. Cooper, CVS Caremark, 1, Accordant Health Services, 3 ; **L. Hall**, Accordant Health Services, 3 ; **A. Krueger**, CVS Caremark, 1, Accordant Health Services, 3 ; **S. S. Lim**, 9, Emory University, 3, Accordant Health Services, 5 .

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Baseline (BL) Characteristics of Gout Subjects Influence Urate-Lowering (UL) Efficacy During Febuxostat and Allopurinol Treatment. M. A. Becker[1], P. MacDonald[2], S. Chefo[2] and R. L. Jackson[2], [1]University of Chicago, Chicago, IL, [2]Takeda Global Research & Development Center, Inc., Deerfield, IL

Purpose: To assess the impact of BL subject characteristics on the UL efficacy of febuxostat and allopurinol in subjects with gout and hyperuricemia.

Methods: Subjects in the CONFIRMS trial (N=2,269) were randomized (1:1:1) to receive 6 months of daily treatment with either febuxostat 40 mg, febuxostat 80 mg, or allopurinol 300 mg (or 200 mg if BL estimated creatinine clearance <60 mL/min). Effects of BL subject characteristics on achievement of serum urate level (sUA) <6 mg/dL at the final visit were explored via a multivariate regression model. BL factors and treatment were entered into an initial logistic regression model, and the backward selection technique was employed, keeping treatment effect in the model at every step. Model selection was completed once no additional factors were removed at the 0.05 significance level.

Results: Overall proportions of subjects achieving target sUA were 45%, 67%, and 42%, respectively, in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups. The following BL characteristics were retained in the final model: treatment, sUA, age, gender, renal function, body mass index (BMI), tobacco use, and presence of tophi. After adjustment for BL factors, endpoint achievement rates with both febuxostat 40 mg and 80 mg were significantly higher than with allopurinol ($p \leq 0.037$), and were significantly higher with febuxostat 80 mg than with febuxostat 40 mg ($p \leq 0.001$). Furthermore, in subjects with BL moderate renal impairment, a significantly higher response rate occurred with febuxostat 40 mg than with allopurinol ($p < 0.05$). UL response did not differ between febuxostat 40 mg and allopurinol

treatment in subjects with mild renal impairment or normal renal function. In all treatment groups, UL response rates were greater in older subjects, women, adherent subjects, and nonsmokers as well as in subjects with lower BL sUA and BMI and no tophi.

Conclusion: After adjusting for multiple BL subject characteristics, UL with febuxostat 80 mg remained superior to UL with either febuxostat 40 mg or allopurinol. UL response rates in the febuxostat group were higher in those with mild/moderate BL renal impairment than in subjects with normal renal function.

Disclosure: M. A. Becker, Takeda, 5, Regeneron, 5, URL Mutual, 5, Savient, 5, Biocryst, 5, Novartis, 5 ; **P. MacDonald**, Takeda, 3 ; **S. Chefo**, Takeda, 3 ; **R. L. Jackson**, Takeda, 3 .

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Health Care Resource Utilization & Loss of Productivity in a Canadian Population of Patients with & without Lupus Nephritis.

Elaheh Aghdassi[1], Wendy Zhang[2], Yvan St-Pierre[3], Ann E. Clarke[3], Carolina Landolt-Marticorena[4], S. Morrison[2], Jiandong Su[5], Heather Reich[1], A. Herzenberg[4], J. Scholey[4], Christian A. Pineau[6], Janet Pope[7], CA Peschken[8], CaNIOS LuNNET Investigators, Joan E. Wither[9] and P. R. Fortin[2], [1]The University Health Network, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]McGill University Health Center, Montreal, QC, [4]University Health Network, Toronto, ON, [5]University of Toronto, Toronto, ON, [6]McGill University, Montreal, [7]St Joseph Health Care, London, ON, [8]University of Manitoba, Winnipeg, [9]University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: To determine whether Health Care Resource Utilization and Loss of Productivity differs between patients with Systemic Lupus Erythematosus (SLE) with & without Nephritis (LN & NLN, based on renal biopsy or ACR criteria).

Method: LN and NLN patients enrolled in a Lupus Nephritis study in Canada, were classified into those with active (ALN & ANLN) and inactive disease (ILN & INLN) based on SLE disease activity index (SLEDAI). Scores≥6 considered active disease. Patients reported on health care resource utilization and loss of productivity (patients & caregivers) from work and non-work activities in the 4 weeks preceding enrollment

Results: 141 patients (121 female, 20 male), 79 with LN (ALN: 53, ILN: 26) and 62 with NLN (ANLN: 38, INLN: 24) were enrolled. LN patients were significantly younger compared to NLN (36.5±1.5 vs 43.8±1.9 years; p=0.003) and had a higher SLEDAI score (9.5±0.8 vs 5.1±0.5; P=0.0001). SLE duration was similar between the two groups. Compared to NLN, patients with LN were more likely to visit health professionals (88.6% vs 74.2%; p=0.026) and had a higher number of visits to rheumatologists (0.8±0.1 vs 0.6±0.1; p=0.09); family physicians (0.9±0.2 vs 0.5±0.1; P=0.041) and nephrologists (0.3±0.1 vs 0.0±0.0; p=0.001). LN patients were also more likely to undergo diagnostic tests (81% vs 62.9%; p=0.016), most commonly including blood (1.7±0.2 vs 1.1±0.2; P=0.036) and urine tests (1.2±0.2 vs 0.5±0.1; p=0.001).

ALN patients had a significantly higher number of visits to all medical professionals (2.8±0.3 vs. 1.5±0.3; P=0.003), with more visits to rheumatologists and nephrologists compared to ILN. Number of diagnostic tests (X-rays, venipuncture, urine tests) were also significantly higher in ALN compared to ILN (4.3±0.5 vs 1.8±0.4; P=0.003).

In NLN, there was no difference in the number of visits to health professionals between ANLN & INLN, however, ANLN were more likely to have diagnostic tests such as blood (69.4% vs 37.5%; p=0.014) and urine tests (44.7% vs 16.7%; p=0.023).

The use of complementary therapies, assistive devices, emergency hospital visits and hospitalization periods were similar between all patient groups. Only 48% of LN and 45% of NLN were employed. Loss of productivity was similar for both patients and caregivers between all patient groups.

Conclusion: Health care resource utilization is much higher in LN patients, especially in those with an active disease. Although less than 50% of patients were employed, the loss of productivity was similar between all patient groups.

Disclosure: E. Aghdassi, None; **W. Zhang**, None; **Y. St-Pierre**, None; **A. E. Clarke**, None; **C. Landolt-Marticorena**, None; **S. Morrison**, None; **J. Su**, None; **H. Reich**, None; **A. Herzenberg**, None; **J. Scholey**, None; **C. A. Pineau**, None; **J. Pope**, None; **C. Peschken**, None; **J. E. Wither**, None; **P. R. Fortin**, Canadian Institute of Health Research, 2, President, 6 .

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Does the Framingham Score Underestimate Cardiovascular Risk in Rheumatoid Arthritis? Cynthia S. Crowson, Elena Myasoedova, Veronique Roger, Eric L. Matteson, Hilal Maradit Kremers, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease (CVD). CV risk scores for the general population may not accurately predict CV risk for RA patients. The purpose of our study was to examine whether the Framingham risk score underestimates CV risk for RA patients.

Method: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA between 1-1-1988 and 1-1-2008 was assembled and followed until death, migration, or 7-1-2008. The presence of CVD (myocardial infarction [MI], CV death, angina, and heart failure [HF]) was ascertained throughout follow-up via medical record review, as was the presence of CV risk factors at RA incidence. The 10 year Framingham risk score for CVD (Circulation 2008;117;743-753) includes MI, CV death, angina, HF, stroke and intermittent claudication (IC). To apply these expected risk estimates to CVD events observed in our study, we multiplied the risk estimates by the ratio of CVD events to the combined stroke, IC and CVD events in the general population. Poisson regression models were used to obtain the standardized incidence ratio (SIR), which is the ratio of observed CVD in RA to expected CVD obtained from the Framingham risk score.

Results: The study included 490 RA patients aged 30-74 years without prior CVD (mean age of 52 years, 69% women). The patients were followed up for a mean of 8.4 years during which 64 patients developed CVD. The 10 year risk of CVD in women was 11.2% (95% confidence interval [CI]: 6.8%, 15.5%) and in men was 26.3% (95% CI: 16.1%, 35.2%). The median Framingham risk score was 4.6% for women (min: 0.6%, max: 31.0%) and 12.0% for men (min: 1.3%, max: 60.8%). The SIR for women was 1.9 (95% CI: 1.3, 2.8; p=0.002) and for men was 1. 6 (95% CI: 1.1, 2.3; p=0.03). This suggests that the Framingham risk score significantly underestimates CV risk in RA in both women (by 86%) and men (by 56%). Analysis of age groups revealed the SIR is largest for women ≥55 years and for men ≥ 45 years. While the Framingham risk score was not designed for patients ≥ 75 years, it is often used in this age-group of patients. Applying the Framingham risk score to RA patients (n=59) aged ≥75 years we found a pronounced underestimation of CV risk for both women (SIR: 5.8; 95% CI: 3.6, 9.5) and men (SIR: 4.8; 95% CI: 2.5, 9.1).

Conclusion: The Framingham risk score substantially underestimates CVD risk in RA patients of both genders, especially in older ages. In patients ≥75 years, the deficit in CV risk estimates was particularly large. This underscores the need for more accurate tools to predict the risk of CVD in RA patients.

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Trends in Distal Forearm Fractures Among Older Women in U.S., 1991-2008. Fidel J. Martinez[1] and Carlos H. Orces[2], [1]Laredo Specialty Hospital, Laredo, TX, [2]Laredo Medical Center, Laredo, TX

Purpose: Distal forearm fractures are one of the most frequent osteoporotic fractures among older women. Moreover, this type of fracture increases the risk of sustaining subsequent osteoporotic fractures. Despite these facts, there is scarce data about the incidence of distal forearm fracture among older women in U.S. Therefore, the purpose of this study was to analyze trends in the incidence of distal forearm fractures among women 50 years or older in U.S. from 1991 to 2008.

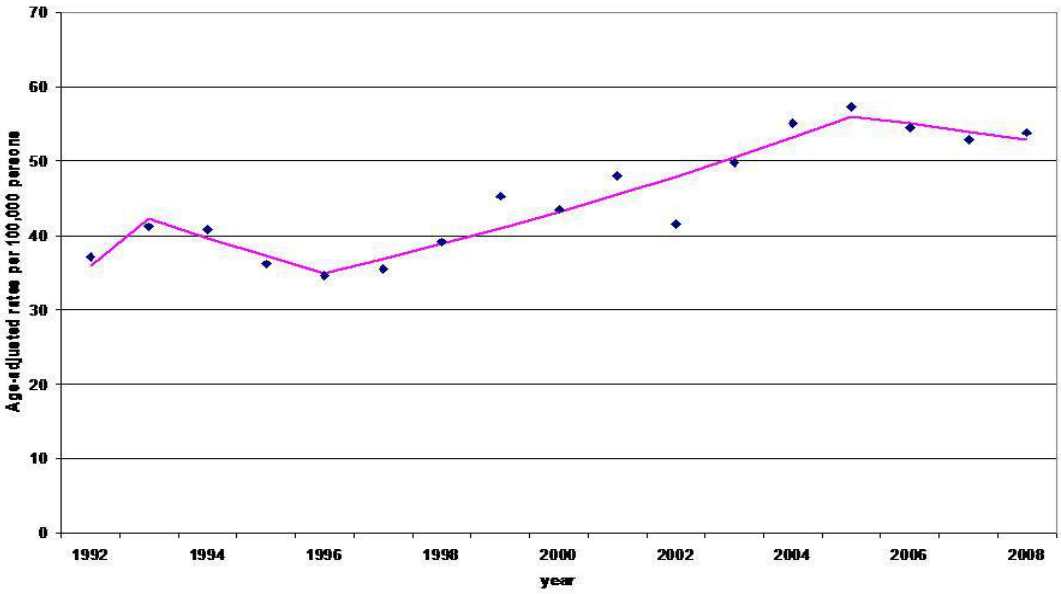
Method: The National Electronic Injury Surveillance System All Injury Program (NEISS-AIP) was used to estimate emergency department visits for distal forearm fractures. The expanded system, NEISS-AIP, collects data about treatment of patients for all types and causes of injury in U.S. hospitals, regardless of whether the injuries are related to consumer products. The U.S. Census population data were used as the denominator to calculate age-specific distal forearm fracture rates per 100,000 persons. Fracture rates were age-standardized using the direct method for adjustment to the year 2000 U.S. population. Joinpoint Regression Program was used to evaluate temporal trends in fractures. The joinpoint regression starts with no joinpoint and tests whether one or more joinpoints are statistically significant and need to be entered into the model (a maximum of three joinpoints by default) to best fit the data over the period of study. In the final model, annual percentage change (APC) and corresponding 95% confidence interval (95% CI) were estimated for each trend segment detected. In the figure, the observed rates are represented by symbols and the predicted trends from the joinpoint regression model are represented by lines.

Results: An estimated of 304,106 distal forearm fractures occurred among women 50 years of age and older in U.S. during the study period. The number of fractures rose from 10,910 in 1991 to 26,721 in 2008, a 144% increase. The median age of women was 69 years. The

majority of fractures (62%) occurred at home. Thirty percent of distal forearm resulted from falls on the floor and 20% from falls on steps. Ninety percent of women were treated and released from EDs, whereas only 8% of fractures were hospitalized. Distal forearm fractures increased considerably in all age groups between 1991 and 2008. However, the highest increase in incidence rates was observed in women aged 60 to 69 years at an annual rate of 4.3% (95% CI, 4-5.6). After age-adjustment, fractures rates increased from 30.1/100,000 in 1991 to 53.8/100,000 persons in 2008, a 78% increase. Although the age-adjusted rates increased 3.1% (95% CI, 2.3-41) per year between 1991 and 2008, joinpoint analysis demonstrated a significant increase in rates between 1996 and 2005 at an annual rate of 5.3% (95% CI, 2.6-8.2) during this period (Figure 1).

Conclusion: The present study indicates that distal forearm fractures increased considerably among older women in U.S. between 1991 and 2008. The increase in fracture rates can not be explained simply by demographic changes of the population. Preventive measures should be implemented to decrease the burden of this type of fracture.

Figure 1. Distal Forearm Fractures Among Women Aged 50 Years or Older in U.S., 1991-2008



Disclosure: F. J. Martinez, None; **C. H. Orces**, None.

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Which Comes First: Knee Malalignment or Joint Space Narrowing? David T. Felson[1], Yuqing Zhang[2], J. Niu[3] and D.J. Hunter[4], [1]Boston University School of Medicine, Boston, MA, [2]BUMC, Boston, MA, [3]BUSM, Boston, MA, [4]NEBH, Boston, MA

Purpose: While knee malalignment is strongly associated with increasing structural damage in osteoarthritis (OA) progression others have found that malalignment is not associated with knee OA incidence. Clarification of the temporal sequence between knee malalignment and OA occurrence is important because it will help us to understand the etiology of OA and guide us to develop effective clinical and preventive strategies for the disease. We performed sequence symmetry analysis to assess the temporal sequence between the knee alignment and joint space narrowing (JSN) in the Boston Osteoarthritis of the Knee Study (BOKS).

Methods: Subjects in BOKS had semi-flexed weight-bearing AP radiographs at baseline, 15-, and 30-month clinic visits (short-limb). The short-limb radiographs were read using a standard protocol and Efilm viewing software for anatomic axis (AA) (inter-observer ICC=0.96)

and were also read for JSN grade (0-3) in the medial (M-JSN) and lateral (L-JSN) compartments. The same protocols were used to assess JSN and AA across 3 time points. We defined a knee as having malalignment if AA was ≥ -2 (varus) or ≤ -6 (valgus). A knee was defined as having JSN in each compartment if the JSN score was ≥ 1. We performed sequence symmetry analysis to assess the temporal relation between JSN and malalignment using the time sequence symmetry ratio (i.e., the number of knees with JSN occurring before malalignment sequence divided by the number of knees with malalignment occurring before JSN sequence).

Results: Included were 38 knees that had both JSN and malalignment occurred during the 30-month follow-up period and each of these features presented at the different visits. Of them, JSN occurred before malalignment in 23 knees, and malalignment occurred before JSN in 15 knees. The time sequence symmetry ratio was 1.5 (95% CI: 0.8-3.2). When the analysis was limited to knees with both M-JSN and varus alignment (n=26), the time sequence symmetry ratio was 2.7 (95% CI: 1.1-7.6), suggesting M-JSN was more likely to occur before varus alignment.

Conclusion: While the number of knees in which JSN and malalignment occurred at different time points is small in our study, the results suggest that JSN was more likely to occur before malalignment but not in reverse. Further studies with more repeated assessments of JSN and knee alignment in a relatively short time interval are required to confirm the findings.

Disclosure: D. T. Felson, None; **Y. Zhang**, None; **J. Niu**, None; **D. J. Hunter**, None.

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Assessment of the Adequacy of Conclusions in Superiority RCTs: The Example of 3 Rheumatic Diseases- Rheumatoid Arthritis, Spondyloarthropathies and Osteoarthritis. Sylvain Mathieu[1], Isabelle Boutron[2], Bruno Giraudeau[3], Martin Soubrier[1] and P. Ravaud[2], [1]Rheumatology. Gabriel Montpied Teaching Hospital, Clermont-Ferrand, France, [2]University of Paris VII, Bichat Hospital, Paris, France, Paris, France, [3]INSERM, CIC 202, France ; CHRU de Tours, France, Tours, France

Purpose: To assess the proportion and to define the causes of misleading conclusions in published randomized controlled trials (RCTs) assessing rheumatoid arthritis (RA), osteoarthritis (OA) or spondyloarthropathies (SPA). To determine whether conclusions were based on the primary outcome (PO).

Method: We searched Medline, Embase and the Cochrane Collaboration for RCTs assessing RA, OA or SPA published between January 2006 and April 2008. Characteristics of each article were extracted (journal information, funding source, financial ties of authors, Jadad scale, results for POs and authors' conclusions). The abstract conclusion was judged to be misleading according to the following criteria: PO not reported, conclusion based only on secondary outcome or sub-group results, discrepancy between results and conclusion, negative results suggested as equivalent and lack of balance benefit/risk discussion.

Results: Of the 145 reports selected, 18 (12.4%) were registered with a clear and similar PO in the registry and the published text and no misleading conclusion in the abstract. We analysed the 108 articles with a clear PO. Twenty-seven per cent had a misleading conclusion in the abstract (n=29). Abstract conclusion in disagreement with results (n=10; 34.5%) and lack of PO reporting (n=8; 27.6%) were the most frequent reasons. Negative results suggested as equivalent, conclusion based only on secondary outcome or on sub-group analysis represented respectively 17.2% (n=5); 13.8% and 13.8% (n=4) of cases of misleading conclusions. Finally, lack of benefit/risk balance discussion in cases of serious adverse events was found in 10.3% (n=3) of articles. Of the 108 studies analysed, 63 (53.3%) had positive results and 43 (39.8%) negative results. Studies with negative results had a higher frequency of misleading conclusions in the abstract than those with positive results (22/43 versus 5/63; $p<0.001$). Articles assessing OA, studies with an industrial affiliation of authors or those without clinically relevant results were more likely to report misleading conclusions in univariate analysis. Other factors did not reach statistical significance. In multivariate analyses, only negative results increased the risk of misleading conclusions (OR=9.27 [1.89-45.45]).

Conclusion: This study found a proportion of 27% of misleading conclusions in the abstracts of a sample of RCTs assessing RA, OA and SPA. Negative and clinically irrelevant results were risk factors of misleading conclusion.

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The Prevalence of Psoriasis and Psoriatic Arthritis in Sweden – A Health Care Register Study. Sofia Löfvendahl[1], Elke Theander[2], Åke Svensson[3], Martin Englund[4], Aleksandra Turkiewicz[1] and Ingemar Petersson[5], [1]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, [2]Dept of Rheumatology, Malmö University Hospital, Malmö, Sweden, [3]Dept of Dermatology, Malmö University Hospital, Malmö, Sweden, [4]Lund University, Lund, Sweden, [5]Lund University, Department of Clinical Sciences, Lund, Lund, Sweden

Purpose: The occurrence of psoriasis and psoriatic arthritis (PsA) leading to health care contacts is not well described before. The aim of this study is to estimate the prevalence of psoriasis and PsA in Sweden.

Method: In the Skåne Health Care Register (SHCR) (covering 1.2 million people or 1/8 of the Swedish pop.) full coverage on individual data on age, sex, health care provider, date of visit, ICD-10 diagnosis codes are continuously registered for both in- and outpatient care. We identified all individuals (no age restriction) with at least one clinic visit to a physician (both primary care and specialized care) between Jan. 1, 2001 and Dec. 31, 2007 having received any of the following psoriasis diagnoses (ICD-10 codes): psoriasis vulgaris (L40.0), generalized pustular psoriasis (L40.1), guttate psoriasis (L40.4), arthropathic psoriasis (L40.5), other psoriasis (L40.8) and psoriasis unspecified (L40.9). By cross-referencing with personal ID numbers from the Population Register (total pop. in southern Sweden Dec. 31, 2007= 1 199 357) those individuals identified in SHCR as deceased or relocated out of the county by Dec. 31, 2007 were excluded. For the individuals diagnosed with psoriasis between Jan. 1, 2001 and Dec. 31, 2007 we identified the number of patients with any of the following PsA diagnoses (ICD-10 codes): distal interphalangeal psoriatic arthropathy (M07.0), arthritis mutilans (M07.1), psoriatic spondylitis (L40.2), other psoriatic arthropaties (M07.3) and juvenile arthritis in psoriasis (M09.0). Those diagnosed using ICD-10 diagnosis code L40.5 or a combination of a psoriasis and a PsA diagnosis code were defined as having PsA. Prevalence estimate by Dec. 31, 2007 was calculated for psoriasis and PsA. The prevalence estimates were adjusted for the uncertainty generated by the loss of patients only seen by private practitioners for their psoriasis or PsA (appr. 15%).

Results: 13 716 individuals had sought health care, been diagnosed with psoriasis and were still alive and residents in the region by the end of 2007. The prevalence of diagnosed psoriasis in residents of southern Sweden (all ages) was 1.35% (95% CI 1.32, 1.37). Out of the individuals diagnosed with psoriasis, 2 491(18.2%) were identified as having PsA. This indicates a prevalence of diagnosed PsA in residents of southern Sweden of 0.24% (95% CI 0.23, 0.25) by the end of 2007. Among those diagnosed with PsA 1 163 (46.7%) were diagnosed using ICD-10 diagnosis code L40.5 and 1 328 (53.3%) were diagnosed with a combination of a psoriasis and a PsA diagnosis code.

Conclusion: Using register data of true health care consumption gives more relevant prevalence estimates of psoriasis and PsA. Thus, we found that at least one fifth of all individuals diagnosed with psoriasis also had health care contacts for diagnosed PsA.

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Developing a Cinical Score for Knee OA in the Osteoarthritis Initiative. Charles B. Eaton[1], Timothy McAlindon[2], Joan M. Bathon[3], Mary Roberts[4], Michael C. Nevitt[5] and C. K. Kwoh[6], [1]Alpert Medical School of Brown University, Pawtucket, RI, [2]Tufts Medical Center, Boston, MA, [3]Johns Hopkins University, School of Medicine, Baltimore, MD, [4]Pawtucket, RI, [5]University of California, San Francisco, San Francisco, CA, [6]UPitt, Pittsburgh, PA

Purpose: There is no validated assessment to measure knee osteoarthritis clinical progression over the long term in an observational setting. Instruments such as KOOS and WOMAC and their subscales are highly inter-correlated and rely exclusively on self-report. We evaluated the use of principal component analysis of the baseline OAI data set in the attempt to define independent or orthogonal factors that could be summed to define the clinical severity of an index knee. Such a knee-specific clinical score could be used to assess clinical progression.

Method: Of the 4796 subjects, 3310 had complete data in the baseline OAI dataset 0.2.2. We evaluated 73 "clinical" variables related to an index knee that could vary from exam to exam in OAI data set that represented symptoms, pain, activity avoidance, KOOS, WOMAC, physical exam, medication use, physical activity, strength testing, walking times to define a non-singular matrix. Using eigenvalues of 1.0 for variable selection, repeated rotated factor pattern analysis was done. Orthogonal factors were defined based upon loading scores >0.5 for each of 38 individual clinical variables. **Results:** Overall sampling frequency was 0.829. We found 8 orthogonal factors that explained 91% of the variance of the clinical symptoms associated with an index knee. Below are the eight factors defined and the percent variance explained by each orthogonal factor.

Factor	Components	% variance
Factor 1	Pain, WOMAC/KOOS subscales, overall pain rating	22.18
Factor 2	Pain ratings compared to past (X-sectional)	14.08
Factor 3	Good Strength Chair- Production/relaxation limits	11.20
Factor 4	20meter and 400 meter walk test	10.41
Factor 5	Good Strength Chair- Maximum Force- flexion and extension;	9.55
Factor 6	Activity limited due to knee pain; limitation of activities to prevent knee pain	9.52
Factor 7	Use of glucosamine and chondroitin in the past six months	7.11
Factor 8	Chondroitin and/or glucosamine current use	7.11
Total		91.15

Conclusion: Eight independent, uncorrelated clinical "factors" defined by 38 variables allow for a summary score to be developed for each knee with excellent explanatory power. Future research will focus on how this clinical score changes over time, responds to therapy, and correlates with radiographic, MRI and biomarker changes.

Disclosure: C. B. Eaton, Pfizer Inc, 5 ; **T. McAlindon**, Gelita, 2, Gelita, 5, Stryker Biotech, 5, NIH, 2 ; **J. M. Bathon**, Biogen-IDEC, 9, Bristol Myers Squibb, 9, Amgen, 9, Crescendo Biosciences, 9, Roche , 9, Merck Serono, 9 ; **M. Roberts**, Pfizer Inc, 5 ; **M. C. Nevitt**, None; **C. K. Kwoh**, None.

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Prevalence of Staphylococcus Aureus Colonization Among Those Using Biologic Therapy. Atul A. Deodhar[1], Shellie Yamashita[1], Benjamin Ehst[1], Antony Bakke[1], Andrew Blauvelt[1], Brian Andrews[1], Robert Vega[2] and Kevin Winthrop[1], [1]Oregon Health & Science University, Portland, OR, [2]Oregon State Public Health laboratory, Portland, OR, Portland, OR

Purpose: Methicillin-resistant *Staphylococcus aureus* (MRSA) infection rates in the community are increasing. There is little community-level data regarding *S. aureus* colonization prevalence and infectious risk in patients with autoimmune inflammatory diseases, particularly those receiving anti-tumor necrosis factor (TNF) and other biologic immunomodulating therapies.

Method: We prospectively identified patients with autoimmune inflammatory disease within the rheumatology and dermatology clinics of Oregon Health & Science University in Portland, Oregon. Participating patients receiving or being considered for biologic therapy (etanercept, infliximab, adalimumab, rituximab, abatacept) were surveyed for the presence of *S. aureus* infection risk factors and were assessed for *S. aureus* colonization. Specimens collected from the bilateral nares and inguinal folds of all subjects were cultured utilizing standardized laboratory *S. aureus* isolation procedures and further screened for the presence of MRSA utilizing Spectra™ MRSA test media (Remel Scientific®) and mannitol salt agar containing 4 mcgs of oxacillin (MSAO, Remel Scientific). Screen positive organisms isolated from either of these two media were further screened with Mueller Hinter agar containing 6 mcgs of oxacillin and tested for the presence of PBP2' (a penicillin binding protein encoded by the mecA gene).

Results: We have enrolled a total of 222 inflammatory disease patients (rheumatoid arthritis n=58, psorisias or psoriatic arthritis n=140, ankylosing spondylitis n=10, combination of two conditions n=12, other n=2). At baseline, 78 (35%) of patients were colonized with *S. aureus*, of which 4 (5%) were methicillin-resistant (MRSA). One hundred thirty (57%) patients were on biologic therapy at time of assessment. Colonization rates were similar between biologic users and non-users (33% and 38% respectively), between RA and psoriasis patients, and similar to that historically reported for the general U.S. population (30%). Colonization did not differ between biologic agents, but was more common in RA patients if they were receiving prednisone at baseline (RR 0.40, 95% CI 0.1-1.2), but this did not reach statistical significance (p=0.06).

Conclusion: Inflammatory disease patients in Portland, Oregon, have similar rates of *S. aureus* colonization as the general population, and the risk of colonization in this cohort is not modified by the receipt of biologic therapy. Prospective follow-up is necessary to ascertain if colonization increases the risk of subsequent *S. aureus* infection.

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The Association of Social Network Factors with Total Hip Replacement (THR) in the SOF Cohort: The Study of Osteoporotic Fractures Research Group. B.L. Wise[1], N. Parimi[2], M. Nevitt[3], J. Cauley[4], R.K. Chaganti[3] and N.E. Lane[1], [1]UCDMC, Sacramento, CA, [2]CPMC, SF, CA, [3]UCSF, SF, CA, [4]U Pitt, Pittsburgh, PA

Purpose: The decision making process that patients use when deciding whether to have a joint replacement is reported to be influenced by their social support. This study examines the association of social network with THR in elderly Caucasian women.

Method: We conducted a nested cohort study among women who were participants in the Study of Osteoporotic Fractures, a cohort of 9704 white women 65 years of age or older at baseline followed for 14 years. At visit 2 and visit 4, the Lubben Social Network Scale was completed, and hip x-rays were obtained at baseline and visit 5. Two sets of participants were selected: the first set included participants who had completed information at baseline and visit 2 with self reported THR ascertained at visit 5; the second set included those with completed information at visit 4 and visit 5 with self reported THR ascertained at visit 8. We restricted the analysis to participants who reported hip pain on most days of the month and had radiographic osteoarthritis defined by a modified Croft grade>=2. Participants who reported rheumatoid arthritis, Paget's disease, had bilateral THR prior to visit 2, or who had hip fracture prior to the reported THR were excluded. The two sets of participants were combined into one dataset with incident THR used as a dichotomous outcome measure. Descriptive analyses and multivariate logistic regression were performed using GEE to account for within-person correlation, with outcome as THR versus no THR and using the Lubben Social Network Scale and other covariates most closely preceding the reported THR. Models were adjusted for age, BMI, education, hip pain while resting and hip pain on internal rotation, and self-reported health change in the prior 12 months.

Results: There were 112 case (THR) hips in 104 women and 301 non-case (no THR) hips in 244 women. At baseline, cases were less obese (BMI 26.2 vs 27.5; p=0.009), had more education (45.2% had >12 years vs. 32.4% in controls; p=0.022), had fewer co-morbid conditions (average of 0.25 conditions vs 0.33; p=0.274), more often had hip pain on internal rotation (16.4% vs 5.2%; p=0.004) and more often had hip pain when resting (56.5% vs 29.7%; p<0.001). Descriptive analyses suggest that those who had a THR were slightly more independent: 25.3% saw their closest friend every day as compared with 28.1% in controls (p=0.123); 37.4% of cases saw their closest relative daily versus 45.2% in controls (p=0.245). However, no individual or summary component of the Lubben Social Network Scale was significantly associated with THR as an outcome in the adjusted regression analysis.

Conclusion: We found no evidence for a significant influence of social network factors on risk of THR. Hypothesis generating trends suggested that those that undergo THR may have fewer social interactions with family and friends, thereby possibly being more independent.

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The Georgia Lupus Registry: A Population-Based Estimate of the Incidence and Prevalence of Childhood-Onset SLE. S. Sam Lim[1], Rana Bayakly[2], C.G. Helmick[3], Caroline Gordon[4], Kirk Easley[1], Neeta Shenvi[1], Larry B. Vogler[1] and Cristina M. Drenkard[1], [1]Emory University, Atlanta, GA, [2]Georgia Department of Human Resources, Atlanta, GA, [3]Centers for Disease Control and Prevention, Atlanta, GA, [4]University of Birmingham, Birmingham, United Kingdom

Introduction and Purpose: There are no population-based studies estimating the prevalence and incidence rates of childhood-onset SLE in the US. Our aim was to describe these rates in Atlanta from 2002 through 2004.

Methods: The Georgia Lupus Registry is a population-based registry designed to estimate the incidence and prevalence of SLE in Atlanta, Georgia (Fulton and DeKalb counties). Case-finding utilizes multiple sources. Trained abstractors document nearly 250 demographic and clinical elements from medical records of potential SLE patients. All sources with potential SLE patients (<20 years old) have been abstracted. 31 incident and 51 prevalent patients met the case definition for this study: having either ≥4 ACR criteria or 3 ACR criteria and diagnosis of SLE by a rheumatologist.

Results:

Table 1. Annual average standardized incidence rates in Atlanta (2002-2004)

		Age Group	Population (0-19 years old)	Cases[a]	Age Standardized IR[b] (95% CI)[c]	Crude IR (95% CI)[c]
Overall			1,293,062	31	2.5 (1.6-3.4)	
Black	Total		745,397	27	3.6 (2.3-5)	
	Male		376,039	6	1.6 (0.3-2.9)	
		0-9		0		0 (0-2)
		10-14		2		2 (0.2-7.1)
		15-19		4		4.4 (1.2-11.4)
	Female		369,358	21	5.7 (3.2-8.1)	
		0-9		1		0.6 (0-3.1)
		10-14		6		6.1 (2.2-13.2)
		15-19		14		15.3 (8.4-25.7)
White	Total		492,777	2	0.5 (0-1.1)	
	Male		253,073	0	0 (0-0)	
	Female		237,704	2[d]	0.9 (0-2.2)	
		0-9		0		0 (0-2.8)
		10-14		2		3.6 (0.4-13.1)
		15-19		0		0 (0-7.2)

Table 2. Standardized prevalence rates in Atlanta (2002)

	Age Group	Population	Cases[a]	Age Standardized	Crude PR

			(0-19 years old)		PR[b] (95% CI)[c]	(95% CI)[c]
Overall			424,128	51	12.6 (9.1-16.1)	
Black	Total		249,276	45	18.4 (13-23.8)	
	Male		125,788	9	7.3 (2.5-12.1)	
		0-9		0		0 (0-5.9)
		10-14		4		11.9 (3.2-30.5)
		15-19		5		17 (5.5-39.6)
	Female		123,488	36	29.5 (19.9-39.2)	
		0-9		1		1.6 (0-9.1)
		10-14		13		39.6 (21.1-67.8)
		15-19		22		74.1 (46.4-112.1)
White	Total		157,378	1	0.7 (0-2.1)	
	Male		81,591	0	0 (0-0)	
	Female		75,788	1	1.5 (0-4.5)	
		0-9		0		0 (0-8.9)
		10-14		0		0 (0-21)
		15-19		1		6 (0.2-33.6)

[a] remainder of cases were Asians with CI's too wide and estimates too unreliable to report

[b] incidence rates (IR) and prevalence rates (PR) per 100,000; calculated by direct method using US census data (2000)

[c] calculated by exact method

[d] both of Hispanic ethnicity

Conclusion: This is the first population-based assessment in the US of incidence and prevalence rates in childhood-onset SLE. As in adults, cases were disproportionately female and black. Rates were highest in the late teens (after menarche). The black to white ratio appears to be greater than that reported in the adult literature.

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The Association of Obesity On Prevalent Hyperuricemia and Incident Gout in Women in the Atherosclerosis Risk in Communities (ARIC) Study. Mara A. McAdams[1], Janet W. Maynard[2], Alan N. Baer[2], Anna Kottgen[1], Allan C. Gelber[2] and Josef Coresh[1], [1]Johns Hopkins School of Public Health, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Previous research in gout has focused on men. The effect of anthropometric risk factors on prevalent hyperuricemia and incident gout in women is unclear. In the Atherosclerosis Risk in Communities (ARIC) Study, we evaluated the association of obesity with hyperuricemia and gout in women.

Methods: ARIC is a population-based cohort of 15,792 individuals (8,710 women) aged 45-64 at enrollment who participated in four examinations (3 years apart). We restricted our study population to Caucasian and African-American women with no history of gout at their first study visit. Serum urate was measured at visits 1 and 2, and we used the mean of these two measures. Hyperuricemia was defined as a mean serum urate greater than 7.0 mg/dL. Anthropometric variables were obtained at baseline and included body mass index (BMI) and waist-to-hip ratio (WHR). BMI was examined as continuous and categorical (<25, 25-30, 30-35, >35 kg/m^2) variables. Obesity was defined as BMI greater than 30. High WHR was defined as > 0.8. Weight change was calculated by subtracting the participant's weight at cohort entry from her self-reported weight at age 25. Weight change was categorized as: no weight change (weight loss or gain <10 lbs), low weight gain (weight gain of >10 to <30lbs), and high weight gain (>30 lbs). The multivariable model was adjusted for baseline age, race, diuretic and oral contraceptive pill use, menopausal status, hypertension, diabetes, and chronic renal insufficiency. Incident cases of gout were identified by self-report at visit 4.

Results: Of the 8,505 women with serum urate measurements, 14.9% were hyperuricemic. Obesity, WHR, and weight change were significantly associated with baseline hyperuricemia. The association remained after adjusting for known risk factors for hyperuricemia. Additionally, 113 women (1.3%) developed gout over nine years of follow-up. At baseline, all of the women who developed gout were obese, yet only 38% were hyperuricemic.

	Unadjusted risk of hyperuricemia		**Adjusted risk of hyperuricemia**	
	PR	CI	PR	CI
BMI (5 kg/m^2) change	1.53	1.49, 1.57	1.40	1.35, 1.45
BMI				
<25 (reference)	1.0		1.0	
25-30	2.68	2.24, 3.21	2.21	1.84, 2.64
30-35	4.90	4.11, 5.85	3.55	2.95, 4.26
35-40	7.33	6.18, 8.70	4.88	4.04, 5.90
Obese	3.33	3.01, 3.69	2.44	2.18, 2.73
High WHR	4.35	3.24, 5.84	3.04	2.26, 4.09
Weight change				
No change (reference)	1.0		1.0	
Low weight gain	1.43	1.14, 1.81	1.41	1.12, 1.77
High weight gain	4.03	3.29, 4.94	3.09	2.52, 3.79

Conclusion: In a population-based cohort of middle-aged women, we found obesity, high WHR and weight gain to be strongly associated with hyperuricemia. Additionally, all women who developed gout over nine years of follow-up were obese at baseline. Obesity is a risk factor for hyperuricemia and may be useful for prediction of incident gout in women.

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Health Literacy in Childhood Arthritis. Elizabeth Levey, Jonathan Erlich, Linda Wagner-Weiner and Karen Onel, Univ of Chicago, Chicago, IL

Purpose: Health literacy is defined as an individual's capacity to obtain, process and understand health information. Poor literacy has been associated with worse health status. In adults, low literacy has been linked to a poorer understanding of the disease and worse self-management skills. The degree to which parental health literacy affects outcomes for children with chronic disease is less certain. Juvenile Idiopathic Arthritis (JIA) presents an appropriate model to explore this relationship between parental literacy and child health outcome. We present here results of literacy assessments done in an urban pediatric rheumatology center to establish baseline frequency of poor literacy in families with JIA.

Method: Sixty-eight children with JIA and their parents were recruited for the study. Demographic information was collected. Health literacy skills, including reading, vocabulary and numeracy, were assessed by administration of Newest Vital Signs (NVS), Rapid Estimate of Adult Literacy in Medicine (REALM) and Rapid Estimate of Adolescent Literacy in Medicine for teenagers (REALM-Teen). Disease activity was assessed using the Physician and Parent Global Assessment (GA). Descriptive statistics were performed using Microsoft Excel and STATA. A p-value <0.05 was used to define statistical significance.

Results: 49 (72.1%) parents of children with JIA were considered to have adequate literacy, while 19 (27.9%) parents were considered to have limited literacy using both NVS and REALM. There was a strong correlation between adult and child literacy scores in the same families. There were no differences in ages between both groups. The adequate literacy group had a greater percentage of subjects who lived with two parents (75.5% v. 42.1%, $p<0.01$) and who had a household income above $30,000 (89.4% v. 29.4%, $p < 0.001$). There was a large discrepancy between the two groups for the type of insurance carried; 80% of adequate literacy subjects had private health insurance while only 26% of the limited literacy group did, with the remaining 74% relying on Medicaid, Medicare or out-of-pocket payments ($p<0.0001$). No significant difference was found between the groups for Physician or Parent GA scores, however, while there was a statistically significant correlation between the physicians and parents score for the adequate literacy group, there was not for the limited literacy group ($r=0.42$, $p<0.05$; $r=0.21$, $p>0.05$).

Conclusion: We found significant baseline differences between parental literacy ability when analyzing demographic data. Further, there was strong relationship between limited parental and child literacy. Finally, there was a large discrepancy in insurance types between the two literacy groups. Of concern, there was a lack of correlation between the ratings of parents with limited literacy on GA and the physician's GA. Previous studies have suggested that children with private insurance do better than those without despite seeing the same physicians in the same office. This outcome gap may be explained in part by the disparity in health literacy between the two groups preventing understanding of disease severity. We plan to follow these patients over time to better understand effects of parent/child literacy on health outcomes.

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Comparison of Baseline Characteristics and Outcome After One Year in Three European Early Arthritis Clinics. Maria D. Mjaavatten[1], Jennie Ursum[2], Tiina Veldi[3], Dirkjan van Schaardenburg[2], Kati Otsa[3] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Jan van Breemen Institute, Amsterdam, Netherlands, [3]East Tallinn Central Hospital, Tallinn, Estonia

Purpose: To compare baseline characteristics and outcome after one year between early arthritis clinics (EAC) in The Netherlands, Estonia, and Norway.

Method: Adult patients with ≥ 2 swollen joints with symptom duration ≤ 16 weeks included from Jan 1st 2005 and who were eligible for one year follow-up time from three early arthritis clinics (Jan van Breemen Inst., Amsterdam (JBI)/Tallinn/Norwegian Very Early Arthritis Clinic (NOR-VEAC)) were included in this study. The EACs in Estonia and Norway use the same protocol. Baseline characteristics and inflammatory activity (measured by Disease Activity Score-28 (DAS28)) at inclusion and after one year in the three clinics were compared by ANOVA and Chi-square statistics. DAS28 outcome was also compared using ANCOVA adjusted for the following factors: age, sex, anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) positivity, disease duration, and baseline DAS28.

Results: 629 patients were included in the study (JBI 153, Tallinn 71, NOR-VEAC 405). Baseline characteristics differed significantly between the EACs for age, disease duration, gender distribution, percentages of anti-CCP and RF positives, joint counts, DAS28 (table), as well as for ESR, patient global VAS, and HAQ (data not shown). Patients improved substantially over one year in all three EACs. DAS28 after one year was not significantly different between EACs when adjusted for baseline characteristics (p=0.15, ANCOVA), while age, sex, anti-CCP, duration and baseline DAS28 were significant variables in the ANCOVA analysis.

Conclusion: Patients in three European EACs differed significantly with regard to several characteristics and disease activity, possibly due to a higher incidence of reactive arthritis in Tallinn and Norway. A substantial improvement of inflammatory activity was seen after one year in all clinics. DAS28 outcome was similar when adjusted for differences in baseline characteristics. Age, sex, disease duration, anti-CCP positivity and DAS28 level at inclusion had impact on the outcome.

Table. Comparison of baseline characteristics and disease activity in the three EACs.

	JBI	Tallinn	NOR-VEAC	p-value
Age (years)	53.9	46.4	46.7	<0.001
Females (%)	68.0	78.9	55.9	<0.001
Anti-CCP pos (%)	48.4	25.4	20.6	<0.001
IgM RF pos (%)	45.1	25.4	18.2	<0.001
Duration (days)	61.0	42.7	41.4	<0.001
28-SJC	5.85	3.87	4.22	0.001
28-TJC	6.12	6.10	4.71	0.019
DAS28 baseline	4.73	4.73	4.45	0.039
DAS28 one year	2.89	2.21	2.33	<0.001

Values are expressed as means unless stated otherwise.

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Frequency and Cost of Joint Replacement Surgery for Patients with Rheumatoid Arthritis: A Population-Based Study in Canada.

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Purpose: Rheumatoid arthritis (RA) causes joint damage, often necessitating surgical joint replacement. Clinic- and hospital-based studies have estimated that 7%–27% of patients with RA require total joint replacement surgery; however, variable follow-up periods and/or small sample sizes limit generalizability of these results. This study used a population-based database to estimate the frequency, timing, and cost of joint replacements for patients with RA.

Method: A retrospective cohort study was conducted using the population-based, longitudinal Régie de l'Assurance Maladie du Québec patient-level, physician-billing, provincial database. The incident RA cohort included continually registered patients with ≥2 physician *International Classification of Diseases, Ninth Revision* (ICD-9) diagnoses of RA (714.0, 714.1, or 714.2) from 1998–2007, with first RA diagnosis in 1998. Total joint replacements were classified according to the *Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures* (CCP) codes 93.5 (hip) and 93.41 (knee), and *Canadian Classification of Health Interventions* (CCI) codes 1.VA.53 (hip) and 1.VG.53 (knee). Frequency of total joint replacements (hip+knee), mean and median time to surgery were estimated. Only 1 hip or

knee replacement per patient was included in the analysis. Direct hospitalization costs were estimated using Case Mix Group resource use and cost data from the Canadian Institute for Health Information.

Results: The incident cohort included 3,340 patients diagnosed with RA in 1998, of which 2,367 (70.9%) were female. The median age at entry was 52 years. Of these 3,340 patients, 300 (9.0%) had ≥1 total joint replacement; 24 (0.7%) had both total hip and total knee replacements; 144 (4.3%) had total hip replacement; and 180 (5.4%) had total knee replacement. The mean and median time to total hip replacement from first diagnosis of RA was 3.7 and 3.2 years (*interquartile range* [IQR], 1.3–5.8), respectively. For total knee replacement, mean and median time from cohort entry were 4.1 and 4.2 years (IQR, 1.7–6.0), respectively. Hip and knee replacement surgeries were estimated to cost approximately $3.18 million Canadian dollars (2009; 95% confidence interval [CI], 3.10–3.30 million) or an average of $9,370 (95% CI, $9,129–$9,735) per knee replacement and $10,367 (95% CI, $10,100–$10,770) per hip replacement.

Conclusion: Joint replacement surgeries contribute substantially to the burden of RA. In this large, longitudinal, population-based study, almost 1 in 10 patients with RA required joint replacement surgery, with 25% of these surgeries occurring within the first 2 years after diagnosis. Early, appropriate treatment of RA may prevent joint damage and result in fewer or delayed joint surgeries.

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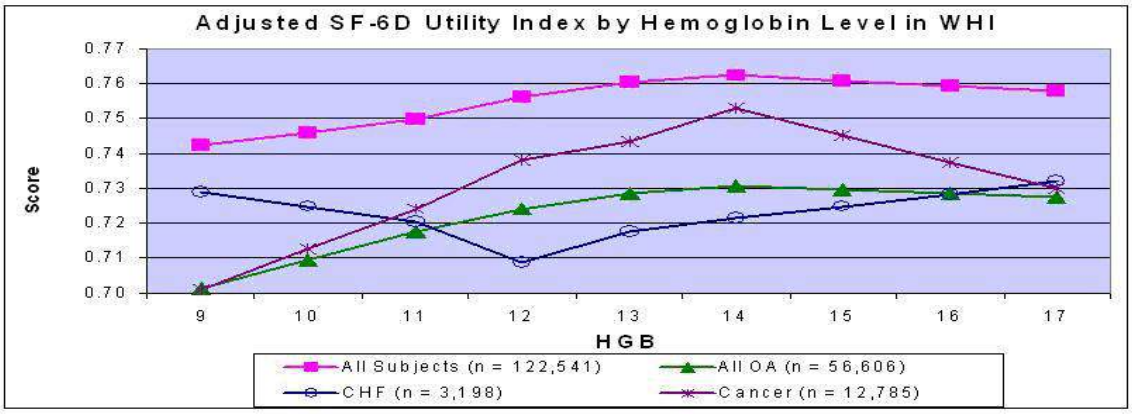
Health Utilities and Hemoglobin Levels in Post Menopausal Women with Osteoarthritis, Cancer and Congestive Heart Failure: The Women's Health Initiative. Brooke Harrow[1], Charles B. Eaton[2], Annlouise R. Assaf[3] and G. Sands[4], [1]Abt Bio-Pharma Solutions, Inc., Lexington, MA, [2]Alpert Medical School of Brown University, Pawtucket, RI, [3]Pfizer, Inc. and Alpert Medical School of Brown University, Providence, RI, [4]Pfizer Global Pharmaceuticals, New York, NY

Purpose: Chronic disease and their treatments can lead to differential blood loss and anemia. The assignment of utility weights to hemoglobin (HGB) levels can provide an excellent resource for future studies of the cost-effectiveness of interventions developed to mitigate blood loss. We examined the mean utility weights adjusted for co-morbidities, as measured by the Short Form Medical Outcomes Health Utility summary scale (SF-6D) for varying hemoglobin levels in post-menopausal women using data from the Women's Health Initiative (WHI). We looked at how these weights vary for women with self-reported CHF, Cancer, or Osteoarthritis.

Method: Health utility weights as measured by the (SF-6D) scale were examined for various HGB levels. Utility weights are preference measures or values that are assigned to health states on a scale from zero to one where one represents perfect health and zero represents death. Multiple linear regression analyses were used to evaluate the independent association between HGB and the SF-6D, while adjusting for potential confounding by socio-demographic characteristics, medication use, depression, associated disease states. Adjusted least squared means were calculated based upon the regression analyses. These mean values for the SF-6D utility weights were stratified by hemoglobin level for the sample as a whole as well as separately for those with self-reported CHF, Cancer and/or “Osteoarthritis”. “Osteoarthritis” was defined as self-reported arthritis and not reporting rheumatoid arthritis.

Results: This figure shows the adjusted mean utility weights for the entire baseline sample, and the Osteoarthritis, CHF and Cancer cohorts within WHI by HGB level.



Conclusion: The relationship between health utility and hemoglobin appears different depending upon the presence or absence of certain chronic conditions. In the anemic range, health utilities associated with osteoarthritis and cancer appears worse than in the non-anemic range especially compared to those without chronic conditions and comparable levels of hemoglobin.

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Predictors of Serious Infections in Seniors with Rheumatoid Arthritis (RA): Results of the OBRI Administrative Database Analysis.

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Purpose: The Ontario Biologics Research Initiative (OBRI) represents a collaboration of rheumatologists, patients & researchers aiming to improve RA management through clinical & administrative database linkages. Our study's purpose was to assess predictors of serious infection using a case-control sample nested within a cohort of seniors with RA.

Method:

Our population-based RA cohort was assembled using billing & pharmacy data (1992-2007) for persons aged >65. Cohort entry criteria were an RA diagnosis based on ≥2 RA billing diagnoses, >60 days apart but within 5 years. Cohort members were required to have ≥1 prescription for a corticosteroid, traditional disease-modifying agent (DMARD), or biologic.

Our primary outcome was a 1st-time infection requiring hospitalization, based on hospital discharge diagnoses, assessed over 1998-2007. Cases were matched (on age, sex, year of cohort entry) to RA controls using risk-set sampling. Multivariate logistic regression assessed the independent effects of factors, including demographics (age, income rurality index), comorbidity & markers of RA severity/activity (rheumatology visits, history of joint replacement, extra-articular features, NSAID use) & RA-related drug exposures. Drug exposures were obtained from electronic provincial prescription data. Measures of comorbidity included the Charlson-Deyo Index & the number of drugs dispensed in the year prior to the index date (date of infection for each case-control set).

Results:

We identified 36,789 individuals aged >65 with RA, who were followed for a total of 267,227 person-years [mean (SD) follow-up: 7.3(5.8) years]. We compared 4,641 RA subjects with first-time serious infections to 10,847 controls. Factors affecting risk of serious infections in this adjusted analysis are presented in the table below:

Characteristics		Cases N=4641	Controls N=10847	Adjusted OR (95%CI)
Comorbidity	Charlson comorbidity score(%)			
	0	16.0	19.3	Ref
	1	21.4	17.1	1.23(1.03,1.47)
	≥2	42.1	21.4	1.51(1.26,1.79)
	Mean # drugs used (SD)	14.8(6.7)	10.6(5.8)	1.08(1.07,1.09)
	Chronic lung disease	44.4%	28.7%	1.59 (1.01, 1.55)
	Diabetes	26.6%	18.3%	1.10(0.96, 1.26)
	Renal disease	11.9%	5.6%	1.25(1.04, 1.40)
Markers of Disease Activity	# of Rheumatology Visits, mean (SD)	21.5(41.9)	11.9(23.5)	1.012(1.011,1.013)
	At least 1 extra-articular feature of RA	27.1%	13.8%	2.49(2.14,2.89)
	Previous Joint Replacement	21.3%	15.0%	1.05 (1.01, 1.09)
Low-income senior, n (%)		1427 (30.7)	2897 (26.7)	1.21 (1.13, 1.21)
Current Glucocorticoid Exposure		34.9%	22.6%	1.42(1.25,1.61)

Conclusion: Comorbidity, more markers of disease activity & glucocorticoids are important independent risk factors for infections requiring hospitalization in RA. Additionally, crude estimates suggested increased risk with current exposures to biologics & most DMARDs, but adjusted estimates were imprecise. Ongoing prospective data collection in the context of the OBRI will provide additional insights.

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A Faster Clinical Response to Certolizumab Pegol Treatment Is Associated with Better Improvements in Household Productivity in Patients with Rheumatoid Arthritis. R. Westhovens[1], Vibeke Strand[2], Edward C. Keystone[3], O. Purcaru[4], D. Khanna[5], J. S. Smolen[6] and A. Kavanaugh[7], [1]UZ Gasthuisberg, KU Leuven, Leuven, Belgium, [2]Stanford University, Portola Valley, CA, [3]Professor of Medicine/University of Toronto, Toronto, ON, [4]UCB, Brussels, Belgium, [5]UCLA, Los Angeles, CA, [6]Medical Univ Vienna, Vienna, Austria, [7]UCSD, San Diego, CA

Purpose: Certolizumab pegol (CZP), a PEGylated Fab' anti-TNF approved for the treatment of rheumatoid arthritis (RA), has been shown to provide rapid improvements in RA signs and symptoms and disease activity, as well as improvements in productivity at work and home, when added to methotrexate (MTX). The objective of our analysis was to determine if a more rapid clinical response to CZP treatment was associated with better long-term improvements in household productivity in patients with active RA.

Methods: Data from patients treated with CZP 200 or 400 mg + MTX in RAPID 1 were pooled for analysis. Patients who achieved response at Week (Wk) 12 were divided into subgroups depending on response at Wk 6: Wk 6 responders and Wk 12 responders (ie, those who were non-responders at Wk 6). Responder definitions were based on ACR20 response or DAS28 decrease ≥1.2 points from baseline (BL). The

number of household days lost due to RA, days with productivity reduced by ≥50%, the rate of RA interference with household productivity, and days lost of social activities in the last month were compared between responder subgroups using a repeated measures negative binomial regression adjusted for BL score and demographic variables. Analysis of work productivity was not possible due to an imbalance in patient numbers between the Wk 6 and Wk 12 responder groups.

Results: BL demographics were similar between the 2 responder subgroups. Wk 6 DAS28 and ACR20 responders lost significantly fewer days of household work than Wk 12 responders from Wks 4 to Wk 52 (Table). Wk 6 responders also had fewer days with reduced household productivity and a lower rate of RA interference with household productivity.

Conclusion: A faster response to treatment with CZP + MTX is associated with improved household productivity in patients with active RA over 52 wks. Rapid (Wk 6) responders lost fewer days of household work and had fewer days with reduced productivity than the later (Wk 12) responders. These observations are in line with other studies highlighting the importance of a rapid response to RA treatment.

Table. Household productivity in Wk 6 versus Wk 12 responders at Baseline, Wk 4, and Wk 52

Responder definition	**# Household days lost[a]**			**# Household days with reduced productivity[a]**			**# Family, social, leisure days missed[a]**			**Rate of RA interference[b] (0-10)**		
	BL	Wk4	Wk52	BL	Wk4	Wk52	BL	Wk4	Wk52	BL	Wk4	Wk52
Change in DAS28 ≥1.2												
Wk 6 responder (N=378)	5.1	4.4[e]	0.7[c]	7.7	4.9	1.7	2.2	1.8	0.2	5.2	3.6[d]	1.7[d]
Wk 12 responder (N=118)	5.0	6.8	1.5	6.0	5.5	2.3	2.0	1.8	0.3	4.8	4.3	2.3
ACR 20												
Wk 6 responder (N=344)	4.9	4.2[e]	0.6[c]	7.8	5.0	1.7[d]	2.2	1.6	0.1[d]	5.2	3.5[c]	1.7[c]
Wk 12 responder (N=152)	5.4	6.0	1.5	6.9	5.5	2.8	2.1	1.8	0.6	4.9	4.3	2.3

[a]Days in the proceeding month. [b]Over previous month.[c]P≤0.001, [d]P≤0.01, [e]P≤0.05 vs Wk 12 responders.

Disclosure: R. Westhovens, UCB, 2, UCB, 5 ; **V. Strand**, UCB, 5, UCB, 8, UCB, 5 ; **E. C. Keystone**, UCB, 5, UCB, 2, UCB, 8 ; **O. Purcaru**, UCB, 3 ; **D. Khanna**, Actelion, Gilead, Takeda, Savient, ,NIH, 2, Actelion, Takeda, Savient, UCB, Wyeth, 5, Actelion, Abbott, Gilead, Takeda , 8 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **A. Kavanaugh**, UCB, 2, UCB, 5 .

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Delayed Diagnosis Is Associated with Total Hip Replacement in Patients with Spondyloarthritis: Report From the SPARK International Survey. Maxime Dougados[1], Frédéric Lavie[2], P. Mease[3], Joachim Sieper[4], C. Combescure[5] and Désirée M.F.M. van der Heijde[6], [1]Hôpital Cochin, Paris, France, [2]Abbott Laboratories, Rungis, France, [3]Seattle Rheumatology Associates, Seattle, WA, [4]Charite - Campus Benjamin Franklin, Berlin, Germany, [5]University of Geneva, Geneva, Switzerland, [6]Leiden University Medical Center, Leiden, Netherlands

Purpose: Hip involvement is frequent in ankylosing spondylitis (AS) and affects disability and health-related quality of life, often leading to total hip replacement (THR).[1] We evaluated characteristics of patients with AS with and without a history of hip surgery.

Methods: SPondyloarthritis: Assessment of CuRrent Epidemiology, Management, and Knowledge (SPARK) was a multinational survey conducted in the United States, Canada, and 9 European countries to evaluate the epidemiology, diagnosis, and management of spondyloarthritis in rheumatology practices. Characteristics of patients with and without hip surgery were compared between each country. Univariate (Fisher's exact test) and multivariate linear regression analyses were conducted.

Results: Of the 2,703 patients surveyed in SPARK, 68 (2.5%) had ≥1 THR. Of those patients, 55 (80.9%) had at least a diagnosis of AS, according to their rheumatologist. Frequency of THR did not differ significantly between countries (range: 0.0–4.3%). Characteristics associated with THR in univariate analyses were greater age, male sex, HLA-B27 positivity, AS diagnosis (vs. other diagnoses), longer disease duration, poorer physician's satisfaction, and current employment status ($p<0.01$). A delay of more than 10 years between first symptoms of AS and diagnosis of AS was also associated with THR in univariate analysis (table).

Delay Between Diagnosis of AS and Frequency of THR

	1 to 10 Years	**≥11 Years**
Total, N	1,598	160
Patients with THR, n (%)	28 (1.8)	8 (5.0)[a]

[a]$p=0.02$, Fisher's exact test.

THR was associated with worse Work Productivity and Activity Impairment Questionnaire outcomes ($p=0.02$) and greater TNF-antagonist usage ($p<0.01$). Multivariate analyses identified AS diagnosis ($p=0.03$), greater age ($p=0.01$), and longer disease duration ($p<0.01$) as independent factors for THR; delay to diagnosis was also significantly associated with THR in multivariate analyses of the 1,738 patients for whom these data were available ($p=0.01$).

Conclusion: This study confirms that requirement for THR is a marker of SpA severity and suggests that this complication is observed primarily in patients with AS. The relationship between delay to diagnosis and requirement for THR emphasizes the need for earlier diagnosis of axial SpA.

Reference: [1] Claudepierre P et al. *Br J Rheum*. 1995,34:1139–45.

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Influenza Immunization Status Among US Adults with Arthritis, 2007. Jennifer M. Hootman and Charles G. Helmick, Centers for Disease Control and Prevention, Atlanta, GA

Purpose: : In April 2009 an outbreak of a novel H1N1 influenza virus was documented in the US and has since spread worldwide. Annual flu immunization is recommended for people age ≥50 years and for those with disease- or drug-induced immunosuppression, who do poorly with an influenza infection. Most arthritis patients are in this target group but little is known about their level of compliance with recommendations. The purpose of this study was to estimate the prevalence and related characteristics of influenza immunization (FLU-IM) among US adults with arthritis.

Method: Data are from the 2007 (n = 430,912) Behavioral Risk Factor Surveillance System, an annual, random-digit dialed national phone survey of US adults conducted in all 50 states and D.C. Arthritis was defined as a 'yes' response to "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" FLU-IM status was defined as having received a flu shot or flu nasal spray in the past 12 months. Estimates (95% confidence intervals, CI) of FLU-IM by arthritis status were calculated using statistical weights to account for the complex sample design. Multivariate logistic regression (adjusted odds ratios and 95% CI) was used to identify factors that might be significantly ($p<0.05$) related to FLU-IM status, including demographics (age, sex, race/ethnicity, education level), general health indicators (obesity, self-rated health, current smoker, presence of diabetes, heart disease or a disability), and health care factors (have health insurance, have a usual health care provider).

Results: The unadjusted FLU-IM prevalence was 52.3% (CI 51.8 – 52.8; 1.2% received nasal spray, 52.0% received injection) among adults with arthritis, significantly higher than among adults without arthritis (31.4%, CI 31.0-31.7), and in multivariate analyses adults with arthritis were 1.4 (CI 1.4 – 1.5) times more likely to receive FLU-IM. Among adults with arthritis who had seen a health care provider in the past 12 months, FLU-IM was significantly lower among non-Hispanic Blacks (0.7, CI 0.6-0.7), Hispanics (0.6, CI 0.5-0.7), non-Hispanic Other/Multiracial (0.8, CI 0.7-0.9), those with less than a high school education (0.7, CI 0.7-0.8), current smokers (0.7, CI 0.7-0.8), the obese (0.9, CI 0.8-0.9), those with no health insurance (0.7, CI 0.6-0.8), and those with no personal health care provider (0.7, CI 0.6-0.9). FLU-IM was significantly higher among older adults (age 45-64 = 1.6, CI 1.5-1.8; age 65+ = 4.5, CI 4.1-4.9) and persons with diabetes (1.7, CI 1.6-1.8), heart disease (1.3, CI 1.2-1.4), or a disability (1.2, CI 1.1-1.3).

Conclusion: Only 1 in 2 US adults with arthritis received FLU-IM in 2007. Among people with arthritis, race/ethnic minorities, smokers, obese persons, and those with low education are higher risk groups and should be targeted for FLU-IMM, although the live attenuated nasal spray vaccine is not recommended for people with immunosuppression.

Disclosure: J. M. Hootman, None; **C. G. Helmick**, None.

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What Is the Lifetime Risk of Rheumatoid Arthritis? Cynthia S. Crowson[1], Elena Myasoedova[1], Peter K. Gregersen[2], Terry M. Therneau[1] and Sherine E. Gabriel[1], [1]Mayo Clinic, Rochester, MN, [2]Feinstein Institute for Medical Research, Manhasset, NY

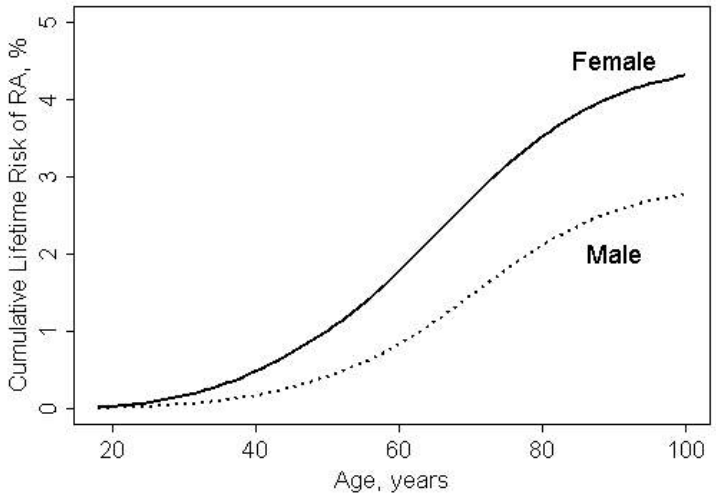
Purpose: Rheumatoid arthritis (RA) is a costly chronic disease. While its incidence and prevalence have been estimated in several populations, there are no available estimates of lifetime risk of RA. To better understand the potential effect of RA disease on the population, we sought to estimate the lifetime risk of developing RA.

Method: Using the incidence rates obtained from our population-based studies of RA from 1955-2005 and mortality rates from life tables for the general population, we estimated age- and sex-specific lifetime risk of RA as the sum of the probability of developing RA each year from ages 18 to 100 years. The yearly probability of developing RA was estimated as the product of the yearly incidence rate of RA and the yearly survival rate. Given the changing RA incidence rates and population mortality rates, lifetime risk was estimated for persons born in a range of calendar years to determine whether lifetime risk is changing over time. The residual lifetime risk for RA was estimated for persons who had no RA at specific baseline ages.

Results: The lifetime risk of RA developing in US adults was 4.3% for females and 2.8% for males. Despite significant changes in the incidence rate of RA over time, as well as the mortality rate over time, the lifetime risk remained remarkably stable over time. The cumulative lifetime risk of RA is higher for females than for males (Figure). The residual lifetime risk for RA was estimated for women without RA at ages 30, 40, 50, 60, 70 and 80 was 4.2%, 3.9%, 3.3%, 2.6%, 1.7% and 0.9%, respectively. Similarly, the residual lifetime risk of RA for men without RA at ages 30, 40, 50, 60, 70 and 80 was 2.7%, 2.6%, 2.4%, 2.0%, 1.4% and 0.7%, respectively. Since some genotypes, such as homozygosity for the shared epitope and/or PTPN22 carry substantially increased risk above the background population rate, it is likely that a significant subset of women in the population have lifetime risks in the range of 10-20%.

Conclusion: The lifetime risk of RA development is significant and is substantially higher in females than in males. Given the increased genetic susceptibility for RA in persons with high-risk genotypes, the lifetime risk may be in the range of 10-20

% for some groups of individuals These findings underscore the need for further investigations to determine whether identification of persons with high genetic risk for RA might justify early detection and intervention to prevent progression to overt clinical disease.



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Comparative Effectiveness Studies of Observational Data: Approaches to Address Confounding. E. Morgan DeWitt[1], Y. Li[1], H. Glick[2], J. Kremer[3], J. R. Curtis[4], G. Reed[5], J. Greenberg[6], K. Anstrom[1], K. Schulman[1] and S. Reed[1], [1]Duke Clinical Research Institute, Durham, NC, [2]Univ of Pennsylvania, Philadelphia, [3]Albany Medical College, Albany, NY, [4]Univ of Alabama at Birmingham, Birmingham, AL, [5]U.Mass Medical, Worcester, MA, [6]NYU, New York, NY

Purpose: Comparative effectiveness studies using observational data confer the benefits of increased sample size, and inclusion of patients treated with therapeutics in clinical practice who would not have qualified for clinical trials, at the cost of potential confounding. To address confounding we can: 1) be more inclusive of subjects and analytically adjust for differences (e.g. disease severity, comorbidities); or 2) restrict the study sample to compare homogeneous groups. We demonstrate the potential impact of such restriction on sample size and patient characteristics in a registry study evaluating comparative effectiveness of TNF antagonists ("Biologics") compared to non-biologic DMARDs.

Method: The study cohort consists of patients enrolled in a US-based registry which collects data at clinic visits. The 'unrestricted' study sample included RA patients who had not previously used a Biologic (naïve) and initiated treatment with a DMARD or Biologic during 2002-2008. To derive homogeneous treatment groups for longitudinal analyses of effectiveness measures, the analysis was further limited to: (1) incident DMARD users; (2) patients making an initial treatment switch from 1st DMARD to 2nd DMARD or 1st DMARD to 1st Biologic (+/- DMARD); (3) patients without contraindications (cancer, CHF); (4) patients with similar demographic and disease-related characteristics as determined by propensity scores and a matching (greedy) algorithm.

Results: The table shows sample size and patient characteristics (mean age, CDAI, swollen joint count (SJC), tender joint count (TJC)) by treatment group for each group. The restricted groups have higher CDAI, joint counts, and similarity.

Analysis group	N		Age (yrs)		CDAI		SJC		TJC	
	DMARD	Biol	DMARD	Biol	DMARD	Biol	DMARD	Biol	DMARD	Biol
Unrestricted, (n=4,766)	N= 2073	N= 2677	59.9	56.6	16.1	18.3	5.8	6.1	4.4	5.5

Incident DMARD users (n=1991)	N= 1991	N/A	59.3	N/A	17.3	N/A	6.4	N/A	4.7	N/A
Switchers, (n=625)	N=243	N=382	58.1	56.2	20.0	21.9	7.6	8.0	5.3	6.4
No contra-indication (n=579)	N=217	N=362	57.7	55.9	19.7	21.8	7.7	8.0	5.2	6.4
PS match, (n=244)	N=122	N=122	56.7	54.9	19.1	19.5	6.9	6.9	5.1	5.6

Conclusion: Comparative effectiveness research is methodologically challenging. Deriving comparable treatment groups through restriction reduced our sample size and patient heterogeneity, arguably the main advantages to using observational data, and resulted in a study sample with more severe disease. Alternatively, analytic adjustment allows inclusion of larger, more heterogeneous study samples, but requires modeling assumptions and may raise issues as to whom the results can be generalized. Both methodological approaches can provide useful information on comparative effectiveness, but their limitations and assumptions should be fully transparent to those who may use this information for decision making.

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Mortality and Cardiovascular Burden in Rural Lupus Patients. C. M. Bartels[1], M. Visekruna[2], S. Nekkanti[2], K. A. Buhr[3], J. Goldberg[2], R. Greenlee[2] and C. L. Bell[1], [1]Univ of WI School of Medicine and Public Health, Madison, WI, [2]Marshfield Clinic, Marshfield, WI, [3]Univ of Wisconsin - Madison, Madison, WI

Purpose: We aimed to assess the actual mortality and cardiovascular disease (CVD) burden among a population-based cohort of rural patients with systemic lupus erythematosus (SLE) with previously described older onset and milder disease activity.

Methods: This retrospective cohort study investigated all incident cases of SLE 1991-2008 in a population-based cohort to examine rates of death and fatal and non-fatal CVD events including MI, stroke, or hospitalization for congestive heart failure. Recent validation indicated capture of >90% visits and 99% of deaths among nearly 80,000 residents. Incident “definite lupus” was defined by the 1997 revised 1982 ACR SLE diagnostic criteria. Comparison used 2,630 age and gender matched controls present in the cohort at date of case SLE diagnosis. CVD event searches used validated protocols with chart verification. Searches included chart audits, electronic record systems, and state death matches. Kaplan-Meier (KM) survival and CVD event-free survival were calculated. Comparison between SLE cases with and without CVD used Wilcoxon and Chi-Square tests.

Results: From 1991-2008, 71 incident SLE cases showed a mean onset age of 52 years and a mean follow-up of 9 years. Severe lupus was rarely encountered including only 2.8% with CNS disease over the period. Matched controls showed comparability between groups including no significant difference in baseline hypertension, hyperlipidemia and diabetes. However, SLE patients were twice as likely as controls (22.5% vs. 10.2%, p>0.0005) to have CVD codes in the 2 years preceding diagnosis. In 614 years of SLE patient follow-up 19 deaths and 17 new CVD events occurred. Five, ten, and fifteen year KM mortality was 12%, 23%, and 37% for SLE subjects vs. 9%, 16% and 23% for controls (HR 2.06, p=0.002). New CVD events occurred in 17 SLE subjects. Among SLE patients, rates of combined CVD events and death were 22%, 30%, and 43% compared to 14%, 23%, and 31% for controls (HR 1.8, p=0.009).event-free survival was 78%, 70%, and 57% at years five, ten, and fifteen respectively. Comparing SLE cases with and without new CVD events, baseline hypertension,

diabetes, and prior CVD were stronger predictors than any lupus features though adjustments for age and gender mitigated risks of prior CVD.

Conclusion: This well defined rural cohort of older onset, mild SLE patients still demonstrated increased mortality and CVD events compared to peers. Despite similar baseline traditional modifiable risk factors, event risk increased with SLE. Compared to baseline in controls, lupus patients also experienced more CVD in the 2 years preceding lupus diagnosis compared to controls. Increased CVD 2 years prior to diagnosis raises questions of delayed SLE diagnosis versus early accelerated CVD.

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Fulfillment of the ACR20 Response Criteria in Patients Receiving Tocilizumab (TCZ) Is Not Influenced by Its Direct Effects On the Acute Phase Response (APR). Daniel Aletaha, Farideh Alasti and Josef S. Smolen, Medical University of Vienna, Vienna, Austria

Background:TCZ is a novel biological agent targeting the interleukin-6-receptor. In addition to its significant effects on clinical and radiographic outcomes of RA, TCZ exerts a direct suppression of the hepatic APR via IL-6 receptors on the hepatocellular membrane. The ACR20 response criteria were the primary endpoint of TCZ clinical trials, and include APR improvement as an optional criterion. It is unclear how the direct effects of TCZ on the APR influence a patient's ability to achieve an ACR20 response.

Purpose: To assess the relevance of APR for the achievement of ACR20 response in patients with active disease despite MTX or other DMARD therapy in clinical trials of TCZ + MTX when compared to the ATTRACT trial on infliximab (INF) + MTX.

Method: We obtained a random 80% of patient level data from 3 TCZ clinical trials on patients with active disease despite MTX or other DMARD therapy (LITHE, OPTION, TOWARD), pooled the 8mg/kg TCZ arms, and evaluated the presence of the ACR20 response at trial endpoints (6 months; n=919). The ACR20 response requires 20% improvement of both tender and swollen joints (SJC, TJC) and improvement of 3 of 5 additional variables: APR (ESR or CRP), patient and evaluator global assessment of disease activity (PGA, EGA), pain, and physical function. Thus all variables other than joint counts are optional as long as 3/5 are fulfilled. We evaluated whether there was a difference in APR representation among the fraction of patients who just fulfilled 3/5 of the optional criteria (patients with 4/5 or 5/5 criteria. would have fulfilled the criteria in any way). We compared these to the results of a similar analysis obtained in an 80% sample of the ATTRACT trial on INF+MTX in established RA (n=211 at 6 months). All analyses were based on completers.

Results: In the TCZ studies and in ATTRACT, the ACR20 response rate at 6 months was ~68% (Table). In only 10.5% and 14.7%, respectively, of ACR20 responders, this response was attained by just fulfilling 3/5 optional criteria. In total, the fraction of patients, in whom the response in APR qualified for the ACR20 response was similar in the TCZ and INF trials, and amounted to 10% and 11%, respectively (Table).

Conclusion: The APR response was crucial for achieving an ACR20 response in only 10% of patients regardless of treatment regimen.

Table. Rates of ACR 20 responses, frequency of fulfilment of additional variables (3/5, 4/5, or 5/5), and frequencies of variables among patients fulfilling only 3/5 additional variables (i.e. variables were crucial for response classification) for patients treated with TCZ (n=919) or INF (n=211).

		Tocilizumab	**INFLIximab**
ACR20 response	***N (%)***	***622 (67.7%)***	***143 (67.8%)***
Number of optional variables	***>3/5 (%)***	*557 (89.5%)*	*122 (85.4%)*
	=3/5 (%)	*65 (10.5%)*	*21 (14.7%)*
Measures improved among patients fulfilling 3 of 5 of the additional variables (% of all ACR20 responders)	**APR**	61 (9.8%)	16 (11.2%)
	HAQ	27 (4.3%)	11 (7.7%)
	PAIN	24 (3.9%)	10 (7.0%)
	PGA	25 (4.0%)	6 (4.2%)
	EGA	58 (9.3%)	20 (14.0%)

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Disclosure: D. Aletaha, Roche Pharmaceuticals, 8, Centocor, Inc., 8 ; **F. Alasti**, None; **J. S. Smolen**, Roche Pharmaceuticals, 8, Centocor, Inc., 8 .

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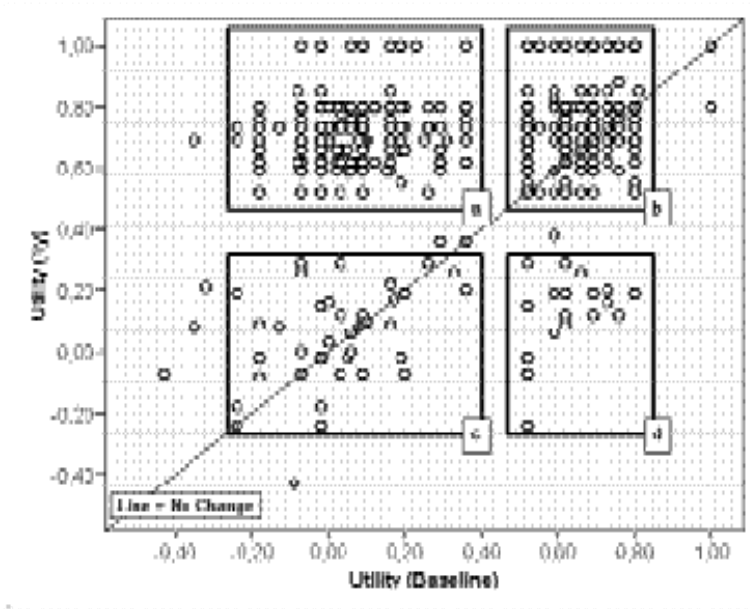
Biologic Therapy and Health-Related Quality of Life: Treatment Effect Heterogeneity in Patients with RA. M. Neovius[1], A. Gülfe II[2], Le Kristensen[2], Jan-Åke Nilsson[3], J. Karlsson[4], P. Geborek[5] and South Swedish Arthritis Treatment Group (SSATG), [1]Karolinska Institutet, Stockholm, Sweden, [2]Lund University, Lund, Sweden, [3]Department of Rheumatology. Malmö University Hospital, Malmo, Sweden, [4]Lund University, [5]Lund University, Department of Clinical Sciences, Lund, Sweden

Purpose: The average treatment effect of biologics on utility is large in RA, but treatment effect heterogeneity across subgroups remains largely unexplored. We aimed to investigate treatment effect heterogeneity across baseline utility in RA patients treated with biologics.

Method: The population-based SSATG register with data from clinical practice was used to conduct an observational study of health-related quality of life, measured by EQ-5D, in RA patients initiating a biologic and continuing treatment for one year (n=633; 56±13y; 74% women). Treatment effect was defined as utility change over one year and investigated across level of baseline utility.

Results: The average treatment effect at one year was 0.26 (95% confidence interval 0.23, 0.29). However, significant treatment effect heterogeneity was observed. For patients with utility in the ranges <0, 0-0.24, 0.25-0.49, 0.50-0.74, and 0.75-1.0 the one-year utility changes were 0.63 (0.58, 0.68), 0.52 (0.48, 0.57), 0.33 (0.26, 0.40), 0.06 (0.04, 0.08), and 0.00 (-0.03, 0.04), respectively. Four distinct patient clusters could be discerned (Figure), with the first (a) consisting of patients with low pre-treatment utility who experienced major improvements. The second (b) and third group (c) with high or low pre-treatment utility changed little on average, while a small fourth group (d) with high utility at baseline deteriorated.

Conclusion: RA patients with the worst quality of life make the greatest utility gains on biologic treatment, strongly influencing the average treatment effect. Although some heterogeneity may be explained by regression to the mean, the large subgroup differences are likely to be important, not least for cost-utility analyses where utility change may be the sole driver in the denominator.



Disclosure: M. Neovius, None; **A. Gülfe**, None; **L. Kristensen**, None; **J. Å. Nilsson**, None; **J. Karlsson**, None; **P. Geborek**, None.

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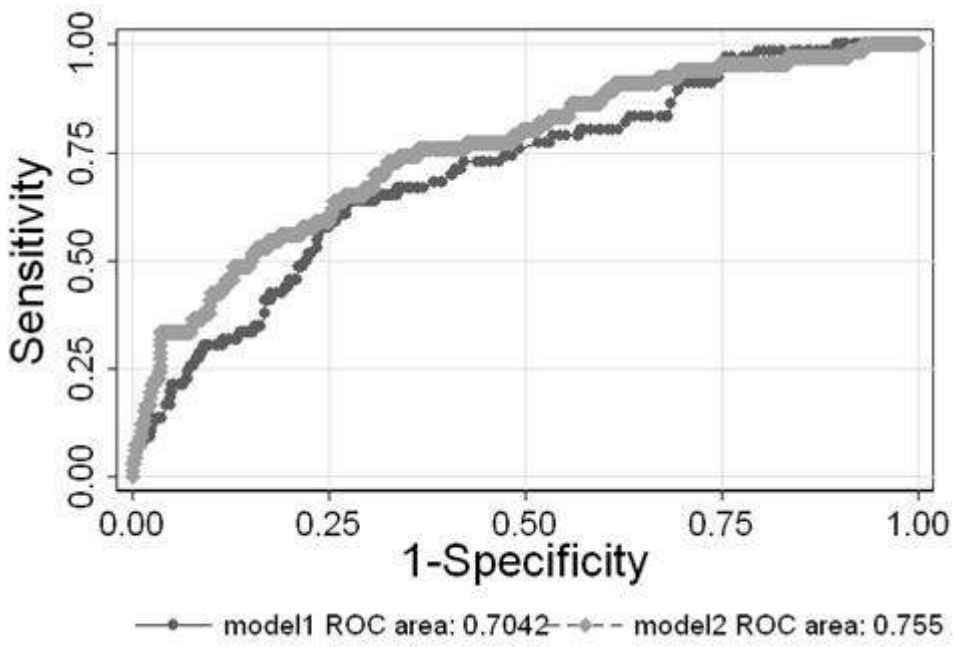
Stratification of the Individual Five-Year Cardiovascular Risk in Patients with Rheumatoid Arthritis. Inmaculada del Rincon[1], Samvel Pogosian[2], Daniel F. Battafarano[3], Daniel H. O'Leary[4], Joseph Polak[5] and Agustin Escalante[2], [1]UTHSCSA, San Antonio, TX, [2]Univ of Texas HSC San Antonio, San Antonio, TX, [3]San Antonio Military Medical Center (SAMMC), San Antonio, TX, [4]Tufts University School of Medicine, Dorchester 02124-5666, MA, [5]Tufts-New England Medical Center, Boston, MA

Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular (CV) disease. Stratification of individual CV risk would enable efficient application of CV prevention guidelines. Our objective was to develop a method to stratify individual CV risk in patients with RA.

Methods: We studied patients with RA who were free of CV disease. We directly assessed the patients for CV risk factors, clinical and laboratory manifestations of RA, and use of anti-rheumatic medications. We imaged the carotid arteries for plaque using high-resolution ultrasound. We followed patients prospectively until they either developed an acute coronary syndromes (ACS), reached the censoring date of December 31, 2004, or were lost to follow-up. ACS were defined as unstable angina, myocardial infarction, cardiac arrest, or death if ischemic heart disease was listed as first cause of death. Using patient characteristics ascertained at baseline as independent variables, we used logistic regression models to develop a predictive model. We used the area under receiver operating characteristic (ROC) curves to quantify the accuracy of the model in predicting ACS.

Results: We studied 599 patients with RA, who were followed for 3,085 person-years of observation, or an average of 5.15 years (range 0.04 to 8.9 years). During this time, 66 first-time ACS occurred, an incidence of 2.1 per 100 person-years (95% CI 1.7, 2.7). A logistic model that included age, sex and the number of CV risk factors (diabetes, hypercholesterolemia, hypertension and smoking), predicted five-year CV risk with a ROC curve area of 0.70 (95% CI 0.64, 0.77) (model1 in Figure). Adding the baseline erythrocyte sedimentation rate (ESR), the cumulative glucocorticoid dose and the presence of carotid plaque, significantly increased accuracy to a ROC curve area of 0.75 (0.69, 0.82), P = 0.03 (model 2 in Figure).

Conclusion: It is possible to predict ACS with reasonable accuracy in RA. Adding the ESR, use of glucocorticoids and carotid ultrasound data significantly increases predictive accuracy.



Disclosure: I. del Rincon, None; **S. Pogosian**, None; **D. F. Battafarano**, None; **D. H. O'Leary**, None; **J. Polak**, None; **A. Escalante**, None.

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Do Patients Hip OA Patients Referred to Orthopedic Surgeons by General Practitioners and Rheumatologists Differ? Maxime Samson[1], Carine Roy[2], Christian Cadet[3], Philippe Ravaud[4] and Jean Francis Maillefert[5], [1]Dijon University Hospital, Dijon, France, [2]AP-HP, Hôpital Bichat, Paris, France, [3]Rheumatology, Paris, France, [4]University of Paris VII, Bichat Hospital, Paris, France, [5]Chu Dijon Hopital General, Dijon

Purpose: There is currently no consensus regarding the indication for total hip arthroplasty (THA) in hip osteoarthritis (OA) patients. In addition, variations in surgical rates have been previously demonstrated. Patients can be referred to orthopedic surgeons either by their general practitioner (GP) or their rheumatologist. The aim of this study was to evaluate whether the views of GPs and rheumatologists regarding the right time to undergo THA differ.

Methods: GPs and rheumatologists were asked to include 1 patient suffering from hip OA and for whom a consultation with a surgeon was planned to determine if THA was indicated. The following variables were collected: age, sex, occupational status, body mass index, comorbidities,duration of hip OA, patient's global assessment, WOMAC pain and function scores, New Zealand (NZ) score, quality of life (SF12), medical treatment of hip OA, and joint space narrowing on radiographs (semi-quantitative 0 to 3 scale). Surgeons' decision was obtained by follow-up questionnaires. Statistical analysis evaluated differences between patients referred by GP and Rheumatologists using univariate then multivariate analysis in which the variable to be explained was the referring physician.

Results: A total of 558 patients were included (377 by GPs and 109 by rheumatologists) and the surgeon's decision was available in 486. GPs and rheumatologists differed in terms of sex (97% versus 74% men; $p<0.0001$) and GPs worked more frequently in a rural area (30.3 versus 0.76%; $p<0.0001$). THA was prescribed in 71.6 % of patients referred by rheumatologists versus 57.6% of patients referred by GP ($p=0.008$). Patients referred by rheumatologists were younger (66.3 versus 69.3 year; $p=0.006$), less frequently retired (72.9 vs 84.2%; $p=0.007$), presented with a more severe NZ score (54.3 versus 48.1; $p=0.0009$), and more structural degradation (severe narrowing in 73.4% versus 52.2 % of patients, $p=0.0004$). The other variables, especially the WOMAC pain and function scores, the comorbidities, and medical

treatments of hip OA did not differ. On multivariate analysis, the only variable related to patients referred by rheumatologists was the NZ score.

Conclusion: Orthopedic surgeons recommended THA more frequently when patients were referred by rheumatologists. Since 1- the patients referred by rheumatologists were younger and less frequently retired, 2- the New Zealand score includes items related to pain, functional impairment, but also to other factors, such as physical examination and ability to work- the difference might be due to differences in pain and functional status captured by the NZ score but not by the WOMAC, or to differences in the handicap, and/or patients' willingness to undergo surgery.

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Assessing HRQoL Burden of Disease and Comparison to the U.S. Population in RA Patients Treated with Golimumab: Results From the GO-FORWARD Trial. G. Hammond[1], A. Raju, S. Parasuraman, J. Buchanan and T. Gathany[2], [1]Lincoln, RI, [2]Johnson and Johnson Pharmaceutical Services, LLC, Malvern, PA

Purpose: Assess the disease burden of RA relative to the U.S. population using SF-36 scale, summary measures. To contrast the percentage of individuals meeting or exceeding the age, gender adjusted population means.

Methods: A prospective, multisite, randomized control study of 444 patients with active rheumatoid arthritis despite methotrexate therapy was assessed at baseline, wk 14, and wk 24. Eligible patients were 18 or older with a confirmed diagnosis of active rheumatoid arthritis (RA) despite MTX therapy. Patients were randomized 3:3:2:2 to receive one of four treatments: 1) MTX plus placebo (tx 1), 2) GLM 100mg plus placebo (tx 2), 3) GLM 50mg plus MTX (tx 3), or 4) GLM 100mg plus MTX (tx 4). Comparisons to population and disease specific norms (heart disease and rheumatoid arthritis norms) in continuous SF-36 scores were made at baseline, wk 14 and wk 24 (not displayed) using multiple *t*-tests. Separate χ^2 tests were used to compare proportions of individuals meeting and exceeding pop norms at wks 14, 24.

Results: At baseline all 8 scale and 2 summary SF-36 measures were significantly lower than age and gender adjusted U.S. and disease specific norms, indicating significant impairment. At wk 14 (Table), scores improved, but remained significantly lower than general population norms. Scores were comparable to the heart disease sample with the exception of PF, RP, and RE. The wk 14 trial sample showed increased PF, GH, MH and PCS impairment relative to the rheumatoid sample. At wk 14, 17.4% (tx 4), 17.1% (tx 2), and 25.6%* (tx 3) of individuals exceeded the population average value for PCS, relative to 10.9% for tx 1. At wk 24, 18.4% (tx 4) 28.3%* (tx 2) 27.4%* (tx 3) and 14.0% (tx 1) exceeded norm values (*χ^2 versus tx 1, $p<.05$).

Conclusion: Significant differences were still observed between trial and general population means, despite marked improvement with treatment. Disease specific populations were comparable. Regarding percentage return to normal functioning, results corroborate existing clinical findings that additional improvements are achieved by using GLM in combination with MTX. 50 mg Golimumab + MTX showed best overall profile of improvement, with a significant proportion of patients exceeding norm values relative to MTX plus placebo.

	GO-FORWARD		**Norms**			**Significance Testing**		
	Baseline (n=442)	**Wk 14 (n=429)**	**U.S. Pop. (n=2031)**	**Heart Disease (n=188)**	**Rheumatoid (n=136)**	**U.S. Pop.**	**Heart Disease**	**Rheumatoid**
Scales	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean Diff. (Comparator-Trial)**		
PF	**32.5**	**36.8**	**48.7**	**40.3**	**42.2**	11.9**	3.5*	5.5**
RP	**34.8**	**40.5**	**49.5**	**43.6**	**43.2**	9.0**	3.1*	2.8
BP	**35.6**	**41.5**	**49.2**	**41.9**	**41.6**	7.7**	0.5	0.1
GH	**37.3**	**39.7**	**49.8**	**39.9**	**42.5**	10.1**	0.2	2.8*

VT	**41.6**	**46.2**	**50.2**	**44.3**	**46.1**	4.0**	-1.9	-0.1
SF	**38.2**	**42.4**	**49.9**	**44.2**	**44.7**	7.5**	1.8	2.3
RE	**39.0**	**42.3**	**50.2**	**45.5**	**45.5**	7.9**	3.2*	3.2
MH	**40.5**	**43.7**	**49.9**	**44.3**	**46.6**	6.2**	0.6	2.9*
PCS	**33.5**	**38.6**	**49.0**	**40.7**	**41.3**	10.4**	2.1	2.7*
MCS	**43.0**	**45.9**	**50.5**	**46.5**	**47.6**	4.6**	0.6	1.7

: $p<.01$, ***:p<.05

Disclosure: G. Hammond, None; **A. Raju**, None; **S. Parasuraman**, JJPS, LLC, 3 ; **J. Buchanan**, JJPS, LLC, 3 ; **T. Gathany**, Johnson & Johnson, 3 .

ACR/ARHP Poster Session B

Genetics, Genomics of Rheumatic Diseases
Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Cytokine Response Profiling Identifies An Immunologic Signature of Myocardial Dysfunction in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Elena Myasoedova, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: Persons with rheumatoid arthritis (RA) have an increased risk of heart failure (HF), which may be partially mediated by inflammatory mechanisms. This study sought to develop immunologic signatures that might be useful to identify patients at risk for left ventricular diastolic dysfunction (LVDD), a pre-clinical stage of HF, and to develop hypotheses about pathogenesis.

Methods: A population-based sample of subjects with RA (1987 ACR criteria) was studied. Data on clinical characteristics (i.e. RA features, cardiovascular risk factors) were collected. LVDD was rigorously assessed by 2D/Doppler echocardiography using a validated algorithm and categorized as none, mild, or moderate-severe LVDD. Fresh PBMC from subjects were stimulated *ex vivo* under eight conditions, including: anti-CD3/anti-CD28 (CD3/CD28); phytohemagglutinin (PHA); bacterial CpG oligonucleotides (CPG); or human heat shock protein 60 (HSP60). The profiles of cytokine release were analyzed using 17-plex immunoassays. Differences in the stimulated cytokine values between the 3 categories of LVDD were tested using mixed effects models, adjusting for assay effects and clinical characteristics.

Results: The study included 267 subjects (mean age: 60.8 ± 13.9 yrs; disease duration: 9.6 ± 6.6 yrs) with low disease activity (mean CRP: 2.7 ± 4.9 mg/L). Of these, 134 subjects (50%) had normal left ventricular function, 53 (20%) had mild LVDD, 25 (9%) had moderate/severe LVDD or HF; 55 (21%) with indeterminate data were excluded. A 13-cytokine signature was developed that discriminated patients with moderate-severe LVDD or HF from the remainder. The signature included decreased responsiveness to CD3/CD28 of Th1 (IFN-g, MIP1b, TNFa) and Th2 (IL-10) subsets; increased responsiveness to PHA of Th2 (IL-4, IL-5, IL-13); decreased responsiveness to CPG (IL-7, IL-8); and increased responsiveness to HSP60 of Th17 or myeloid subsets (IL-17A, G-CSF, GM-CSF). These associations remained significant after adjusting for age, sex, cardiovascular risk factors, known coronary heart disease, rheumatoid factor, anti-CCP, HAQ disability index, and CRP.

Conclusion: In patients with RA, a 13-cytokine signature determined by *ex vivo* cytokine response profiling of PBMC discriminated patients with moderate/severe LVDD or HF. Our data support the hypothesis that a blood-based immunologic signature may be useful to identify patients at risk for adverse disease outcomes such as heart failure. Further, the regulation of the Th17/IL-17 pathway may play an important role in the pathogenesis of myocardial dysfunction in patients with RA.

Disclosure: J. M. Davis, None; **K. L. Knutson**, None; **M. A. Strausbauch**, None; **C. S. Crowson**, None; **E. Myasoedova**, None; **T. M. Therneau**, None; **S. E. Gabriel**, None.

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Anti-Destructive Effects of Trichostatin A (TSA) Are Partly Mediated through Altered Expression of Histone Deacetylase 7 (HDAC7). Hossein Hemmatazad[1], Hanna Maciejewska Rodrigues[1], Lars C. Huber[1], Renate E. Gay[1], Christoph Kolling[2], Beat A. Michel[1], Steffen Gay[1] and Astrid Jüngel[1], [1]Center of Experimental Rheumatology, Zurich Center of Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland

Purpose: Joint destruction in rheumatoid arthritis (RA) is mainly mediated by matrix metalloproteinases (MMPs). There are several reports indicating that histone deacetylase inhibitors (HDACi) modulate the expression of MMPs and therefore block cartilage destruction. In the present study, we investigate the role of specific HDACs with respect to the reported anti-destructive effects of TSA in RA synovial fibroblasts.

Method: Synovial fibroblasts were obtained from RA patients undergoing surgical joint replacement and used at passages 4-6. The constitutive and TNF-α (10ng/ml)/IL-1β (1ng/ml) stimulated expression of HDACs (1-11) together with the expression of MMP1 and MMP3 was measured after incubating the cells with TSA (2μM for 24h) by TaqMan Real-time PCR. Specific gene knockdown of HDAC7 was achieved by siRNA. To assess the expression on protein level, antibodies against MMP1 and MMP3 were used for Western blot.

Results: In unstimulated cells (n=3), the expression of HDAC6, 7 and 9 was reduced significantly after treatment with TSA, while the expression of HDAC3 was increased. Furthermore, in TNF-α/IL-1β-stimulated fibroblasts (n=3), TSA down-regulated the expression of HDAC5, 6, 7, 8 and 9 significantly while the expression of HDAC1, 2, and 3 was up-regulated. Of interest, the most considerable change in the expression of HDACs was observed for HDAC7, which was down-regulated by 86 ± 6 and 87 ± 5% (n=3, $p<0.05$) in both, unstimulated and TNF-α/IL-1β-stimulated cells. In addition, TSA could down-regulate the mRNA expression of MMP1 and MMP3 in TNF-α/IL-1β-stimulated cells (n=6) by 89 ± 9 and 85 ± 7% respectively ($p<0.05$), while the expression in unstimulated cells was unaffected. These results were confirmed on the protein level using Western blot. Most interestingly, after specific gene knockdown of HDAC7 in stimulated RASF (n=8), the mRNA expression of MMP1 and MMP3 was significantly reduced by 48 ± 25 and 48 ± 27% ($p<0.05$).

Conclusion: We conclude that the anti-destructive effect of TSA observed in RASF is at least in part, due to the down-regulation of HDAC7. This observation may present HDAC7 as a novel target to prevent joint destruction in RA.

Disclosure: H. Hemmatazad, None; **H. Maciejewska Rodrigues**, None; **L. C. Huber**, None; **R. E. Gay**, None; **C. Kolling**, None; **B. A. Michel**, None; **S. Gay**, None; **A. Jüngel**, None.

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Diagnosing Autoantibody-Negative Rheumatoid Arthritis in An Early Arthritis Clinic Using Peripheral Blood CD4+ T-Cell Gene Expression Profiling. Arthur G. Pratt[1], Daniel C. Swan[2], Gillian Wilson[3], Catharien MU Hilkens[1], David A. Young[1] and John D. Isaacs[1], [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom, [3]The Freeman Hospital, Newcastle upon Tyne, United Kingdom

Purpose: Seronegative rheumatoid arthritis (RA) is an important but difficult diagnosis to make in the early arthritis clinic. We aim to develop molecular biomarkers that identify the condition amongst early arthritis clinic attendees, enabling more rapid therapeutic intervention for this diagnostically challenging patient group.

Method: Total RNA from highly purified peripheral blood CD4+ T-cells of consecutive early arthritis patients, naive to immunomodulatory therapies, was expeditiously extracted and stored. Transcriptional profiling of 67 samples, retrospectively selected based on subsequent definitive diagnosis, was undertaken using Illumina WG6v3 BeadChip oligonucleotide array technology. 18 RA samples from patients fulfilling ACR classification criteria for the disease, but negative for anti-citrullinated peptide autoantibodies (ACPA), were compared with a "mixed control group" of 49 alternative diagnoses. Groups were matched for sex and acute-phase response (CRP). After data normalisation, batch correction, and filtering of expressed transcripts (n=17,873), a list of differentially expressed genes was derived based on the t-test. Validation and refinement of the gene list was carried out using quantitative real-time PCR (qRT-PCR) low density arrays, and a putative

ACPA-negative RA "gene signature" further cross-validated by using support vector machines (SVM) and constructing receiver operator characteristic (ROC) curves.

Results: Initial analysis yielded a list of 192 transcripts whose expression differed between ACPA-negative RA and controls (>1.2 fold-change; $p<0.05$). A "leave-one-out" cross-validation (SVM) of 67 of these transcripts led to just a (9%) misclassification rate of samples. 137 transcripts were selected for validation using qRT-PCR, and this was achieved for 60 of them (44%). Based on $2^{-(\Delta Ct)}$ normalised expression data for these transcripts, further SVM cross-validation led to a higher misclassification rate (13%), but the discriminatory utility of the combined 60-gene profile remained good (area under ROC curve = 0.85; SEM = 0.05; $p<0.001$). External validation of this putative diagnostic tool is planned in an independent cohort of ACPA-negative early arthritis patients.

Conclusion: A high-throughput transcriptomics approach holds promise as a potential diagnostic tool in early arthritis.

Disclosure: A. G. Pratt, Wyeth Pharmaceuticals, 2 ; **D. C. Swan**, None; **G. Wilson**, None; **C. M. Hilkens**, None; **D. A. Young**, None; **J. D. Isaacs**, None.

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Host B Cell Gene Expression Responses Following Epstein-Barr Virus Exposure Differ Based Upon IRF5 Genetic Risk Haplotype.

Amanda Templeton[1], Brian Poole[2], Nicolas Dominguez[1], Rufei Lu[1], Gabriel S. Vidal[1], Jeremy Levin[3], Andrea L. Sestak[1], Jennifer A. Kelly[1], Kenneth M. Kaufman[4], Gail R. Bruner[1], Patrick M. Gaffney[1], John B. Harley[4], Judith A. James[5] and Joel M. Guthridge[1], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Brigham Young University, Provo, UT, [3]OMRF, [4]OMRF, VA & OUHSC, Oklahoma City, OK, [5]OMRF & OUHSC, Oklahoma City, OK

Purpose: Systemic Lupus Erythematosus (SLE) is a complex, systemic autoimmune disease. Both gene and environment interactions are thought to play a role in SLE development. Epstein-Barr virus (EBV) exposure is one environmental factor that has been shown to influence the development of SLE. EBV binds to cell surface receptors such as CR2/CD21 on B cells and EBV remains latent after infection in B cells. B cells also play key roles in SLE development. Some previously described genetic associations with SLE, such as the interferon regulatory factor 5 gene (*IRF5*), regulate the interferon responses of cells, a pathway previously linked with SLE pathogenesis. In this study, we examined the effect of carrying the *IRF5* lupus risk haplotype upon the host's B cell gene expression response to binding or infection with EBV.

Method: Whole genome microarray expression profile data was collected from peripheral blood B cells from lupus cases and healthy controls selected based upon their *IRF5* risk and protective haplotypes based on genotypes at SNPs rs2004640 and rs10954213. B cells isolated by negative selection using magnetic beads were exposed to EBV for 16 hours after which total cellular RNA was isolated. Whole genome gene expression was performed using Illumina whole genome human gene expression chips. Gene set enrichment analysis (GSEA) was utilized to analyze differential gene expression between SLE patients and controls.

Results: *IRF5* haplotypes appear to differentially regulate genes that are part of three biologically relevant pathways in EBV stimulated B cells: 1.) B cell receptor pathway genes, 2.) Interferon pathway genes and 3.) Toll-receptor pathway genes. The haplotype specific regulation by EBV stimulation was seen in both lupus cases and controls with the respective haplotypes. The main SLE specific differences in gene expression among individuals carrying the IRF5 risk and non-risk haplotype, was in a subset of the interferon response gene signatures. Patients with the *IRF5* risk haplotype have a heightened interferon signature under all experimental conditions; whereas, the patients with the *IRF5* protective haplotype have a B cell interferon signature similar to that of unrelated, matched controls.

Conclusion: Over expression of interferon pathway genes in B cells from individuals carrying the *IRF5* risk haplotype following viral exposure suggests that the *IRF5* risk alleles alone can modulate ones biological response to the environmental insult. Patients carrying either the IRF5 risk or non-risk alleles appear to already be predisposed to having a higher interferon signature even without exposure to virus, suggesting the other genetic factors are also influencing the interferon response, independent of virus.

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Massive Parallel Sequencing (MPS) Provides Full-Repertoire Analysis of the B- and T-Cell Receptors in Humans and Mice. P.L. Klarenbeek[1], Paul P. Tak[2], M.E. Doorenspleet[1], B.D.C. van Schaik[1], F.M. Wensveen[1], L. Gottschal[1], M.E. Jakobs[1], I.A.M. Derks[1], E. Eldering[1], A.H.C. van Kampen[1], F. Baas[1] and N. de Vries[1], [1]Academic Medical Center/Univ. of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: The adaptive immune-system protects the body from invading pathogens. However, these responses have also been implicated in many autoimmune diseases, e.g. rheumatoid arthritis. During adaptive immune responses, activated T- and B-cells can undergo clonal expansion. Both identification of expanded clones and monitoring of clones has proven difficult due to the extremely high diversity of the T- and B-cell receptor (TCR/BCR) repertoires. Current techniques are laborious, lack resolution, are at best semi-quantitative, and are vulnerable to artefacts. Here, we show that an MPS-protocol overcomes current limitations and can be successfully applied for TCR and BCR repertoire analysis, both in humans and mice.

Method: Primersets were developed that cover all functional V and J gene segments of the TCR β-chain (human and murine) and the BCR heavy-chain (human). Unbiased amplification of all receptor mRNA molecules was developed using a multiplex linear amplification. PBMC's from two healthy donors (HD) and splenocytes from 6 mice were analyzed on a Genome Sequencer FLX (Roche) providing >100,000 receptor sequences per run. Bioinformatic tools were developed to identify gene segments and apply corrections for sequencing errors. Quantification was validated using dilution series of Jurkat T-cells in a background of human CD4 T-cells. The technique was validated against the 'golden standard' of cloning and sequencing (C&S) in murine models of influenza infection and ovalbumin immunization using tetramer responding T-cells as read-out.

Results: The technique successfully yielded the sequences of the V and J segments and the complete CDR3 region in all repertoires. The human TCR analysis recovered 13/13 J and 47/49 functional V genes in the HD blood sample. In a murine blood sample 13/13 J and 22/22 V genes were found. The BCR analysis showed 6/6 J and 44/44 V genes in human blood. The Jurkat dilution experiment showed a linear relation between input (Jurkat cells/CD4) and output (Jurkat/CD4) (R^2=0.99 $p<0.0001$). In the influenza and OVA models all clonal expansions found by C&S (153 reads) in individual mice (defined by CDR3 sequence) were also recovered in the MPS-protocol (6825 reads) in approximately the same distributions.

Conclusion: Our new MPS-protocol rapidly provides unbiased quantitative information about complete TCR and BCR repertoires in humans and mice. Clonally expanded cells could easily be identified in a background of resting cells for all repertoires analyzed. This technique for the first time enables in-depth monitoring of TCR and BCR usage in adaptive immune responses. This will help to monitor individual autoimmune responses and may help to develop more selective therapeutic targeting of such responses in autoimmune disease.

Disclosure: P. L. Klarenbeek, None; **P. P. Tak**, None; **M. E. Doorenspleet**, None; **B. D. C. van Schaik**, None; **F. M. Wensveen**, None; **L. Gottschal**, None; **M. E. Jakobs**, None; **I. A. M. Derks**, None; **E. Eldering**, None; **A. H. C. van Kampen**, None; **F. Baas**, None; **N. de Vries**, None.

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Transcriptomic Profiling of the Arthritic Synovial Macrophage. Lucy E. Ballantine[1], Sabina I. Patel[2], J. Alastair Gracie[1] and Iain B. McInnes[1], [1]University of Glasgow, Glasgow, United Kingdom, [2]Discovery Technology Group, Stevenage, United Kingdom

Purpose: In rheumatoid (RA) and psoriatic arthritis (PsA) pannus tissue is characterised by an infiltration of activated monocyte / macrophages that produce pro-inflammatory cytokines including TNFα, responsible in part for the chronic inflammation and joint destruction seen in both diseases. Little is known about the genetic profile of the synovial macrophage in either disease, or indeed how the genetic profile may change as these cells enter the joint. We have used mRNA microarray technology to examine differentially expressed genes in peripheral blood and synovial fluid $CD14^+$ cells in RA and PsA patients.

Method: Matched synovial fluid and blood was obtained from 8 RA and 8 PsA patients and healthy blood was obtained from 8 donors. $CD14^+$ cells were isolated from each sample by magnetic bead positive selection and placed into Trizol. mRNA was extracted from the samples and hybridized to Affymetrix U9133 plus 2.0 chips. Data were normalised using the GC-RMA algorithm and filtered based on a p value ≤ 0.05 and a fold difference of ≥ 4.

Results: Principle component analysis (PCA), identifying correlations between sample conditions was performed on the microarray data. These analyses demonstrated that the genetic profile of both RA and PsA blood monocytes is very similar to those from healthy donors. Furthermore, the transcriptomes of both RA and PsA synovial fluid monocytes were surprisingly similar to each other. Analysis of the

differentially expressed genes between diseased blood and synovial fluid monocytes revealed that 947 genes were identified in both RA and PsA patients, 365 genes were expressed only in RA and 208 genes only in PsA derived cells. Analysing the genes that are differentially expressed in both RA and PsA synovial monocytes demonstrates significant upregulation of a group of genes which are involved in lipid homeostasis and are often reported present in atherosclerotic plaques.

Conclusion: This is the first report of a microarray on samples of matched blood and synovial fluid $CD14^+$ cells from both RA and PsA patients. PCA indicates that blood CD14 cells are similar in RA, PsA and healthy volunteers. Synovial RA and PsA $CD14^+$ cells are markedly different from blood but share striking similarities between diseases. Upregulation of genes involved in lipid metabolism in both RA and PsA synovial macrophages strongly supports the notion of common effector pathways underlying co-morbid risk in RA and PsA.

Disclosure: L. E. Ballantine, None; **S. I. Patel**, GlaxoSmithKline, 3 ; **J. A. Gracie**, None; **I. B. McInnes**, None.

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Genome-Wide Association Analysis of the Effector Phase of Murine Arthritis Corroborated Complement Component C5 and Kinase Pip4k2c Rheumatoid Arthritis Loci and Identified Novel Genes Related to Lymphocyte Activation and Cartilage Remodeling.
Vyacheslav A. Adarichev[1] and Elena Kudryavtseva[2], [1]Albert Einstein College of Med, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY

Purpose: Genome-wide association studies (GWAS) are very effective for discovering rheumatoid arthritis (RA) susceptibility genes. Experimentally-induced arthritis and antibody or lymphocyte responses can be measured in mice in a systematic and comprehensive way and correlated with RA pathology. This study was undertaken to develop genetic association analysis using inbred murine strains and to find genes controlling murine inflammation.

Method: Computations were based on a single gene model, hence, independent statistical test for every polymorphic genome position was performed using linear regression model for genotype-phenotype association. Information about several million SNPs analyzed in more than 70 inbred murine strains was available via the Center for Genome Dynamics. Two-phase GWAS analysis was proposed. First, 100k SNP genome-wide set was used. On a second phase, all available SNPs within the regions that were found positive after the first phase were tested.

Results: To address the efficiency of gene discovery in inbred murine strains, we performed statistical modeling using coat color trait. Tyrosinase encoding gene was identified as a single major genome-wide peak when more than 45 strains were used. Two SNPs within tyrosinase gene were strongly associated with coat color ($-\log P > 15.3$, corresponding genome wide $-\log Q > 9.9$). Signal-to-noise ratio for the major peak was $10^{\wedge 9}$ to 1; locus size was smaller than 1,500 bp. The two-phase GWAS analysis was applied for murine serum-transfer induced arthritis. Analysis successfully confirmed two RA loci previously found near complement component C5 and phosphatidylinositol-phosphate kinase Pip4k2c encoding genes. Both genes showed highly significant association with clinical score of murine arthritis: $-\log P > 9.4$ and $-\log P > 10$, respectively. Novel genetic loci containing serpine2 ($-\log P > 9$), fibrillin Fbn2 ($-\log P > 8$), nuclear factor of activated T cells Nfatc4 ($-\log P > 7$), and Nfkb1 ($-\log P > 7$) were also found to be significantly associated with the effector phase of murine arthritis.

Conclusion: Resolution of gene mapping for most chromosome loci reaches 1,500 bp when more than 45 strains are included into analysis; this genomic resolution corresponds to the locus size that is smaller than a single gene. The novel approach opens an avenue for discovering genes associated with both arthritis and allied conditions in a short period of time avoiding long and expensive genetic linkage studies.

Disclosure: V. A. Adarichev, NIH-NIAMS, 2 ; **E. Kudryavtseva**, None.

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About Half of S100 Cluster Genes On Chromosome 1q21.1 Are up-Regulated in the RA, SLE, Polyarticular Type Juvenile Idiopathic Arthritis (polyJIA), and Systemic-Onset JIA (sJIA).
Hidehiko Sugino[1], Chieko Aoki[2], Hooi-Ming Lee[1], Yasuo Adachi[2], Kenichi Matsubara[3], Takahiro Ochi[4] and Norihiro Nishimoto[2], [1]Osaka University, Osaka, Japan, [2]Wakayama Medical University, Osaka, Japan, [3]DNA Chip Research Inc., Kanagawa, Japan, [4]Osaka Police Hospital, Osaka, Japan

Purpose: Back ground: S100 gene family encodes the EF-hand super-family of calcium binding proteins including at least 14 family members clustered relatively closely on chromosome 1q21.1. Recently, up-regulation of S100 proteins, S100A4, A8/9 and A12, in RA

patients has been reported. Objective: To know the pathological roles of S100 proteins, we investigated the comprehensive gene expression profiling of 17 kinds of S100 proteins using DNA microarray in paptients with active RA, SLE, polyJIA, and sJIA. These 17 kinds of S100 proteins contain the clustered 14 molecules. Moreover, to clarify the molecular functions of S100 proteins in RA, we compared the amino acid sequence of up-regulated S100 proteins.

Method: Total RNA was extracted from the peripheral blood obtained from 114 patients with RA, 12 patients with SLE, 6 patients with polyJIA, 51 patients with sJIA, and 53 healthy individuals, and used to prepare amino allylRNA (aRNA). aRNA was subjected to Cy3 and Cy5 labeling and hybridized with an oligonucleotide-based DNA microarray. The data among patients and healthy individuals were analyzed by parametric statistical group comparison. The amino acid sequences of S100 proteins were aligned by multi-sequence Clustal X analysis. Evolutionary trees were obtained by NJ analysis (1000 bootstrap).

Results: S100A4, A6, A8/9, A11 and A12 are significantly up-regulated in RA and polyJIA compared to healthy controls. S100A6, A8/9, A11 and A12 were also up-regulated in SLE and sJIA. S100A4 was increased in the groups of RA and polyJIA but not in the groups of SLE and sJIA.Except for these six S100 proteins, other eleven S100 proteins remained stationary among the RA, SLE, sJIA, polyJIA and healthy controls. Phylogenetic tree of S100 proteins shows that the S100A8/9 and A12, which have been frequently reported in inflammation, recently branched off from the same origin and average percent similarity is 74.3 %. In contrast, S100A4, A6 and A11 are diversified with each other in the amino acid levels.

Conclusion: We confirmed the up-regulation of S100A4, A8/9 and A12 in RA and newly found the up-regulation of S100A6 and A11 in RA, SLE, polyJIA and sJIA. All the genes are encoded by human chromosome1q21.1. The structural similarities and diversifications among the 6 kinds of S100 proteins, which up-regulated in RA patients, may reflect the different contributions to the etiologies of RA.

Disclosure: H. Sugino, None; **C. Aoki**, None; **H. M. Lee**, None; **Y. Adachi**, None; **K. Matsubara**, None; **T. Ochi**, None; **N. Nishimoto**, None.

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Associations Between Ten Single-Nucleotide Polymorphisms of the Efficacy and Toxicity Rheumatoid Arthritis Patients Treated with Methotrexate. J. Swierkot, R. Slezak and P. Karpinski, Wroclaw, Poland

Purpose: We evaluated the relationship of ten single-nucleotide polymorphisms in genes encoding proteins in folate and transcobalamin pathways to toxicity and efficacy of MTX in patients with RA. MTX remains a cornerstone in the treatment of rheumatoid arthritis (RA). Approximately 10–30% of patients with RA discontinue MTX because of toxicity and 35 -55% because of inefficacy. One possible cause of the differences in the efficacy and adverse drug reactions is genetic variation in how individuals metabolize drugs.

Method: Ten polymorphisms in five cellular pathway genes (RFC 80G>A, GGH 401C>T, MTHFR 1298A>C and 677C>T, TSER*2/*3, TYMS 6 bp deletion, TCII 198M>T, 376L>S, 219I>L and 259P>R) were examined for their effects on MTX efficacy and toxicity in 274 RA caucasian patients who had been treated with MTX (up to 25 mg per week) and folic acid (5-10 mg per week) for at least 6 months or they stop MTX because of adverse events. Adverse events (AEs)(gastrointestinal effects, elevated liver enzymes, pneumonitis, alopecia, infections, hematological AEs and other AEs) were monitored during MTX treatment. Genomic DNA was obtained from the peripheral blood. We use a SNP typing methods based on the RFLP-PCR and ARMS-PCR

Results: The effect of the ten SNPs on MTX-related efficacy and AEs was studied in 274 patients with RA. The SNPs genotypes had no effect on MTX response.

54% of patients described some toxicities during at least one study visit and 21% had AE leading to MTX withdrawal . Overall MTX-related AEs were more frequent in patients with the MTHFR 677T allele (CT and TT genotypes) than in those with the 677CC genotype ($p = 0.03$, OR:1.9) and GGH 401CC genotype than in those with GGH 401 CT and TT genotype ($p=0.05$, OR:3.4).

Furthermore, the 677T allele was associated with aminotransferases elevations among the subgroup of patients with MTX-related liver toxicity ($p = 0.02$; OR: 3.4). Other SNPs did not show significant associations with overall toxicity.

However MTX-related hepatotoxicity and alopecia was more frequent in patients with the RFC80 AA genotype than in those with the RFC 80 GG and RFC 80GA genotype (p=0.01, OR:3.57 and p=0.04, OR: 2.38). In patients with MTHFR 677CC genotype and RFC80GG or AG genotype the possibility of hepatotoxicity was only1% and in the whole group 7,5%. A multivariate model that included the six SNPs showed that three risk genotypes, (GGH 401CC, MTHFR 677TT/CT, RFC80AA) were associated with MTX hepatotoxicity.

Conclusion: There was no relationship between the ten SNPs and the efficacy of MTX treatment. MTHFR 677CC and GGH401 TT and CT polymorphisms were associated with a reduction in MTX related adverse effects.

Composite allele and haplotype analyses may help identify subsets of RA patients with adverse outcomes. Pharmacogenetic studies offer novel approaches to prospectively screen patients for genetic markers for optimal drug selection and minimum toxicity.

Disclosure: J. Swierkot, None; **R. Slezak**, None; **P. Karpinski**, None.

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Hypoxic Conditions Differentially Modulate Normal and Osteoarthritic Human Articular Chondrocyte Proteomes. Vanessa Carreira, Cristina Ruiz-Romero, Jesus Mateos, Valentina Calamia, Berta Cillero-Pastor, Patricia Fernandez-Puente and Francisco Javier Blanco, INIBIC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

Purpose: Osteoarthritis (OA) is a degenerative disease characterized by the degradation of articular cartilage. This tissue is avascular, and it is characterized by the low oxygen tension and poor nutrient availability for its cells, the chondrocytes. Hypoxia conditions have been reported to stimulate chondrogenesis and synthesis of extracellular matrix components. We pursued to analyze, by a proteomic approach, the effect of hypoxia on normal (N) and osteoarthritic cartilage cells.

Method: Chondrocytes were obtained from 6 OA patients undergoing joint replacement, and from 6 cartilages (N) from autopsies without history of joint disease. Cultured cells were subjected to normoxia or hypoxia conditions during 96 hours. Whole cell proteins were then isolated and resolved by two-dimensional gel electrophoresis. Gels were stained with SYPRORuby fluorescent dye, images were acquired using a CCD camera and image analysis was performed using PDQuest software. Proteins of interest were picked from the gels and identified by MALDI-TOF/TOF mass spectrometry. Database search and visualization of biological pathways were performed using PathwayStudio 6 software.

Results: We examined a mean of 500 protein spots that were present in the gels. Both qualitative and quantitative changes of protein patterns between normoxia and hypoxia were studied, considering expression changes within 95% confidence interval ($p<0.05$), and standardized average ratios exceeding 1.5. Table 1 shows the number of proteins that were found to be altered under the analyzed conditions. Twenty-eight protein forms were found to be modulated by hypoxia in normal chondrocytes, and 11 in OA cells when compared to their normoxia controls. The more extended modulation that could be detected in normal cells was mainly due to the alteration in these type of cells of several proteins related with metabolism and production of energy (10 out of the 28 modifications), such as nicotinamide methyl transferase, fructose biphosphate aldolase or ATP synthase. On the other hand, the decrease of Heat shock protein beta-1 and Peroxiredoxin-1 was detected in both N and OA cells. Finally, when comparing OA versus normal chondrocytes under hypoxia, we detected differences in abundance on 43 proteins. In this case, the major difference was observed in a group of 9 proteins involved in the glycolysis pathway, which are significantly decreased in OA. On the other hand, cytoskeleton-related proteins such as vimentin, vinculin or gelsolin were found to be increased in OA cells.

Conclusion: Hypoxic conditions induce diverse modifications in the proteomic profile of normal and OA human articular chondrocytes. Our results highlight the different capacity of normal and OA chondrocytes to react under a hypoxic environment.

	Hypoxia vs Normoxia in N Cells	Hypoxia vs Normoxia in OA Cells	N vs OA Cells under Hypoxia
Nº Proteins increased	8 (Actin, vinculin, pyruvate kinase)	1 (Pyruvate kinase)	10 (Gelsolin, vimentin, cyclophilin)
Nº Proteins decreased	20 (ATP synthase, HSPB1, SOD2)	10 (Tropomyosin)	33 (Annexins, glycolysis proteins)

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MicroRNA Expression Profiles in Normal and Osteoarthritic Human Chondrocytes. Silvia Diaz-Prado[1], Claudia Cicione[2], Emma Muiños[2], Mª Carmen Arufe[1], Isaac Fuentes[1], Francisco Javier de Toro[2] and Francisco Javier Blanco[2], [1]INIBIC - University of A Coruña, A Coruña, Spain, [2]INIBIC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

Purpose: MicroRNAs (miRNAs) are single-stranded and small non-coding RNA molecules of 18-24nt in length that negatively regulate the expression of target genes in a post-transcriptional manner. Recent evidences have also indicated that these small RNA molecules play a role in the pathogenesis of human disorders, exhibiting tissue-specific or developmental stage-specific expression patterns associated with human diseases. A number of human diseases are associated with changes in the copy number or expression of microRNAs, indicating that miRNA expression levels are closely associated with developmental and physiological states as well as disease process. However, at present, little is known if aberrant microRNA expression is associated with osteoarthritis (OA) development.

Objective:Identify and characterize the expression profiles of 723 human miRNAs from normal and OA chondrocytes which could have important diagnostic and therapeutic potential

Method: Human chondrocytes from 4 healthy donors and from 4 OA patients were obtained. After S1 passage, cells were moved to aggregate culture for 1 week. Evaluation of in vitro aggregate culture was carried out using histochemical and immunohistochemical stainings. MiRNAs were isolated with miRVana Isolation kit. MiRNA expression levels were studied using Human miRNA Microarray kit ver.2 (Agilent, Spain). Images were scanned and quantified using Feature Extraction (FE) Software ver.10.1.1 and GeneSpring GX10 (Agilent, Spain). All microarray hibridization experiments and data analysis were performed at the CNIO (Spain).

Results: The microRNA profiling of normal and osteoarthritic chondrocytes revealed a few number of miRNAs differentially expressed in normal and OA chondrocytes. As shown in the table, of the 723 human miRNAs immobilized on the array, only 3 miRNA were up-regulated in OA chondrocytes and 6 miRNA were up-regulated in normal chondrocytes.

miRNA name	Accession number	Fold Change	p value
hsa-miR-483-5p	MI0002467	2,04	$2,35 \times 10^{-4}$
hsa-miR-145	MI0000461	3,79	$1,43 \times 10^{-4}$
hsa-miR-630	MI0003644	-2,76	$1,48 \times 10^{-4}$
hsa-miR-149	MI0000478	-1,76	$2,28 \times 10^{-3}$
hsa-miR-582-3p	MIMAT0004797	-1,94	$3,31 \times 10^{-4}$
hsa-miR-1227	MI0006316	-1,80	$2,54 \times 10^{-5}$
hsa-miR-634	MI0003649	-1,75	$7,66 \times 10^{-4}$

hsa-miR-576-5p	MIMAT0003241	-4,74	$6{,}68 \times 10^{-4}$
hsa-miR-641	MI0003656	-2,36	$1{,}71 \times 10^{-3}$

miRNA differentially expressed in OA versus normal chondrocytes.

Conclusion: We identified 9 miRNAs differentially expressed in OA and in normal chondrocytes, whose expression profiling might provide a useful tool for the pathophysiology research of the chondrocytes. Data indicate that these miRNAs might be used as new diagnostic and prognostic biomarkers.

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Investigating the Role of the Pain Modulating DREAM Pathway Genes in Musculoskeletal Pain. Kate L. Holliday[1], John McBeth[2] and W. Thomson[1], [1]University of Manchester, Manchester, United Kingdom, [2]The University of Manchester, Manchester, United Kingdom

Purpose: A genetic component to the aetiology of musculoskeletal pain has been reported but the genes involved are yet to be identified. One candidate is the transcriptional repressor, *DREAM*. *DREAM* knockout mice exhibit hypoalgesia as a result of increased dynorphin expression and increased κ opioid tone suggesting a key role for DREAM in pain modulation. The aim of this study was to determine if genetic variation in the DREAM pathway genes influences susceptibility to musculoskeletal pain in the population.

Method: Pain data was collected at 3 time-points over 4 years via a postal survey as part of the EPIFUND study. Subjects indicated the presence of any pain on a blank body manikin from which a total pain score which ranged from 0 (no pain) to 29 (pain in all sites of the body) was derived. For each subject the maximum number of pain sites across the 3 time-points was determined. Chronic widespread pain (CWP) was classified at each time-point using ACR criteria. DNA samples were collected from 1189 subjects. Pair-wise tagging SNPs ($r^2 \geq 0.8$) were selected for 3 genes (*DREAM*, prodynorphin (*PDYN*) and the κ opioid receptor (*OPRK1*)) and their 10 kb flanks. SNPs were genotyped using Sequenom MassARRAY technology. Zero-inflated negative binomial regression (ZINB) was used to test for association between SNPs and the number of reported pain sites. ZINB reports the association with the presence of any pain (Odds ratios (OR) and 95% confidence intervals (CI)) and the proportional change in the maximum number of pain sites in subjects reporting pain (Rate Ratios (RR) and 95%CI). Logistic regression was used to test for association between SNPs and CWP (reported as OR (95%CI)) in a nested case-control study. Cases had CWP at ≥2 time-points and controls were pain-free at all three time-points.

Results: Of the 39 SNPs selected, 35 were successfully genotyped in 1062 subjects. One SNP in *DREAM*, 4 SNPs in *PDYN* and 2 SNPs in *OPRK1* were significantly associated with the maximum number of pain sites in subjects reporting pain e.g. rs6136667 in *PDYN* (RR=0.86 (0.77-0.95) p=0.004 for each copy of the minor allele). In the CWP analysis (n=183 cases and n=179 controls), two SNPs in *OPRK1*, rs1365097 and rs6473797, were associated with an increased risk of having CWP e.g. for rs1365097 OR=1.62 (1.17-2.25) p=0.004 for each copy of the minor allele. These two SNPs were also associated with an increased risk of reporting any pain in the population e.g. rs1365097 OR=1.64 (1.16-2.27) p=0.005 for each copy of the minor allele.

Conclusion: This is the first study to examine and observe associations between genetic variation in the DREAM pathway genes and musculoskeletal pain in the general population. SNPs in *OPRK1* were also associated with CWP and the presence of pain but not the extent of pain in the population. Replication of these findings in an independent cohort is now required. If confirmed these findings may lead to identification of new therapeutic targets for pain or may influence response to therapeutics targeting this pathway.

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Investigation of Potential Non-HLA RA Susceptibility Loci in a European Cohort Increases the Evidence for 10 Markers. Darren Plant[1], Francois Cornelis[2], Solbritt Rantapää-Dahlqvist[3], George Goulielmos[4], Merete L. Hetland[5], Lars Klareskog[6], Karim Raza[7], Torsten Witte[8] and Jane Worthington[1], [1]The University of Manchester, Manchester, United Kingdom, [2]Evry University, Paris, France, [3]Norrland University Hospital, Umeå, Sweden, [4]University of Crete, Heraklion, Greece, [5]DANBIO, Copenhagen University Hospital at Hvidovre, Copenhagen, Denmark, [6]Karolinska Institutet, Stockholm, Sweden, [7]University of Birmingham, Birmingham, United Kingdom, [8]Hannover Medical School, Hannover, Germany

Purpose: Genetic factors play a substantial role in determining development of rheumatoid arthritis (RA), and are likely to account for 50-60% of disease susceptibility. In patients of European ancestry, the strongest genetic effects are conferred by the HLA-DRB1 locus on chromosome 6 and protein tyrosine phosphatase 22 (PTPN22) on chromosome 1p13. Recent whole genome and candidate gene disease association studies have identified further RA susceptibility loci (i.e. AFF3, CCL21, CTLA4, CD226, CD40, I2/IL21, IL2RA, IL2RB, KIF5A, PRKCQ, PTPN22, STAT4, TNFAIP3, and TRAF1/C5), defined by single nucleotide polymorphism (SNP) markers, which associate with susceptibility with low-to-moderate risk. The purpose of this study was to investigate recently identified RA susceptibility SNPs using RA cohorts from six European countries, and perform a meta-analysis of these data with all previously published results.

Method: 3,529 patient DNA samples were collected from 6 countries (UK, Germany, France, Greece, Sweden and Denmark). 1,585 control DNA samples were collected from 4 countries (not Sweden or Denmark). Eighteen SNPs were selected for genotyping using Sequenom® MassArray™ technology. Samples with a >85% success rate and only those SNPs with a genotype success rate of >85% were included in the analysis. Scandinavian patient data was pooled and previously published Swedish control data was accessed as a comparison group. Meta-analysis was used to combine results for all cohorts in the current study, and for all cohorts identified in the literature.

Results: 3,423 patients and 1,569 controls were successfully genotyped. 7 SNPs (rs1160542 (*AFF3*), rs1678542 (*KIF5A*), rs2476601 (*PTPN22*), rs3087243 (*CTLA4*), rs4810485 (*CD40*), rs5029937 (6q23) and rs7574865 (*STAT4*) were associated with RA (at the 5% significance threshold) with effect sizes similar to those previously reported. In the meta-analysis incorporating previously published results, all 18 SNPs were associated with RA. Data from the current study increased the significance for association with RA for 10 SNP markers in the meta-analysis and for the first time takes to 12 the number of markers associated with RA at genome-wide significance ($p<5x10^{-7}$).

Conclusion: In a large European RA cohort we provide further evidence to support the association of 18 SNPs with RA, 12 at genome-wide significance.

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Genetic Risk Score Predicting Risk of Rheumatoid Arthritis Phenotypes and Age of Symptom Onset. Lori B. Chibnik, Brendan T. Keenan, Jing Cui, Robert M. Plenge and Elizabeth W. Karlson, Brigham and Women's Hospital, Boston, MA

Purpose: Cumulative genetic profiles can help identify individuals at high-risk for developing RA. We examined the cumulative impact of 22 validated genetic risk alleles on the risk of RA phenotypes characterized by serologic and erosive status.

Method: Blood was obtained from 32,826 women in the Nurses' Health Study (NHS) and 29,611 women in the Nurses' Health Study 2 (NHS2). An additional 33,040 NHS participants provided buccal cell samples. Incident RA and erosive changes were confirmed by medical record review for ACR criteria. We evaluated single nucleotide polymorphisms (SNPs) at 13 validated RA risk loci and 8 Human Leukocyte Antigen (HLA) alleles among 484 Caucasian RA cases and 481 age matched Caucasian controls from NHS and NHS2. We created a weighted genetic risk score for 22 alleles (wGRS). The weight for each risk allele was calculated as the log of the published odds ratio (OR) from GWAS analyses with replication or from a comprehensive meta-analysis. We examined wGRS as 7 ordinal groups based on the distribution in controls. We used logistic regression adjusting for age and pack-years of smoking (packs per day X years smoked) to assess the relationship between wGRS groups and the odds of developing seronegative RA (RF- and CCP-), seropositive RA (RF+ or CCP+), erosive RA and seropositive erosive RA phenotypes. A common control group was used for all phenotypes. Each group was compared to the median group. In separate case only analyses, we assessed the relationships between age of symptom onset and continuous wGRS using linear regression and between age of symptom onset and grouped wGRS using an ANOVA.

Results: In 484 RA cases, 289 (60%) were seropositive, 146 (30%) had erosions and 95 (20%) were seropositive and had erosions at RA diagnosis. The mean age at RA onset was 55.7 ± 10.4. In the top wGRS risk group compared to the median group, we found an OR of 1.3 (95% CI = 0.7 – 2.3) for seronegative RA and an OR of 2.9 (95% CI = 1.8 – 4.6) for seropositive RA. The strongest relationships were in predicting erosive RA, with an OR of 3.6 (95% CI = 1.9 – 6.6) for erosive RA and an OR of 5.7 (95% CI = 2.8 – 12.0) for seropositive erosive RA for the highest wGRS group. No significant relationship was seen between continuous or grouped wGRS and age at symptom onset.

Conclusion: We saw significant associations between a cumulative genetic risk score with 22 alleles and odds of seropositive, erosive and seropositive erosive RA. No associations were seen with age of symptom onset. Further studies are needed to assess the potential of the wGRS in predicting other phenotypes of RA.

wGRS Group	OR (95% CI)			
	Sero- RA	Sero+ RA	Erosive RA	Sero+ Erosive RA
1	1.0 (0.5 – 2.1)	0.5 (0.2 – 1.2)	0.6 (0.2 – 1.8)	0.7 (0.2 – 2.8)
2	0.7 (0.4 – 1.3)	0.7 (0.4 – 1.2)	1.0 (0.5 – 2.0)	0.8 (0.3 – 2.2)
3	1.0 (0.6 – 1.7)	0.7 (0.4 – 1.1)	0.8 (0.4 – 1.6)	0.5 (0.2 – 1.4)
4	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
5	1.1 (0.6 – 1.9)	1.7 (1.0 – 2.8)	1.5 (0.8 – 3.1)	1.5 (0.6 – 3.7)
6	1.7 (0.9 – 3.2)	1.8 (1.0 – 3.2)	2.1 (1.0 – 4.5)	2.7 (1.1 – 6.5)
7	1.3 (0.7 – 2.3)	2.9 (1.8 – 4.6)	3.6 (1.9 – 6.6)	5.7 (2.8 – 12.0)

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Rheumatoid Factor Interferes with Multiplex-Based ELISA in Patients with Rheumatoid Arthritis. Derrick J. Todd[1], Nicholas Knowlton[2], Elizabeth W. Karlson[1], Nancy A. Shadick[3], Michael E. Weinblatt[1], Peter H. Schur[1], Ronenn Roubenoff[4], Elena Izmailova[5], M. Centola[6] and David M. Lee[1], [1]Brigham and Women's Hospital, Boston, MA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Biogen-Idec Pharmaceuticals, Cambridge, MA, [5]Millennium Pharmaceuticals, Cambridge, MA, [6]OK Med Research Foundation, Oklahoma City, OK

Purpose: Heterophilic antibodies such as rheumatoid factor (RF) potentially interfere with immunoassays. Multiplex-based ELISA arrays allow serum to be tested for multiple analytes. Data derived from these arrays are published with increasing frequency in RA research. We sought to answer whether serum RF in patients with RA might interfere with multiplex ELISA arrays.

Method: Serum was obtained from 9 patients with RA. Aliquots of each sample were then RF-depleted (RD) or mock-depleted (MD) by affinity absorption against human IgG-conjugated or unconjugated sepharose, respectively. All absorptions were incubated vol:vol for >4 hr at 4°C. RF levels were measured by nephelometry. Using Searchlight™ multiplex ELISA, RD and MD samples were tested in duplicate for 16 analytes: A-SAA, E-selectin, IFNg, ICAM1, IL1ra, IL2R, IL6, IL7, MMP1, MMP3, MMP9, RANTES, TIMP1, TIMP2, TNFRI, and TNFRII (PerBio/ThermoFisher, Woburn, MA). RF interference (RFI) was defined as >2-fold false elevation of analyte signal in the non-RF-depleted sample (MD:RD >2).

Results: RF ranged from 13-680 IU in MD samples and was undetectable in all RD samples (<10 IU). For 16 analytes tested in 5 patients with RF <100 IU, the mean MD:RD ratio was 1.47, and RFI occurred in 15/80 (19%) tests. In 4 patients with RF >100 IU, the mean MD:RD ratio was 3.61, and RFI was present in 43/64 (67%) tests. RFI for MMP1 (Table 1) was representative of that observed for A-SAA, ICAM1,

IL1ra, IL6, IL7, MMP3, MMP9, TIMP2, TNFR1, and TNFRII. Table 1: MMP1 concentration in mock-depleted (MD) and RF-depleted (RD) samples in 9 patients with RA as measured by Searchlight™ multiplex ELISA. RF levels in MD samples are also shown.

Patient	RF (IU)	MD ± SEM (ng/ml)	RD ± SEM (ng/ml)	MD:RD Ratio
1	13	3.5 ± 0.5	2.3 ± 0.1	1.5
2	19	9.0 ± 1.3	4.8 ± 0.3	1.9
3	28	5.3 ± 0.4	4.1 ± 0.4	1.3
4	76	3.1 ± 0.8	4.0 ± 0.1	0.8
5	76	6.7 ± 0.6	4.2 ± 0.1	1.6
6	139	14.9 ± 2.9	3.4 ± 0.0	4.4
7	178	5.3 ± 1.6	2.9 ± 0.1	1.8
8	353	12.0 ± 3.1	1.2 ± 0.0	10.2
9	680	22.7 ± 7.5	0.9 ± 0.0	24.7

Conclusion: In RA patients, serum RF interferes with a portion of analyte measurements in multiplex-based ELISA arrays. In a separate series of experiments, RFI was also present in samples tested by Ray Biotech protein arrays as well as Luminex assays from BioRad, Millipore, and Invitrogen. Additional studies are needed to determine whether RFI is assay-specific or analyte-specific, and whether blocking agents can dampen interference. These findings are important to consider when interpreting data generated by multiplex arrays in patients with RA.

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Genome Wide Association Study of Genetic Predictors of Quantitative Anti-CCP Level in RA. Jing Cui[1], Anita DeStefano[2], Michael E. Weinblatt[1], Robert M. Plenge[1], Nancy A. Shadick[3] and Elizabeth W. Karlson[1], [1]Brigham and Women's Hospital, Boston, MA, [2]Boston University Schools of Public Health and Medicine, Boston, MA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Purpose: Anti-cyclic citrullinated peptide (anti-CCP) antibody is a marker for progressive erosive rheumatoid arthritis (RA), and a stable quantitative trait. To identify genes that influence quantitative anti-CCP level in RA patients, we carried out a genome wide association study (GWAS) using 909,622 SNPs genotyped in 507 anti-CCP+ RA patients from the Brigham Rheumatoid Arthritis Sequential Study (BRASS).

Method: Anti-CCP was measured using a second generation ELISA assay (Inova Diagnostics, Inc). Samples were genotyped using Affymetrix 6.0 genotyping platform ("900K array"). To ensure high quality data and to minimize false positive results due to technical artifact, filtering criteria were set as: genotype call rate ≥0.95 per SNP and ≥0.95 per individual), minor allele frequency (MAF) ≥0.01, p-value for Hardy-Weinberg equilibrium test ≥0.0001. There were 734,008 SNPs from 491 self-reported Caucasians (81.9% female) that met the criteria. Anti-CCP measures were transformed to a normal distribution by taking the inverse normal of the rank. Association between SNPs and transformed anti-CCP level was tested using general linear model assuming additive model in PLINK. The empirical p value from permutation was utilized to evaluate genome wide significance.

Results: Mean age was 58.7 and disease duration was 16.7 years. Median anti-CCP titer was 119 (range 20-448). We identified 5 SNPs at p value ~10^{-6}, 46 SNPs at p~10^{-5}, and 721 SNPs at p~10^{-4}. The best SNP within the MHC region has association at p ~10^{-4}. Genome wide

permutation testing was pursued to further evaluate the GWAS findings. Under the null, if there is no genetic determinant for anti-CCP level, by chance, we would expect approximately 728 false positive SNPs to be identified at 10^{-4} significance level, however we observed 775. The excess of observed compared to expected results were significant (p=0.04).

Conclusion: We carried out an initial genome wide scan on the quantitative trait anti-CCP level. The top 5 SNPs association with anti-CCP level did not reach genome wide significance, however we plan to validate our findings using two independent CCP+ RA cohorts.

Table. Top 20 SNPs associations with Anti-CCP level

Chromosome	SNP	gene	Beta	P value
7	rs4296976	FLJ42280	0.323	2.6E-06
2	rs2034273	HAAO	0.324	6.4E-06
19	rs6966	PPP1R13L	-0.374	7.9E-06
9	rs4364717	CDKN2B	-0.277	8.2E-06
1	rs1608926	---	-0.767	8.8E-06
17	rs3744741	GEMIN4	0.383	1.2E-05
20	rs6064542	---	-0.763	1.3E-05
14	rs958187	FAM14A	-0.363	1.7E-05
2	rs10170593	HAAO	0.328	1.8E-05
9	rs12555056	FREQ	0.318	1.9E-05
17	rs4793523	---	0.290	2.1E-05
20	rs3787457	SLC23A2	0.304	2.2E-05
18	rs6507907	LAMA3	-0.470	2.3E-05
12	rs12230811	SRGAP1	-0.738	2.4E-05
9	rs10123925	PAX5	-0.325	2.5E-05
14	rs8021596	TXNDC1	-0.353	2.6E-05
6	rs2472867	FARS2	-0.345	2.7E-05
2	rs3771686	BAZ2B	-0.334	2.9E-05
20	rs17001360	CBLN4	-0.430	3.6E-05
8	rs12546054	---	0.525	3.9E-05

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Variation in Rheumatoid Arthritis (RA) Susceptibility Genes Predicts Response to Anti-Tumour Necrosis Factor Treatment in RA Patients. Laura J. Gibbons[1], Rachael Tan[1], Catherine Potter[2], K. L. Hyrich[1], Ann W. Morgan[3], Anthony G. Wilson[4], John D. Isaacs[2], Braggss and A. Barton[1], [1]arc Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Musculoskeletal Research Group, Newcastle University, Newcastle Upon Tyne, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Sheffield Uni /Medical School, Sheffield, United Kingdom

Purpose: Anti-tumour necrosis factor (TNF) therapy has proven highly successful in the treatment of rheumatoid arthritis (RA); however, 30-40% of patients demonstrate little or no response. The use of genetic predictors of response in addition to clinical data may allow individual tailoring of treatment. In other diseases, such as type 2 diabetes, genes associated with susceptibility to disease have also been shown to influence treatment response. Therefore, we aimed to test the hypothesis that genes influencing susceptibility to RA might also demonstrate effects on anti-TNF treatment response.

Method: Twenty single nucleotide polymorphisms (SNPs) mapping to 15 confirmed RA genetic susceptibility loci were genotyped, using Sequenom® iPLEX technology, in 1,092 RA patients receiving treatment with one of the anti-TNF drugs: etanercept, infliximab or adalimumab. Multivariate linear regression analyses were performed under an additive model, using absolute change in 28 joint-count disease activity score (DAS28) between baseline and 6-month follow-up as the outcome variable and adjusting for confounders: baseline DAS28, baseline Health Assessment Questionnaire (HAQ) score, DMARD co-therapy and gender. Samples and SNPs were subjected to a ≥80% genotyping success quality control (QC) measure and *P* values <0.05 were considered statistically significant. Associated markers were genotyped in an additional 338 samples and a combined analysis of 1,430 anti-TNF treated RA subjects was performed.

Results: In the initial cohort (n = 1,012 after QC), significant associations with response to anti-TNF treatment were observed at 3 loci: *CD226*, *AFF3* and *STAT4*. Analysis of the combined cohort (n = 1,334 after QC) revealed statistically significant evidence of association at *CD226* and *AFF3*. The *STAT4* association was driven by the heterozygous genotype, which seems a biologically implausible model of association. The major allele (G) at rs10865035, mapping to *AFF3*, conferred improved response to treatment (additive coef. -0.14 [95% CI -0.25, -0.03] *P* = 0.015). At rs763361 in *CD226*, the minor allele (C) was associated with reduced response to treatment (additive coef. 0.11 [95% CI 0.00, 0.22] *P* = 0.048).

Conclusion: These results implicate the RA susceptibility genes, *CD226* and *AFF3*, as having additional roles in influencing response to anti-TNF treatment, while further investigation of *STAT4* is warranted. *CD226* encodes a type I membrane molecule involved in T- and natural killer cell-mediated immune responses. The AFF3 protein is a member of a family of transcription factors expressed on lymphoid cells.

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Association Between Anti-TNF Treatment Response and Genetic Variants within the TLR and NFκB Signalling Pathways. Catherine Potter[1], Heather J. Cordell[1], Anne Barton[2], Ann K. Daly[1], Kimme Hyrich[2], Derek A. Mann[1], Ann W. Morgan[3], Anthony G. Wilson[4] and John D. Isaacs[1], [1]University of Newcastle, Newcastle, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Sheffield University, Sheffield, United Kingdom

Purpose: To investigate association between response to anti-TNF therapy and genetic variation within genes integral to the toll-like receptor (TLR) and NFκB signalling systems, two cardinal regulators of inflammatory and immune responses, in a large UK-wide cohort of patients with rheumatoid arthritis (RA).

Method: DNA samples from 923 patients receiving anti-TNF therapy (etanercept, infliximab or adalimumab) for the treatment of RA were available from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS). Pairwise-tagging SNPs spanning 24 candidate genes were selected from the HapMap dataset (www.hapmap.org) and genotyped using Sequenom iPLEX™ technology. Multivariate regression analyses were performed to test association between individual SNPs, under an additive model, and treatment response at 6-months follow-up. Treatment response was assessed using both the absolute change in DAS28 and the EULAR response criteria. Separate analyses were also performed to investigate association with individual anti-TNF drugs. P values ≤ 0.05 were considered statistically significant.

Results: A total of 189 SNPs were successfully genotyped and analysed in 909 individuals. These patients had long-standing (mean duration = 14 years), active disease (mean DAS28 = 6.7) with a high degree of disability (mean HAQ score = 2.1). At 6 months follow-up, 20% of patients were non-responders, 53% moderate and 27% good responders according to the EULAR criteria. The mean change in DAS28 was an improvement of 2.5 points. Twelve SNPs spanning 9 genes (*CHUK, IKBKB, IRAK-3, MyD88, NFkB-2, NFKBIB, PTGS2, TLR-2, TLR-10/1/6*) demonstrated association with the absolute change in DAS28 and/or the EULAR response criteria (p≤0.05). In particular, associations to the *MyD88* (rs7744) and *CHUK* (rs11591741) loci were demonstrated under each model applied. These variants map to the

3′UTR and intron 9 of the *MyD88* and *CHUK* genes, respectively. In addition, both SNPs act as tagging markers for additional variants spanning the two genes, signifying a number of potential functional effects. Finally, a greater number of SNPs, including those mapping to *MyD88* and *CHUK*, demonstrated associations specifically in the etanercept subgroup (n=386) compared to the infliximab (n=400) or infliximab/adalimumab combined treatment subgroups (n=523) when analysed separately.

Conclusion: Several SNPs mapping to the TLR and NFκB signalling systems demonstrated association to anti-TNF response as a whole and, in particular with response to etanercept. Validation of these findings in independent datasets is now warranted before additional genetic and functional analyses are performed to identify the true causal variants.

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RA Risk Alleles as Correlates of Response to Anti-TNF Therapy in RA. J. Cui[1], S. Saevarsdottir[2], B. Thompson[3], S. Raychaudhuri[1], P. Gregersen[4], F. Batliwalla[4], N. De Vries[5], MM Herenius[5], Paul P. Tak[6], C.F. Allaart[7], N. Shadick[1], M. E. Weinblatt[1], A. Barton[8], A. Morgan[9], L. Klareskog[2], L. Alfredsson[2], S.L. Bridges Jr.[10], L.A. Criswell[11], L. Padyukov[2], T.W.J. Huizinga[7], R.E.M. Toes[7], E. Karlson[1] and R.M. Plenge[1], [1]Brigham and Women's Hospital, Boston, MA, [2]Karolinska Institute, Stockholm, Sweden, [3]Broad Institute, Cambridge, MA, [4]Feinstein Institute for Med Res, Manhasset, NY, [5]University of Amsterdam, Amsterdam, Netherlands, [6]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [7]Leiden University Medical Center, Leiden, Netherlands, [8]arc Epidemiology Unit, Manchester, United Kingdom, [9]University of Leeds, Leeds, United Kingdom, [10]Univ of Alabama, Birmingham, AL, [11]UCSF, San Francisco, CA

Purpose: Anti-tumor necrosis factor alpha (anti-TNF) therapy is a mainstay of treatment in RA, yet there is no effective biomarker predictor of response. The aims of our study are to identify clinical factors and genetic variants that influence response to anti-TNF therapy.

Method: Through an international collaboration consisting of 9 different RA cohorts, we identified 458 EULAR 'good responders' and 349 EULAR 'non-responders' to etanercept, infliximab, and adalimumab: Autoimmune Biomarkers Collaborative Network, Amsterdam Medical College, BeSt study, Brigham Rheumatoid Arthritis Sequential Study, Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, Epidemiological Investigation of RA, an early RA randomized control trial of etanercept vs MTX, the Karolinska Institute, and the Leiden University Medical Center. EULAR good response was defined as ending Disease Activity Score (DAS)<3.2 and DAS improvement >1.2; EULAR non-response was defined as DAS improvement<0.6 or improvement≤1.2, and ending DAS >5.1. We tested clinical factors such as age, sex, disease duration, RF and CCP positivity, concomitant medications, and start DAS as correlates of treatment response using logistic regression. We genotyped 31 validated SNPs associated with risk of RA, including tag SNPs of *HLA-DRB1* 'shared epitope' alleles. We used univariate and multivariate logistic regression models adjusting for clinical factors and cohort to test for allelic associations with treatment response.

Results: In our univariate analysis of clinical factors, younger age (P<0.0001), male gender (P=0.003), and concurrent MTX (P<0.0001) were associated with EULAR 'good response'. In our univariate analysis of 31 RA risk alleles, two SNPs were associated with anti-TNF treatment response: *PTPRC* gene locus (rs10919563; OR=0.66, P=0.005) and *TNFRSF14* gene locus (rs3890745; OR= 1.32, P=0.01). However, these were not significant after adjusting for multiple hypotheses. The 'shared epitope' tag SNPs were not associated with treatment response. Our findings were unchanged in a multivariable model.

Conclusion: We observed statistically significant associations between response to anti-TNF therapy and three clinical factors (younger age, male gender and concurrent MTX), as observed by others. We found associations between treatment response and two RA risk alleles (*PTPRC* and *TNFRSF14*), although additional genetic studies are required to confirm that associations are true positive results.

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TNFalpha Response of Human Synovial Fibroblast Cells Is Strongly Modified by in Vitro Knock-Down of Clusterin. Geraldine Falgarone[1], Abdellatif Essabbani[2], Nicolas Cagnard[2], Sylvie Mistou[2] and Gilles Chiocchia[3], [1]University paris 13; AP-HP, Avicenne hospital, Bobigny, France, [2]INSERM; CNRS; Paris Descartes University, Paris, France, [3]INSERM; AP-HP; CNRS; Paris Descartes University, Paris, France

Purpose: Clusterin (CLU) has been implicated in tumorogenesis, apoptosis, inflammation and proliferation. We recently reported the regulation of CLU, in rheumatoid arthritis (RA) tissue and fibroblast-like synoviocytes (FLS). We and others have reported that CLU was an inhibitor of NF-kB pathway.

This study was designed to decipher the molecular network linked to CLU expression in FLS and evaluate the consequences of its low expression in condition of TNF alpha stimulation.

Method: FLS were transfected with siRNA for CLU or scrambled nucleotides (control). CLU expression was assayed by Q-RT-PCR and Western blot. These cells were cultured for 24H and 48H with TNF alpha or not. Pan-genomic gene expression was then assayed by DNA micro array. Gene network around CLU and gene interations were analysed with the Ingenuity Pathway Analysis Software ™.

Result: SiCLU transfection in FLS induced a lack of expression of CLU both at the mRNA level and protein level. Down-regulation of CLU resulted in a modification of expression of genes known to be directly linked to CLU and of almost 5% of the tested genes (857 out of 17225); the up-regulation of a small group of gene, among them TIAM1, emphasize the hypothetical role of CLU in the pseudotumoral characteristic of FLS. The comparison of gene expression with or without TNF stimulation allowed the classification of sampled with a good concordance both with and without CLU expression. Moreover differential comparison showed that CLU down regulation in RA led to a profound modification of TNF alpha response as 3 sets of genes emerged: 497 genes were modulated mainly by siCLU transfection in the context of TNF stimulation, 356 genes were modified because of TNF stimulation whatever CLU expression, and 484 genes were modulated in FLS during TNF stimulation with CLU expression. These modifications included changes in IL-8 and Wnt signaling gene expressions.

Conclusion: DNA Chips can assay for RA FLS gene expression after CLU inhibition under the TNF alpha pressure. The results showed that CLU inhibition resulted in the modulation of expression of genes linked in networks which are known to be linked to rheumatoid arthritis. These results argue that CLU down-regulation in FLS participate to the aggressiveness of the FLS and incites further explorations on CLU involvement in RA synovitis physiopathology.

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Interleukin 2 Receptor, Alpha Is Associated with Radiographic Joint Damage in a Japanese RA Population. Taku Suzuki, Katsunori Ikari, Yano Koichiro, So Tsukahara, Kazumasa Nishimoto, Atsuo Taniguchi, Hisashi Yamanaka and Shigeki Momohara, Tokyo Women's Medical University, Tokyo, Japan

Purpose: The Wellcome Trust Case Control Consortium (WTCCC) published genome-wide association study (GWAS) using 1860 rheumatoid arthritis (RA) patients and 2938 controls in a British population. The WTCCC study confirmed the association of SNPs with previously identified loci within the HLA region and PTPN22 gene, and nine more SNPs were found to be associated at the next level (rs6684865, rs11761231, rs11162922, rs3816587, rs743777, rs2837960, rs2104286, rs6920220, rs9550642). Subsequently, they reported 49 SNPs that were associated with RA in the third level, and three of these could be replicated in a validation cohort of 4106 patients and 11238 controls (rs4750316, rs1678542 and rs3218253). The aim of our study is to investigate the impact of these 12 SNPs on radiographic joint damage in Japanese RA patients.

Method: DNA samples of 628 RA patients with the data of Sharp/ van der Heijde score (SHS) of the hands at 5-year disease duration, which represents joint damage, were obtained from the IORRA (Institute of Rheumatology RA cohort) DNA collection. SNP genotyping were performed with TaqMan genotyping assay (Applied Biosystems Japan). Simple linear regression analysis was performed with SHS as a dependent variable, and the number of minor alleles of each SNPs as independent variables. When the result was significant, we also

performed multiple regression analysis on SHS with the SNP and the number of HLA-DRB1 alleles encoding the shared epitope (SE), which was reported to be a strong genetic factor on joint damage. These analyses were performed using the R software package (http://www.r-project.org/).

Results: Though most SNPs showed negative results, rs2104286 on interleukin 2 receptor-alpha (IL2RA) was found to have impact on radiographic joint damage (P=0.046). The multiple regression analysis using rs2104286 and SE also confirmed the result (P=0.042).

Conclusion: IL2RA has an impact on radiographic joint damage in Japanese RA patients.

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Gene Expression Signatures in Synovial Tissue Define Distinct Molecular Subtypes of Rheumatoid Arthritis. Glynn Dennis Jr.[1], Wei Y. Lin[1], Lauri Diehl[1], C. Holweg[1], M. Townsend[1], Judith Endres[2], David A. Fox[3] and Flavius Martin[1], [1]Genentech, Inc, South San Francisco, CA, [2]Univ of Michigan Med Ctr, Ann Arbor, MI, [3]Univ of Michigan, Ann Arbor, MI

Purpose: The study aimed to identify molecular subtypes of rheumatoid arthritis (RA) with linkage to pathological features and therapeutic outcome.

Method: Genome-wide transcriptional profiles for 81 synovial tissue samples obtained by surgery from 50 RA patients were analyzed by bootstrapped hierarchical clustering. Statistical analysis identified differentially expressed genes, over-represented pathways and a gene signature 'proxy' for each molecular subtype. Analysis of tissue histology and immunohistochemistry identified joint pathologies that associated with array-based findings. Gene signatures were tested for association with therapeutic outcome on an independent data set.

Results: Multi-scale bootstrap resampling of 81 samples (10,000 iterations) inferred four molecular subtypes of RA. The largest subtype grouped 34 samples (87% branch support) that shared extensive lymphoid infiltration and follicle-like lymphoid clusters (each $p<0.01$). This signature contained abundant transcripts for immunoglobulins and T cell markers. A second subtype (17 samples, 67% branch support) represented a distinct type of inflammation that was characterized by transcripts involved in respiratory burst and chemotaxis pathways. This signature was inversely associated with joint vascularity ($p<0.05$). Two non-inflammatory subtypes were identified. The first (19 samples, 94% branch support) possessed a signature inversely associated with lymphocyte and CD15+ cell infiltration (each $p<0.01$) and was enriched for wnt-signaling and tumorigenesis pathway genes. The second non-inflammatory subtype (9 samples, 88% branch support), collectively modulated genes involved in cell adhesion and bone remodeling pathways. This gene signature was associated with a higher degree of synovial lining hyperplasia. Finally, this subtype was found to be associated with a poor response to anti-TNF therapy in an independent dataset.

Conclusion: Molecular profiling, bootstrap-resampling and over-representation analysis provided statistical support for four molecular subtypes of RA. Each subtype possessed a unique gene signature that mapped differentially to histology indicators of joint pathology and reflected modulation of distinct signaling networks. One of the molecular subtypes represented patients that responded poorly to anti-TNF therapy, suggesting that RA molecular subtyping has prognostic value for patient response to therapy.

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FCRL3-169CC Is Associated with ACPA Positive RA and with Radiographic Progression. Marthe T. Mæhlen[1], Gry Nordang[2], Silje W. Syversen[1], Désirée M.F.M. van der Heijde[3], T.K. Kvien[1], Till Uhlig[1] and Benedicte A. Lie[2], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands

Purpose: The Fc receptor-like 3 (FCRL3) gene has been reported to be associated with rheumatoid arthritis (RA) in Japanese, Norwegian and Dutch populations with conflicting results in other populations. The CC genotype of a polymorphism in the promoter region -169T>C of FCRL3 showed the strongest association to RA, however associations to Anti-Citrullinated Protein Antibodies (ACPA) and disease severity is unknown. As ACPA positive and ACPA negative RA appear to be two distinct disease entities, with different genetic profile, we aim to investigate the effect of FCRL3 -169T>C on ACPA status and radiographic progression.

Method: 657 patients from two Norwegian cohorts of ACR classified RA patients (Oslo RA registry and the EURIDISS cohort) and 982 Norwegian controls who had previously been genotyped for FCRL3 -169T>C (rs7528684) were included. Presence of ACPA, rheumatoid factor (RF) and shared epitope (SE) were available on all patients. X^2 tests were used to test for associations. The EURIDISS cohort (disease duration <4 years) was followed longitudinally for 10 years with radiographs of hands, assessed at baseline and after 10 years according to van der Heijde modified Sharp score (vdHSS). Patients with average annual progression in vdHSS of hands ≥1.0 units (progressors, n=70) were compared with those <1.0 units (non-progressors, n=47). Logistic regression was used to assess whether the CC genotype predicted radiographic progression.

Results: We found tendency of association with the CC vs. CT/TT genotype for the RA total material (table), and after stratifying for antibody status, the CC genotype was significantly associated with ACPA positive RA and RF positive RA (OR: 1.53; 95% CI 1.12-2.10 p=0.008). No association was found between the FCRL3 polymorphism and the SE. Logistic regression analysis showed that the CC genotype compared to the CT/TT genotype was significantly associated with radiographic progression (OR=3.72; 95% CI 1.17-11.83 p=0.026) in RA patients. This significant association was maintained after adjustment for age, sex and ACPA status (OR 3.91; 95% CI 1.08-14.18 p=0.038).

Conclusion: A promoter polymorphism of FCRL3 was associated to both ACPA and RF positive RA, which supports the proposed association with autoantibody production. In addition we found the FCRL3 -169CC genotype to influence disease severity by conferring increased radiographic progression. This new finding supports that FCRL3 is involved, not only in susceptibility, but also in disease progression.

	CC vs. CT/TT		
	OR	95% CI	P value
RA patients (n=657) vs. Controls (n=982)	1.28	0.99-1.64	0.06
ACPA pos. patients (n=382) vs. Controls	1.57	1.18- 2.10	0.002
ACPA neg. patients (n=247) vs. Controls	0.94	0.64- 1.38	0.76
ACPA pos. patients vs. ACPA neg. patients	1.67	1.10- 2.53	0.02

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Admixture Composition in African-Americans and Its Impact On SLE. Julio Molineros[1], Xana Kim[1], Jennifer A. Kelly[1], Gail R. Bruner[2], Jorge R. Oksenberg[3], Judith A. James[1], GS Gilkeson[4], John B. Harley[5] and Swapan K. Nath[1], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Rsrch, Oklahoma City, OK, [3]School of Medicine, University of California, San Francisco, San Francisco, CA, [4]Medical University of South Carolina, Charleston, SC, [5]Oklahoma Medical Research Foundation, OK

Purpose: Systemic lupus erythematosus (SLE) disproportionately affects individuals with African ancestry with respect to disease prevalence, manifestation, severity and organ damage. It can be hypothesized that genetic factors together with individual ancestry or admixture proportion could explain these disparities. Since recent admixture can create substantial increase of linkage disequilibrium (LD) in

magnitude and range, these individuals can provide a unique opportunity for admixture mapping (AM) for SLE. We compared and contrasted (a) admixture dynamics, (b) risk of developing SLE, (c) ancestry-phenotype correlation, (d) effect of admixture on 3 associated genes, IRF5 (rs2004640), TNPO3 (rs2280714), and ITGAM (rs11436709), and (e) feasibility and power of AM, between a high admixed (AA) and a low admixed "Gullah" (GH) population with African ancestry.

Method: To estimate individual admixture and ancestry proportion we used 114 ancestry informative markers (AIM) on 1558 AA (722 cases, 836 controls),and 303 GH (163 cases, 140 controls). We applied structured association test (SAT) and logistic regression adjusted for individual admixture to account for population stratification. The power of AM was estimated analytically in AA and GH.

Result: Both AA and GH were best explained by admixture of European and African ancestral populations. Mean European ancestry was significantly higher in AA than in Gullah (19.5% vs 8%, P=3x10-31). Case and control ancestry proportion was significantly different only in AA (P=2.5x10-5). We also found that African ancestry was a risk factor for SLE only in AA (OR=3.1; P=5x10-5). While 3 previously reported SLE associated variants were also replicated the association with SLE (P <0.05) in GH (rs2004640 P=0.001; rs2280714 P =0.04 and rs1143679 P=0.003), only 2 were associated in AA (rs2004640 P=0.0003; rs2280714 P=0.61 and rs1143679 P=0.001), these results were unchanged even after admixture correction. Haplotype and conditional regression analysis using rs2004640 and rs2280714 (16kb apart) identified these variants might be independently associated with SLE. Ancestry association identified no AIMs consistently associated with SLE in both AA and GH. For AM, as expected, case-only design is more powerful than case-control design. For examples, to detect genetic association (80% power) of an allele with ancestry relative risk of 2.0, we need 1474 GH samples as opposed to half (705) the samples required in AA with an affected only design, and we need 4 times more samples in a case-control design.

Conclusion: The admixture effect on SLE increased with admixture proportion. SLE risk was greater in AA that GH. Except TNPO3, both ITGAM and IRF5 associations were replicated in AA and GH. AA population is more suited for admixture mapping than GH.

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Novel Modular Analysis of Microarray Data in Adult-Onset Still's Disease. John J. Cush, Virginia Pascual and Florence Allantaz, Baylor Research Institute, Dallas, TX

Purpose: Previous work from our laboratory successfully used microarray analysis to demonstrate the importance of IL-1b in the pathogenesis of Systemic-onset Juvenile Idiopathic Arthritis (SoJIA) and the response to IL-1 blockade at the transcriptional level. A logical corollary to this work was to study blood transcriptional profiles in adults with Still's disease. To this end, we have evaluated the utility and diagnostic accuracy of genomic profiling using microarray technology in patients with manifest fever and systemic features suggestive of adult-onset Still's Disease (AOSD), periodic fever or an autoinflammatory syndrome.

Method: Clinical, laboratory, treatment response data, and biologic specimens on 21 AOSD/periodic fever patients were collected, with longitudinal samples obtained from 10 patients. Disease criteria and activity measures and response to therapy were collected prospectively. Most patients were on prednisone; 10 patients were treated with anakinra, 1 with rilonacept. Whole blood RNA was hybridized to Illumina HT-12 chips and a module-based data mining strategy was used to facilitate biomarker and genomic discovery. Still's patients were compared with 28 healthy adult controls, 12 autoimmune controls, SoJIA patients, and patients with various bacterial and viral infections. Finally, to quantify the overall magnitude of transcriptional changes in individual patients, a molecular distance score was calculated.

Results: Modular analysis showed a significantly increased expression of genes related to cells of the myeloid lineage, including monocytes and neutrophils, inflammation, red blood cells, and coagulation-related genes, reflecting a strong activation of the innate immune response in patients with AOSD. We also observed a consistent downregulation of genes regulating adaptive immunity including genes associated with the function of B cells, T cells, and cytotoxic cells. Finally, a module containing genes involved in immunosuppression was downregulated in those patients. Indeed, all of these findings are similar to those from our genomic studies in SoJIA patients. Dysregulation of these modules rapidly disappeared with anakinra therapy. In fact, for 3 patients treated with anakinra, the modular analysis was able to predict when patients could safely discontinue treatment. This analysis also showed that IFN-regulated genes were induced upon anakinra treatment, again corroborating our findings in the pediatric cohort. Of interest, the molecular score correlated with the severity of systemic disease in

the majority of patients, and approached baseline upon IL-1 blockade. As a final point, analysis of the transcriptional signature in blood from Still's patients can distinguish this disease from other febrile infectious illnesses.

Conclusion: A module-based approach and/or the use of a molecular distance to health score can: 1) differentially diagnose AOSD from other febrile patients; 2) predict responders to IL-1 blockade; and 3) predict when remission has been achieved, heralding the safe discontinuation of biologic therapies,

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Novel Biomarkers for Lupus Nephritis. Mehrnaz Hojjati[1], Tawny Herdegen[2], Jason W. Bauer[3], Joseph C. Wilson[3], P.K. Gregersen[4], Michelle A. Petri[5], Timothy W. Behrens[6] and Emily C. Baechler[3], [1]Univ of Minnesota, Minneapolis, MN, [2]university of Minnesota, Minneapolis, [3]University of Minnesota, Minneapolis, MN, [4]Feinstein Insititute Med Rsch, Manhasset, NY, [5]Johns Hopkins University, Baltimore, MD, [6]Genentech, South San Francisco, CA

Purpose: Kidney involvement is a major clinical problem in systemic lupus erythematosus (SLE) due to its asymptomatic presentation and lack of reliable tests for prediction and monitoring. The discovery of biomarkers for lupus nephritis (LN) may permit identification of patients at risk for LN flare, improve monitoring of LN, and prevent kidney damage. Faced with the lack of reliable markers for renal disease activity, the following study was performed with the goal of identifying candidate biomarkers for renal lupus.

Methods: We studied 73 SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Global SLE disease activity was scored using the SLE Disease Activity Index (SLEDAI) and physician's global assessment (PGA). Renal-specific disease activity was assessed with the Lupus Activity Index renal subscore. Patients were classified into 3 groups: (1) active LN (renal subscore and urine protein dipstick equal or more than 2; n=29), (2) LN in remission (history of LN with biopsy and proteinuria, current renal subscore = 0 and urine protein = 0; n=27), and (3) active non-renal SLE (no history of LN, renal subscore = 0 and urine protein = 0, current SLEDAI equal or more than 6 or PGA equal or more than 1.5; n=17). Serum samples from 30 healthy controls were also included. Serum levels of IL-18, CXCL13, TWEAK and calprotectin were measured by singleplex ELISA, while MMP-7, TNF-a, CXCL10, CCL2, CCL19, IFN-g, IL-1b and IL-10 were measured on a multiplexed ELISA platform (SearchLight, Aushon Inc.). Data were analyzed using non-parametric statistical tests (Mann-Whitney U-test or Spearman's rank correlation).

Results: Serum levels of both MMP-7 and IL-18 were significantly higher in the active LN group as compared to both LN in remission (MMP-7, $p=0.004$; IL-18, $p=0.03$) and active, non-renal SLE (MMP-7, $p<0.0001$; IL-18, $p=0.01$). Neither of these proteins showed a correlation with the extra-renal activity scores, suggesting that these proteins are LN-specific markers. MMP-7, IL-18, and CXCL13 levels were significantly correlated with the renal activity subscore. Levels of CXCL13 and CCL19 were significantly elevated in active LN when compared to LN in remission, while CCL2 and TNF-alpha were increased in active LN vs. active non-renal SLE ($p<0.05$ for all).

Conclusion: . Serum levels of IL-18 and MMP-7, which has not been previously associated with LN, reflect the activity of kidney disease in SLE patients and may be reliable biomarkers for LN.

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Cytokine Response Profiling Identifies Immunologic Signatures of Poor Health Related Quality of Life in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: A significant problem in caring for patients with rheumatoid arthritis (RA) is how to determine whether pain, fatigue, or impaired health-related quality of life (HRQOL) are due to the disease or other factors. Therefore, we sought to discover immunologic signatures of the various domains of HRQOL in patients with RA that could be valuable in evaluating response to therapy.

Methods: Patients with early inflammatory arthritis or RA (1987 ACR criteria) seropositive for rheumatoid factor and/or anti-citrullinated proteins were included. Data on HRQOL were collected, including the Health Assessment Questionnaire (HAQ) disability index and the Medical Outcomes Study short form 36 (SF-36). The HRQOL outcomes were dichotomized according to published thresholds for patient-defined 'acceptable symptom states.' Fresh peripheral blood mononuclear cells (PBMC) from patients were stimulated *ex vivo* under eight conditions, including: anti-CD3/anti-CD28 (CD3/CD28); phytohemagglutinin (PHA); bacterial CpG nucleotides (CPG); human heat shock protein 60 (HSP60. The profiles of cytokine release into culture supernatants were analyzed using multiplex immunoassays with a 17-cytokine panel. Mixed effects models were used to analyze the fold changes in cytokine values between poor vs. good HRQOL groups, adjusting for age, sex, and assay effects.

Results: The study included 57 patients (mean disease duration 9.4 ± 10.1 mo), of whom 51 (89%) fulfilled RA criteria. The group had moderate levels of disease activity (mean DAS28: 4.4 ± 1.2), disability (mean HAQ: 0.8 ± 0.8) and pain (mean VAS: 41.9 ± 28.3). Analyses revealed a 12-cytokine profile that discriminated the groups. A signature was identified for high bodily pain (SF-36 bodily pain <35) and high disability (HAQ>1) that was characterized by increased responses to PHA (IFN-g, IL-4, IL-5, IL-13) but decreased responses to CPG (IL-1b, IL-6) and HSP60 (IL-17A, G-CSF, GM-CSF). Poor general health (SF-36 global health <47) was discriminated by reduced HSP60 responses (IL-17A, GM-CSF) but not by PHA or CPG responses. In contrast, poor vitality (SF-36 vitality <40) was correlated with increased responses to CD3/CD28 (IL-8, IL-10, TNF-a) and increased HSP60-induced IL-17A.

Conclusion: Cytokine response profiling of PBMC revealed an immunologic signature of pain and disability in patients with early active RA, involving significantly increased responsiveness of Th1 and Th2 subsets to PHA and significantly decreased responsiveness of myeloid lineages to CPG and of Th17 cells to HSP60. Our findings suggest that cytokine response profiling could be useful to discriminate disease-associated impairments of HRQOL and monitor response to therapy.

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Investigation of Coeliac Disease Variants Identifies a Novel Rheumatoid Arthritis Susceptibility Locus. S. Eyre[1], UK RA Genetics (UKRAG) Consortium[2], W. Thomson[3], Jane Worthington[1] and Anne Barton[4], [1]The University of Manchester, Manchester, United Kingdom, [2]Manchester, United Kingdom, [3]arc Epidemiology Unit, Manchester, United Kingdom, [4]University of Manchester, Manchester, United Kingdom

Purpose: Genome wide association studies, replicated by numerous well powered validation studies, have revealed a large number of loci likely to play a role in susceptibility to many multifactorial diseases. It is now well established that some of these loci are shared between diseases with similar aetiology. For example, a number of autoimmune diseases have been associated with variants in the *PTPN22, TNFAIP3* and *CTLA4* genes. Here we have targeted variants associated with coeliac disease (CD) in order to identify novel RA susceptibility loci.

Method: We selected 10 SNPs previously identified as being associated with CD for investigation in a sample of 3,962 RA patients and 3,531 controls. Genotyping was performed using the Sequenom platform and genotype frequencies compared between cases and controls under an additive model, implemented using PLINK software.

Results: We found novel evidence for association of the *TAGAP* locus with RA (Table). Interestingly, the opposite allele is associated with RA susceptibility compared with CD. Studies in type 1 diabetes have also shown association of this locus with susceptibility with the same allele as we have found in RA.

SNP	Locus	Genotype: n (%) Cases	Controls	Trend P	Allelic OR (95%CI)
rs182429	*TAGAP*	600 (17.0)	590 (20.5)	0.0005	0.88 (0.82-0.95)
		1770 (50.2)	1421 (49.3)		
		1159 (32.8)	870 (30.2)		

Table: Genotype comparison for SNP rs182429.

OR = odds ratio; CI = confidence intervals

Conclusion: Exploring the genetic overlap between related diseases may reveal key common pathways that could suggest therapeutic targets applicable to more than one disease. With regards to CD and RA, there is strong evidence that variation within the *CTLA-4* and *IL2_21* genes are associated with both autoimmune diseases. In addition, we present evidence for association of RA with a variant in the *TAGAP* gene, which has not been reported previously.

Disclosure: S. Eyre, None; **W. Thomson**, None; **J. Worthington**, None; **A. Barton**, None.

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Polymorphism in NOD1 Causes Aggravated Bone Destruction in Patients with Rheumatoid Arthritis. Theo S. Plantinga[1], Mihai G. Netea[1], Jaap Fransen[1], Jochen Zwerina[2], Piet L. Van Riel[1], Georg Schett[3], Wim B. van den Berg[1] and Leo A. Joosten[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: One of the central disease hallmarks of rheumatoid arthritis (RA) is the onset and progression of cartilage and bone destruction in the joints, which is deleterious for joint motility and results in severe movement disabilities in affected patients. The mechanism underlying this disease process is largely unknown. NOD1, an intracellular pattern recognition receptor expressed by the innate immune system, is involved in microbial recognition. *NOD1* knockout mice developed aggravated joint pathology compared to wild type mice in an arthritis mouse model. Furthermore, the common *NOD1 +32656* insertion/deletion polymorphism in humans has been demonstrated to have clear functional consequences regarding cytokine responses. The aim of this study was to decipher to role of the +32656 *NOD1* in/del polymorphism in RA susceptibility and severity.

Method: RA patients (N=450) and healthy controls (N=431) were genotyped for the *NOD1* +32656 in/del polymorphism. Clinical parameters of disease severity (i.e. inflammation and bone destruction) were correlated with the *NOD1* +32656 genotype. Cytokine production capacity was measured in PBMCs and osteoclasts obtained from individuals with different *NOD1* +32656 genotypes. Furthermore, mRNA profiling of osteoclasts with different *NOD1* +32656 genotypes was performed.

Results: Genetic analysis of the *NOD1* +32656 polymorphism revealed a significant higher number of individuals homozygous for the insertion allele. Furthermore, the insertion allele was demonstrated to be highly correlated with increased bone destruction. Cytokine production capacity of PBMC's and osteoclasts was strongly elevated in cells heterozygous and homozygous for the insertion allele. Gene expression profiling of osteoclasts with different *NOD1* +32656 genotypes demonstrated a increased expression of cathepsin K in osteoclast bearing one or two copies of the *NOD1* +32656 insertion allele.

Conclusion: In the present study we demonstrate for the first time that the *NOD1* +32656 in/del polymorphism is associated with increased bone destruction in RA patients. Functional analysis revealed an increased production of pro-inflammatory cytokines in both PBMCs and osteoclasts from individuals bearing the *NOD1* +32656 insertion allele. Furthermore, osteoclast bone resorption activity was elevated reflected by increased expression of the lysosomal protease cathepsin K. These findings demonstrate the crucial role of NOD1 in RA joint pathology.

Disclosure: T. S. Plantinga, None; **M. G. Netea**, None; **J. Fransen**, None; **J. Zwerina**, None; **P. L. Van Riel**, None; **G. Schett**, None; **W. B. van den Berg**, None; **L. A. Joosten**, None.

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Investigation of Rheumatoid Arthritis Susceptibility Genes in Psoriatic Arthritis. Pauline Ho[1], I. N. Bruce[2] and A. Barton[3], [1]Manchester Royal Infirmary, Manchester, United Kingdom, [2]arc Epidemiology Unit, The University of Manchester, Manchester, [3]arc Epidemiology Unit, Manchester, United Kingdom

Purpose: Genome-wide association studies have identified a number of susceptibility variants for rheumatoid arthritis (RA), some of which show overlap with susceptibility to other arthritic disorders, such as juvenile idiopathic arthritis. Psoriatic arthritis (PsA) shares with RA the fact that both are characterised by TNF-mediated inflammation usually manifesting as synovitis in peripheral joints and both respond to similar therapies including methotrexate and anti-TNF biologic drugs. The aim of the current study was to explore whether they share genetic susceptibility factors by testing for association of RA genetic loci with PsA.

Method: 20 single nucleotide polymorphism (SNP) markers mapping to 14 RA susceptibility loci were tested in patients with PsA. After imposing strict quality control thresholds, genotype frequencies were compared with publicly available data for 2,024 controls using the trend test, implemented in STATA. A p-value of 0.05 was regarded as significant.

Results: 450 PsA samples passed quality control and were available for analysis. SNPs mapping to the *AFF3* and *IL7R* genes were associated with PsA susceptibility (Table).

SNP	Locus	Genotype: n (%)		Trend P	Allelic OR (95%CI)
		Cases	Controls		
rs1160542	*AFF3*	111 (27.7)	574 (19.4)	0.01	1.19 (1.04-1.37)
		217 (48.3)	1493 (50.3)		
		121 (27.0)	900 (30.3)		0.79 (0.67-0.92)
rs6897932	*IL7R*	25 (5.6)	267 (7.6)	0.003	
		166 (37.0)	1482 (42.3)		
		257 (50.1)	1756 (50.1)		

Table: Genotype comparison for SNPs rs1160542 and rs6897932.

OR = odds ratio; CI = confidence intervals

Conclusion: We have previously reported that there was no association of the major RA susceptibility loci, *HLA DRB1* and *PTPN22* with PsA. Here, we show that two other RA loci are associated with PsA suggesting that some of the genetic predisposition will be shared whilst other loci may determine the pattern / severity of arthritis that develops.

Disclosure: P. Ho, None; **I. N. Bruce**, None; **A. Barton**, None.

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Vitamin D Binding Protein Identified in Synovial Proteome Associated with Disease Extension in JIA Patients. David S. Gibson[1], Laura Pascoli[1], Catherine McAllister[2], Caitriona Scaife[3], Michael J. Dunn[3], Stephen R. Pennington[3] and Madeleine E. Rooney[4], [1]Queen's University Belfast, Belfast, United Kingdom, [2]Belfast Health and Social Care Trust, Belfast, United Kingdom, [3]Proteome Research Centre, Conway Institute of Biomolecular and Biomedical Research, Dublin, Ireland, [4]Queen's University Belfast, Belfast, Northern Ireland

Purpose: Juvenile idiopathic arthritis (JIA) comprises a poorly understood group of chronic, childhood onset, autoimmune diseases with variable clinical presentations, outcomes and therapeutic responses. In a prior study, the synovial fluid (SF) proteome of an oligoarticular patient subgroup was compared to patients who show a spread of disease in the first year to involve new joints, the extended oligoarticular subgroup. Current laboratory tests are unable to flag those patients at a higher risk of disease spread to multiple joints, who could benefit form earlier therapy to prevent joint damage.

Method: This study was focused on profiling the SF proteome associated with disease extension from oligo- to polyarticular status by a difference gel electrophoresis (DIGE) approach. To construct a discriminant model, SF samples from 60 JIA patients were analysed: 30 oligo-, 8 extended oligo- and 17 polyarticular disease. Initial SF samples from each patient were labeled with Cy dyes and subjected to protein separation by 2-DE. The abiltiy to distinguish patients at risk of disease extension by a select group of proteins was illustrated by multivariate analysis methods. Protein spots of interest which over expressed beyond a two fold threshold between patient subgroups were identified by MALDI-TOF. Specific antibodies were used to validate putative biomarker expression in synovial fluid by western immunoblotting and in synovial membrane (SM) by immunohistochemistry.

Results: Samespots software analysis of SF gel scans was used to highlight joint-specific proteins which were differentially expressed across disease classifications. Hierarchical clustering based on the expression levels of a previously selected set of 40 proteins matched across the three clinical subgroups segregates the extended oligoarticular patients. Proteolytic fragments of apolipoprotein AII, complement component C3c, and vitamin D binding protein were identified ($p<0.05$) amongst the discriminatory proteins. Apolipoprotein AII and vitamin D binding protein were expressed at significantly higher levels in the polyarticular patients, $p=0.046$ and $p=0.019$ respectively, both with a perivascular distribution in the SM.

Conclusion: Synovial fluid proteome profiles have been used to flag JIA patients at risk of disease spread. The panel of identified proteins may play a role in spread of joint inflammation. With further validation, these putative prognostic biomarkers could improve the clinical management of patients.

Disclosure: D. S. Gibson, None; **L. Pascoli**, None; **C. McAllister**, None; **C. Scaife**, None; **M. J. Dunn**, None; **S. R. Pennington**, None; **M. E. Rooney**, None.

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Gene Microarray Profiling of Bone Marrow Mesenchymal Stem Cells From Osteoarthritis Patients Reveals a Diminished Expression of Collagen Genes. Benjamin Fernandez-Gutierrez[1], L. Rodriguez-Rodriguez[2], A. González-Vigo[3], Roberto Alvarez-Lafuente[4], P. Lopez-Romero[5], E. Urcelay[6] and José Ramón Lamas[2], [1]Hospital Clinico San Carlos, Madrid, Spain, [2]Hospital Clínico San Carlos, Madrid, Spain, [3]Immunology Service, Hospital Clinico San Carlos, Madrid, Spain, [4]PhD, Madrid, Spain, [5]CNIC, Madrid, Spain, [6]Immunology Service, Hospital Clínico San Carlos, Madrid, Spain

Purpose: To gain insight in the underlying mechanisms governing the multilineage differentiation and regenerative potential of Bone Marrow Mesenchymal Stem Cells (BM-MSCs) in osteoarthritis (OA).

Methods: Eight OA patients and eight controls were included. Hip OA was defined by ACR criteria. Control group is composed by patients with hip fracture without signs of OA nor osteoporosis (DEXA T score > -2.5).

At the time of surgery BM was obtained and MSCs were isolated and expanded. RNAs were extracted to perform a large-scale comparative gene expression profiling using the Agilent Whole Human Genome Microarray Kit 4 X 44K. Once array data were filtered and normalized, differentially expressed genes at $p<0.05$ level of significance with at least two-fold differences were eligible. These genes were classified according to their Biological Process Gene Ontology using the *Genecodis2* web-based tool. GSEA Molecular Signature Database was used in order to study specific groups of genes. Quantitative-PCR in 11 OA and 10 controls was used to validate array results. SNPs rs495551, rs1931897 and rs11965969 of the *COL10A1* gene were studied in 191 OA patients and 283 controls by Fast Real-Time PCR System.

Results: BM-MSCs from OA patients showed 533 differentially expressed genes, 293 (54.9%) downregulated and 240 (45%) upregulated. Although in unsupervised mode gene ontology clustering did not show a bias to a clearly defined biological process, supervised mode revealed that type IV, VIII, XI and, in particular, type X collagen genes were downregulated in OA. A GSEA analysis of a specific gene set including all collagens showed a significant difference between OA and control groups specially significant in the case of collagen X. Downregulation of mRNA production in OA patients was confirmed by q-PCR in additional samples.

In order to address the contribution of genetics factors in these findings, we analyzed three SNPs related to *COL10A1* gene and we can observe that rs11965969 (T/G) SNP was differentially represented with GG genotype overrepresented in OA patients p=0,013 OR=1,68 (1,09-2,59).

Conclusion: Our findings provide a reference data set of collagen genes altered in BM-MSCs from OA patients and, importantly, indicate that expression of type X collagen, a marker of hyperthrophic chondrocytes, is altered in OA patients. A genetic polymorphism in *COL10A1* gene is also showed in OA patients. We could hypothesized that hyperthropic chondrocytes located at bone-cartilage interface are altered in OA patients promoting an adult modified subchondral bone responsible for OA developing.

Disclosure: B. Fernandez-Gutierrez, None; **L. Rodriguez-Rodriguez**, None; **A. González-Vigo**, None; **R. Alvarez-Lafuente**, None; **P. Lopez-Romero**, None; **E. Urcelay**, None; **J. R. Lamas**, None.

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Polymorphisms of COTL1 Gene Identified by Proteomic Approach and Their Association with Autoimmune Disorders. Seung cheol Shim[1], Mi-Kyoung Lim[1], Dong-Hyuk Sheen[2], Eun-Heui Jin[3] and Hun-Tag Chung[4], [1]Eulji University Hospital, Daejeon, South Korea, [2]Euli University Hospital, Daejeon, South Korea, [3]Wonkwang University, Iksan, South Korea, [4]Ulsan University, Ulsan, South Korea

Purpose: For rheumatoid arthritis (RA), historically sound epidemiologic data demonstrated the genetic contribution to susceptibility to RA. The automated genotyping technologies that enable the systematic ascertainment of sequence variants in the form of single-nucleotide polymorphisms (SNPs). To identify candidate genes, first, we investigated the protein expressions differentially expressed between RA and healthy controls. After the selection of candidate genes through highly up-regulated or down-regulated proteins, we investigated the association of genetic polymorphisms of target genes with the susceptibility to RA.

Method: We conducted comparative analyses of protein expressions between RA patients and healthy controls using two-dimensional electrophoresis (2-DE) and matrix-assisted laser desorption ionization mass spectrometry (MALDI-TOF-MS). Blood samples and records were obtained from 568 controls (213 females, 355 males), 455 RA patients (371 females, 84 males), and 196 systemic lupus erythematosus (SLE) patients (184 females, 12 males). We performed a case-control study to determine whether the COTL1 gene polymorphisms were associated with the susceptibility to RA or SLE.

Results: We identified 17 proteins up- or down-regulated in RA patients compared to healthy controls. Among them, coactosin-like 1 (COTL1) was highly expressed in

RA patients compared with healthy controls.The COTL1 is a binding partner of 5-lipoxygenase, which is involved in leukotriene biosynthesis in the leukocytes. The genotype frequency of c.-1124G>T and the allelic frequency of c.484G>A in RA patients, and the genotype frequency of c.484G>A in SLE patients were significantly different from healthy controls ($P = 0.009$, 0.027, and 0.025, respectively). We also investigated the association of COLT1 polymorphisms with the levels of rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody in RA patients, or anti-nuclear antibodies (ANA) in SLE patients. The c.484G>A polymorphism in RA patients showed a significant association with the levels of anti-CCP antibody ($P = 0.03$).

Conclusion: Our findings demonstrated that the genetic variances of the COTL1 gene might be associated with the susceptibility to RA and SLE and the development of autoantibodies.

Disclosure: S. C. Shim, None; **M. K. Lim**, None; **D. H. Sheen**, None; **E. H. Jin**, None; **H. T. Chung**, None.

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Cia5a Regulates the Synovial Expression of Pro-Inflammatory Cytokines, Proteases and Nuclear Receptors. Max Brenner and Percio S. Gulko, Feinstein Institute for Medical Research, Manhasset, NY

Purpose: Little is known about the genes that regulate disease severity and joint damage in rheumatoid arthritis (RA). Cia5a is a locus on rat chromosome 10 that regulates disease severity and joint damage in pristane and collagen-induced arthritis (PIA and CIA). The specific Cia5a gene has not yet been identified. We hypothesized that cellular processes regulated by the Cia5a gene can be identified using microarray-based gene expression analyses of synovial tissues from DA rats (severe disease) and DA.F344(Cia5a) congenics (mild disease with no erosive changes). These studies could facilitate the identification of the Cia5a gene, and also point to novel pathways involved in the regulation of arthritis severity and joint damage.

Method: Synovial tissues were collected 21 days post-PIA induction from DA and DA.F344(Cia5a) congenics. RNA was treated with DNase, quantified and assessed for purity and integrity, and used for cRNA transcription and labeling. Samples were hybridized to the Illumina RatRef-12 BeadChips (22,523 probes covering 21,922 rat genes) and scanned on a BeadArray reader. Fluorescence intensity was extracted and normalized with the cubic spline algorithm using BeadStudio 2.0 (Illumina). Genes with a difference in intensity between DA and DA.F344(Cia5a) of ≥1.5 fold and p-value ≤ 0.001 (t-test) were considered significantly different and used for pathway detection analyses using IPA 5.5.1 (Ingenuity) and NCBI databases.

Results: Tissues from DA.F344(Cia5a) (n=8) congenics and DA (n=6) rats were analyzed. 8,046 genes were expressed by all synovial samples. 836 genes were significantly up-regulated in DA synovial tissues including cytokines (IL-18, LTB), cytokine receptors (IFNGR1, IFNGR2, IL-17RA), innate immune responses mediators (TLR2, FCER1G, FCGR3A, NCF1, NCF2), proliferation and survival genes (APAF1, BAK, CASP3, CDC2), and proteases implicated in articular damage (MMP-3, MMP-14, MMP-19). 980 genes were up-regulated in synovial samples from DA.F344(Cia5a) congenics, including anti-inflammatory nuclear receptors (PPARG, LXRA, LXRG, RXRG, RORA), genes related to metabolic homeostatic processes such as amino acid synthesis and lipid metabolism. 21 of the differentially expressed genes mapped to the *Cia5a* interval.

Conclusion: The presence of F344 alleles at *Cia5a* was enough to significantly reduce the inflammatory and proliferative gene expression signatures observed in DA, and to increase the expression of anti-inflammatory nuclear receptors. These observations suggest a potential role for the Cia5a gene in maintaining synovial homeostasis and limiting the synovial inflammatory response that contributes to articular damage.

Disclosure: M. Brenner, None; **P. S. Gulko**, None.

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N-Acetyltransferase 2 Slow Acetylator Genotype Associated with Sulfasalazine Hypersensitivity in Korean Patients with Adult Onset Still's Disease. Yeon-Ah Lee[1], Sang-Hoon Lee[1], Chang-Hee Suh[2], Hyoun-Ah Kim[2], Sung Soo Kim[3], Sang-Heon Lee[4], Hyung-In Yang[1] and Seung-Jae Hong[1], [1]Internal Medicine, School of Medicine, Kyung Hee University, Seoul, South Korea, Seoul, South Korea, [2]Ajou University School of Med, Suwon, South Korea, [3]Ulsan Univ Med Sch Gangneung, Gangneung, [4]Konkuk University Hospital, Seoul, South Korea

Purpose: Sulfasalazine (SSZ) has been widely used in the treatment of various autoimmune diseases including rheumatoid arthritis (RA). Although some patients experience adverse events after taking SSZ for 2-3 weeks, SSZ hypersensitivity is relatively uncommon in RA patients. However, since the report that toxicity is common with SSZ in AOSD, use of this agent has not been recommended in AOSD. As N-acetyltransferase 2 (NAT2) is an important enzyme catalyzing SSZ, we investigated the associations of NAT*2* genotypes with SSZ hypersensitivity, as well as with susceptibility to AOSD.

Methods: DNA was extracted from 48 patients with AOSD, 92 patients with RA, and 101 healthy controls. NAT2 genotyping was performed by full sequencing analysis on an ABI Prism 377 automatic sequencer. N-acetylation phenotypes were deduced from previously published genotype/phenotype correlations. Clinical characteristics were obtained by medical record review.

Results: Eight single nucleotide polymorphisms (SNPs) with the minor allele frequency more than 5% were identified within the exon2 of NAT2 gene. Among them, 2 SNPs revealed the strong associations with the risk of AOSD vs. controls: rs1041983 (OR = 2.73, 95% CI:1.31-5.70, *P* = 0.0061); rs1799930 (OR = 4.64, 95% CI:2.02-8.90, *P* <0.0001) and vs. RA: rs1041983 (OR = 6.02, 95% CI: 1.73-20.93, *P* = 0.014); rs1799930 (OR=3.84, 95% CI:1.84-8.03, *P* <0.0001). The wild type allele (NAT2*4) and 6 types of variant alleles (NAT2*5B, NAT2*6A, NAT2*7A, NAT*7B, NAT*12A and NAT2*13) were detected. Healthy controls and RA patients did not differ in composition of NAT2 genotypes. AOSD patients with at least one slow acetylator genotype (NAT2*5B, NAT2*6A, NAT2*7A and NAT*7B) showed the higher levels of hepatic enzymes and experienced rash more frequently than those without (OR=3.19, 95% CI: 1.13-9.03, *P*=0.023). Slow acetylator phenotype was more frequent in AOSD than in healthy control (66.67% vs 45.54%, *P*=0.016). Of 48 patients with AOSD, 3 of the 4 treated with SSZ developed hypersensitivity compared to none in RA patients receiving this agent. Two of three AOSD patients with SSZ sensitivity had the slow acetylator phenotype.

Conclusion: NAT2 slow acetylation genotype may be a risk factor of individual susceptibility to AOSD in Korean. Higher frequency of slow acetylator genotypes could be one mechanism explaining why SSZ hypersensitivity is more prevalent in AOSD than in others.

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Association of genetic polymorphism in inflammatory cytokines with radiographic knee OA severity and Generalized Osteoarthritis (GOA). Mukundan Attur[1], Jonathan Samuels[1], Svetlana Krasnokutsky[1], Ken Kornman[1], Nazneen Aziz[1], VB Kraus[2], Gary McDaniel[2], Jeffrey D. Greenberg[3], Jack F. Bukowski[4] and Hwa-Ying Wang[5], [1]NYU - Hospital for Joint Diseases, New York, NY, [2]Duke University Medical Center, Durham, NC, [3]New York University School of Medicine, Millburn, NJ, [4]Harvard Med School, Marlborough, MA, [5]Waltham

Purpose: Osteoarthritis is the most common form of arthritis, and the hereditable component of OA has been estimated to be 50-65%. The IL1 gene cluster region has been repeatedly associated with susceptibility to OA in various joints. This finding is consistent with the notion that inflammatory mediators, particularly IL-1, may be important in the pathogenesis and progression of OA. In these studies we examined the association of SNPs in inflammatory genes with the severity of knee OA and with the presence of generalized OA (GOA, here defined as knee plus hand OA).

Method: One hundred forty-four OA patients (81 knee OA and 63 GOA) from two separate centers (NYUHJD, N=94 and Duke, N=50) met inclusion criteria: Caucasians of either sex, free of chronic disease other than osteoarthrits, and with a radiographic diagnosis of knee OA. Synovial fluid was available for the 50 Duke patients. Patients were genotyped for single nucleotide polymorphisms (SNPs). These subjects were divided into two groups: knee OA and GOA (knee and hand OA).We performed statistical analysis using Chi square and logistic regression, adjusting for age, gender and BMI to search for associations of radiographic knee OA severity and GOA with individual SNPs and with haplotypes.

Results: After adjustment for age, gender, and BMI, individual TNF-a, IL1, IL1 receptor antagonist (IL1RN) SNPs were strongly associated with the presence of GOA (Table 1). In three of the four SNPs, alleles associated with increased incidence of GOA have been previously associated with increased cellular production of inflammatory mediators. These alleles are: IL1B (-3737) rs4848306 TT/CT, IL1B (-511) rs16944 CC/CT, and TNF-a (-308) rs1800629 AA/AG. In a separate analysis of knee OA severity based upon JSW, carriage of either one or two copies of a haplotype consisting of IL-1RN rs9005 (A), IL-1RN rs419598 (C), IL-1RN rs315952(T) was associated with lower odds of radiographic severity (OR 0.16; 95% CI 0.06-0.40), greater joint space width (JSW; p=0.0038) compared to those without these haplotypes. Patients with the “protective” haplotype had lower synovial fluid levels of IL-6 (p=0.018) and IL-10 (p=0.038).

Conclusion: Among the cytokines and receptor antagonist studied for genetic association, IL-1RN SNPs (rs9005, rs419598 & rs315952) predicted low risk for knee OA radiographic severity and haplotypes in IL-1B, TNFa ad IL-1RN (rs 315952) strongly associated with increased prevalence of GOA. These genetic markers provide insight into the possible role of inflammatory mediators in knee OA and could prove to be useful biomarkers in DMOAD drug development.

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ACR/ARHP Poster Session B

Imaging - MR, CT, Radiography, Scintigraphy

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Reproducibility of MR Biomarkers of Cartilage Structure and Composition in An Osteoarthritis Population at Risk of Progression. Mike A. Bowes[1], D.J. Hunter[2], Charles B. Eaton[3], C. K. Kwoh[4], RA. Maciewicz[5], Jonathan Samuels[6], Christopher J. Taylor[7], John C. Waterton[5], Tomos G. Williams[7] and Chris B. H. Wolstenholme[1], [1]Imorphics, Manchester, United Kingdom, [2]NEBH, Boston, MA, [3]Alpert Medical School of Brown University, Pawtucket, RI, [4]UPitt, Pittsburgh, PA, [5]AstraZeneca, Macclesfield, United Kingdom, [6]New York University/Hospital for Joint Diseases, New York, NY, [7]University of Manchester, United Kingdom

Purpose: Osteoarthritis (OA) is a slowly-progressing disease, and imaging biomarkers of cartilage structure have failed to detect short-term (< 6 months) change. An imaging biomarker of cartilage quality (i.e., tissue composition and function) such as magnetic resonance transverse relaxation time of hyaline cartilage water protons (T_2), may be more a responsive biomarker of OA progression. T_2 is a proxy for disorder and hydration, and is easily measured without a contrast agent, but there are few data on variability of this marker over time in OA. The purpose of this study was to determine the short-term (1 week) reproducibility of cartilage T_2 and thickness obtained from an anatomically-corresponded regional analysis using statistical shape modelling.

Method: We conducted a multi-centre, non-randomized study at 4 sites with a sample at risk of medial tibiofemoral progression including women, BMI≥25 kg/m^2, symptomatic radiographic evidence of medial tibiofemoral OA (K&L grade 2-3, medial JSN≥ lateral JSN), varus malalignment ≥-2° (anatomic axis), and pain. As part of a larger study, eligible participants had MRI scans of the same knee at baseline and 1 week. The OAI protocol for the index knee was deployed on 3T Siemens Trio systems. A trained operator, blind to time-point but not subject, manually segmented the cartilage from the DESSwe MR images using EndPoint (Imorphics). Anatomically corresponding regions of interest were identified on each image by fitting a bone model, and mean cartilage thickness (with areas denuded of cartilage included as having zero thickness - ThCtAB) within each region was calculated. Voxelwise transverse relaxation rates were calculated from a linear least-squares fit of the log of the signal values against echo time. Mean T_2 values were also recorded in each region from the 50% most exochondral and 50% most endochondral voxels. Coefficients of Variation (CoV) were calculated.

Results: The 29 participants had a mean age of 62 years, mean BMI of 36 kg/m^2, with 8 index knees graded as K&L =2 and 21 as K&L=3. Anatomical mal-alignment ranged from -1.9° to 6.3°, with mean 0.9°, where varus mal-alignment is measured in the positive direction. 28 subjects provided data for reproducibility of ThCtAB and 20 for T_2.

Table 1. Reproducibility MR Measures

	Mean T_2 /msec	CoV T_2	Mean ThCtAB/mm	CoV ThCtAB
Medial Femur	49.5	3.1%	1.59	2.2%
Lateral Femur	49.0	2.6%	1.69	2.8%
Medial Tibia	38.7	2.8%	1.35	2.5%
Lateral Tibia	38.8	2.6%	1.66	3.0%

T_2 was approximately 10% higher in the exochondral vs. endochondral layer in each region.

Conclusion: T_2 can be measured reproducibly in an OA population in multicentre studies and with similar variability to a cartilage structural assessment. These results support further evaluation of T_2 as a candidate biomarker of cartilage composition for assessing interventions.

Disclosure: M. A. Bowes, Imorphics Ltd, 1, AstraZeneca, 2 ; **D. J. Hunter**, AstraZeneca, 2 ; **C. B. Eaton**, AstraZeneca, 2 ; **C. K. Kwoh**, AstraZeneca, 2 ; **R. Maciewicz**, AstraZeneca, 3, AstraZeneca, 1 ; **J. Samuels**, None; **C. J. Taylor**, AstraZeneca, 2, imorphics, 1 ; **J. C. Waterton**, AstraZeneca, 3 ; **T. G. Williams**, AstraZeneca, 2 ; **C. B. H. Wolstenholme**, Imorphics Ltd, 3, Imorphics Ltd, 1 .

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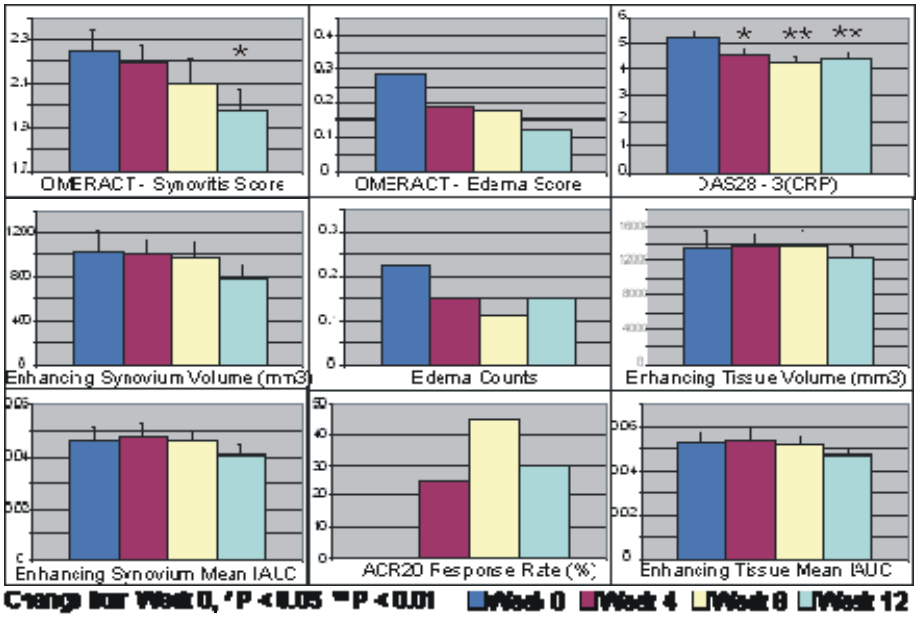
Early Treatment Effects of Anti-TNF Therapy On MRI Biomarkers of RA Activity. Bradley T. Wyman[1], Yanwei Zhang[1], Bradley J. Bloom[1], Orrin M. Troum[2], Nastaran Fatemi[3], Shengong Wu[4], Saara Totterman[4], Ralph E. Bennett[5] and Mark Tengowski[4], [1]Pfizer Inc., New London, CT, [2]Keck School of Medicine/University of Southern California, Santa Monica, CA, [3]Beverly Radiology Medical Group, Los Angelos, [4]VirtualScopics Inc., Rochester, NY, [5]Arizona Arthritis Research PLC, Paradise Valley, AZ

Purpose: X-rays are commonly used to image RA treatment effects in clinical studies but can only monitor the late stage disease effects of bone erosions. MRI, however, has the potential to detect the inflammatory components of RA such as synovitis, and tissue and bone edema. RA treatments target these inflammatory effects, so MRI has the potential to detect efficacy much earlier. The goals of this study were to determine the impact of short term anti-TNF therapy on changes to quantitative and semi-quantitative image endpoints in the MCP joints.

Method: Prior to starting anti-TNF therapy (open-label) 22 RA subjects, at 4 centers, who were on a stable background therapy of methotrexate, were scanned on an OrthoOne 1.0T peripheral MRI scanner. Scans were repeated at 4, 8 and 12 weeks of treatment. MCP joints were imaged with the following sequences: Coronal T2 fat suppressed FSE, coronal and axial 3D GRE, and 2D axial dynamic contrast enhanced (DCE) SPGR acquired continuously starting before bolus injection of 0.1 mmol/kg Gd-DTPA and continuing for 4 minutes.

For all subject visits the semi-quantitative ACR20, EULAR-OMERACT and DAS28 – 3CRP scores were determined. Semi-automated segmentation of the MRI was used to calculate the enhancing synovium, enhancing tissue (synovium, bone, tendons and muscle). Bone edema counts were determined by the average number of distinct edema regions. DCE MRI was used to calculate the initial area under the curve (IAUC) for the enhancing synovium and tissue. All MRI endpoints evaluated the 2^{nd} -5^{th} MCP joints.

Statistical significance was obtained by modeling the log of the follow-up to week 0 ratio of the measure. $P < 0.05$ was significant.



Results: The figure shows the mean and standard error bars for each of the measures at 0, 4, 8, and 12 weeks for the 20 of 22 completing subjects. Only a few of the subjects presented with bone edema, so error bars and significance of change were not calculated. Most measures showed a trend for reduction over 12 weeks but only the OMERACT synovitis score at week 12 and the DAS scores at week 4, 8 and 12 were significant. The OMERACT synovitis score at week 8 and the enhancing synovium volume at week 12 showed a decreasing trend.

Conclusion: The ACR20 response rate at week 12 was unexpectedly low compared to similar anti-TNF studies. This may have also resulted in a lower response rate for the inflammatory MRI biomarkers. However, the DAS-28 and OMERACT synovitis scores showed a statistically significant treatment response

Disclosure: B. T. Wyman, Pfizer Inc, 1, Pfizer Inc, 3 ; **Y. Zhang**, Pfizer Inc, 1, Pfizer Inc, 3 ; **B. J. Bloom**, Pfizer Inc, 3 ; **O. M. Troum**, None; **N. Fatemi**, None; **S. Wu**, VirtualScopics, 1, VirtualScopics, 3 ; **S. Totterman**, None; **R. E. Bennett**, None; **M. Tengowski**, Pfizer Inc, 1, VirtualScopics, 1, VirtualScopics, 3 .

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Scintigraphic Studies in the Detection of Pulmonary Involvement in Systemic Sclerosis (SSc) Patients. John Koutsikos[1], Charalampos Kostopoulos[2], Charalampos Mamoulakis[2], Lia A. Moulopoulos[3], Cherry Zerva[1], Myron Mavrikakis[4] and Anastasia Leondi[1], [1]Nuclear Medicine Department, Alexandra University Hospital, Athens, Greece, [2]Department of Clinical Therapeutics, University of Athens, School of Medicine, Athens, Greece, [3]Department of Radiology, University of Athens, School of Medicine, Athens, Greece, [4]Vascular Laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece

Purpose: Gallium (Ga-67) scintigraphy has been shown to be useful in the assessment of patients with interstitial lung disease associated with SSc. HRCT is considered to be the most appropriate non-invasive modality for its diagnosis. Chronic immunological inflammation which results in fibrosis is the major mechanism of pulmonary involvement (PI) in these patients. Tc-99m labeled non-specific human polyclonal immunoglobulin G (HIG) is a radiopharmaceutical that has been used successfully for the detection of focal and diffuse infection and inflammation. The aim of this study was a head-to-head comparison of these radiopharmaceuticals in the detection of the PI in patients with SSc, using HRCT as gold standard method.

Method: We studied 30 non-smoking patients suffering from SSc with no pulmonary event in their medical history other than in terms of SSc. All patients underwent gallium scintigraphy 48 hrs after i.v. injection of 4 mCi Ga-67 and HIG scintigraphy 3 hrs after i.v. injection of 20 mCi Tc-99m HIG. The maximum time interval between scintigraphic studies and HRCT was 10 days. Receiver operating characteristic (ROC) analysis was performed and the respective areas under the curve (AUC) of the two scintigraphies were calculated. A probability $P<0.050$ (two-tailed) was considered to indicate statistical significance. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were also assessed.

Results: PI according to HRCT abnormalities was detected in 15 patients. HIG scintigraphy ROC curve differed significantly from the non-discrimination line (AUC = 0.733 [95% CI=0.548-0.919], $P<0.03$), while for Ga-67 scintigraphy ROC curve did not (AUC=0.667 [95% CI=0.469-0.895], $P=0.12$). Sensitivity, specificity, PPV and NPV of Ga-67 and HIG were: 73.3%, 60%, 64.7%, 69.2% and 93.3%, 53.3%, 66.7%, 88.9% respectively.

Conclusion: HIG scintigraphy demonstrated good clinical performance in contrast to Ga-67 scintigraphy. This may be explained by the different uptake mechanisms of the two radiopharmaceutics. HIG accumulation due to increased vascularity and vascular permeability seems to play an important role.

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Differential Distribution of a PEGylated Fab' Into Inflamed Versus Normal Tissue Compared to An IgG in Arthritis and Colitis Models. Massimo Marenzana, Alison Eddleston, Alex Vugler and Andrew Nesbitt, UCB, Slough, United Kingdom

Purpose: PEGylation has been shown to affect protein distribution. For example, certolizumab pegol (CZP), a PEGylated Fab', has been shown to distribute to inflamed versus normal tissue at a ratio of 3.8 in a collagen-induced arthritis (CIA) mouse model, whereas adalimumab (ADA), an IgG, had a ratio of 1.9.(1) The objective of these studies was to further compare PEGylated Fab' and IgG distribution by determining the consequence of TNF binding on the distribution of these reagents, and by investigating the distribution of these reagents in a different inflamed tissue model (the DSS gut colitis model).

Methods: An anti-mouse TNF antibody with an affinity for mouse TNF that is similar to the anti-human reagents CZP and ADA was used for this study. Both the PEGylated Fab' and IgG2a versions of this antibody were labeled with one of 2 fluorescent dyes: Alexa 680 for experiments in the CIA model and Alexa 790 for the DSS model. The potency of the labeled reagents was not affected as measured in a L929 bioassay. The labeled reagents were given intravenously at 2 mg/kg in the CIA model and subcutaneously at 10 mg/kg in the DSS model. In both cases, control animals were similarly dosed. In the CIA model, paws were imaged in vivo at various time points up to 26 hours post-administration using an IVIS imager. In the DSS model, the colons were removed after 24 hours and imaged using the IVIS imager ex vivo by drawing a region of interest around the whole excised colon.

Results: Both the IgG and PEGylated Fab' penetrated inflamed tissue more effectively than the non-inflamed tissue in both the CIA and DSS models. However, in both cases, the ratio of distribution in inflamed versus normal tissue was higher for the PEGylated Fab' than the IgG. In the CIA model, the ratio was 2.3 for the PEGylated Fab' vs 1.7 for the IgG after 1 hour ($p=0.01$ as measured by an unpaired two-tailed T test), while in the DSS model, the ratio was 3.1 vs 2.1, respectively, after 26 hours ($p=0.02$). In the CIA model, the ratio was also measured at various time points out to 26 hours, with significant differences at all times tested.

Conclusion: This innovative method of analyzing protein levels in tissue enabled a comparison of the distribution of an anti-mouse PEGylated Fab' and IgG in two different mouse models. In both models, the PEGylated Fab' had a higher inflamed to normal tissue ratio than the IgG. This result confirmed previous observations concerning the effect of PEG (and other macromolecules) on the distribution of proteins and suggests that antigen binding does not greatly affect distribution. Effective targeting of inflamed tissue is a desired property for an anti-inflammatory agent and may be an important consideration for effective treatment of inflammatory disorders.

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Disclosure: M. Marenzana, UCB, 3 ; **A. Eddleston**, UCB, 3 ; **A. Vugler**, UCB, 3 ; **A. Nesbitt**, UCB, 3 .

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The Diagnostic and Predictive Value of Radiographs in Undifferentiated Arthritis: Results of a Systematic Review as Part of the 3E Initiative. R. Koevoets[1], P. Machado[2], C. Bombardier[3] and Désirée M.F.M. van der Heijde[4], [1]LUMC, Leiden, Netherlands, [2]Coimbra University Hospital and LUMC, Coimbra, Portugal, and Leiden, Netherlands, [3]Univ of Toronto, Toronto, ON, [4]Leiden University Medical Center, Leiden, Netherlands

Background: 3E (Evidence, Expert, Exchange) is a multi-national initiative which aims at promoting evidence-based medicine in rheumatology.

Purpose: The 2008-2009 goal was to develop recommendations for the management of undifferentiated arthritis (UA) by integrating evidence with the expert opinion of an international panel of rheumatologists. We present the result of a systematic literature review about the diagnostic and prognostic value of conventional radiographs (CR) in UA.

Method: PubMed, Embase and Cochrane were all searched with an extended search developed in close collaboration with a trained librarian. In addition, the ACR and EULAR abstracts of 2007 and 2008 were hand searched. Articles were included based on predefined inclusion criteria and quality was assessed by using validated quality scales.

Results: In total 6003 references were found. Five articles with a pure UA population were included and 20 articles with a mixed population (mostly UA combined with RA). In studies of UA, inclusion criteria and baseline characteristics were similar and erosions on CR were strong predictors of a diagnosis of RA. In two studies the positive likelihood ratios (LR+) for erosions were 3.5 and 10.9 and negative likelihood ratios (LR-) were 0.7 and 0.8 respectively. One study reported an odds ratio (OR) of 8.7 in a model with anti-CCP and 7.6 in a model without. Another study found that erosions were predictive of RA in a univariate analysis, but not in the multivariate analysis. Only one study addressed the value of erosions on CR for prognosis in UA; Sharp v/d Heijde (SvdH) score at baseline was lower in the mild vs progressive disease group at 1 year. In studies with a mixed population the inclusion criteria and baseline characteristic differed substantially. Twenty studies reporting on 11 cohorts found a relationship between CR findings and a subsequent diagnosis of RA. In four LR+'s for erosions and/or bony decalcifications ranged from 1.8 to 9.7 and the LR-'s from 0.7 to 0.9. In four studies, erosions were found to be less prevalent in patients with UA vs RA at one year. Two additional studies concluded that modified Sharp score was not significantly different between UA and RA at one year and SvdH score was in a univariate analysis associated with diagnosis of RA. In one prognostic study the LR+ for erosions on CR and developing persistent disease was 6.0, the LR- was 0.7. The remaining 9 prognostic studies showed a relation between the level of abnormalities on CR with poor outcome (for example: persistence of disease, low functional outcome, onset of DMARD treatment, radiographic severity).

Conclusion: The limited number of studies in pure UA populations clearly demonstrate that the presence of erosions on radiographs are helpful in predicting a future diagnosis of RA and might be of value in predicting outcomes in RA. However, the absence of abnormalities on radiographs does not rule out a diagnosis of RA.

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Automatic Computer Aided Quantification of Synovitis in Rheumatoid Arthritis Using Dynamic MRI and the Impact of Movement Correction On Signal to Noise Ratio (SNR) and Region of Interest (ROI) Analysis. Mikael Boesen[1], Olga Kubassova[2], Marco A. Cimmino[3], Mikkel Ostergaard[4], Bente Danneskiold-Samsoe[1] and Henning Bliddal[1], [1]Parker Institute, Frederiksberg, Denmark, [2]Image Analysis, Leeds, England, [3]University of Genova, Genova, Italy, [4]University Hospitals Hvidovre and Gentofte, Copenhagen, Denmark

Background: Dynamic Contrast Enhanced MRI (DCE-MRI), based on repeated imaging of the same few MRI slices with a few seconds' interval after intravenous contrast injection, correlates closely to histological inflammatory activity and is a promising tool to asses the early response to treatment, potentially before volume changes and changes in OMERACT RAMRIS scores occur. Analysis of DCE-MRI is usually done by manual selection of areas with most enhancement (regions of interest, ROIs), but variable ROI positioning and movements during imaging, introduce large variation in the results obtained from the dynamic curves using the ROI method (1-2).

Purpose: To analyse DCE-MRI data from RA patients using a newly developed algorithm that eliminate motion artefacts and to evaluate the impact of motion on SNR and ROI results

Methods: DCE-MRI data were acquired in wrists of 50 RA patients and 5 controls, by repeatedly obtaining 3 axial or coronal T1-weighted images every 10-15 seconds immediately after iv 0.1 mmol/kg Gd-DTPA, using a 0.2T Esaote C-scan or E-scan (22-30 repetitions). Motion artefacts were eliminated using an intensity-based algorithm which corrects for movements and changes in brightness and contrast in every pixel. ROIs of 25mm^2 were positioned automatically in the area of most enhancement using a custom made computer programme. Maximum enhancement (ME) and initial rate of enhancement (IRE) were calculated from the ROIs.

Results: Motion artefacts in all 3 planes were reduced from 1.3mm±7mm to 1mm±1.5mm shift and 7±6degree to 1±0.4degree rotation. This increased SNR by a factor 3 on average, removed image blurring and reduced the variations in the shape of dynamic curves extracted from the ROIs. This consequently reduced variation in measurements of ME and IRE (statistical f-test was applied). In controls, the IRE was reduced from 0.21±0.1 to 0.12±0.02 [%/sec] and in ME from 0.35±0.23 to 0.1±0.01 [%]. In patients, IRE increased from 0.5±0.16 to 0.6±0.02 [%/sec] and ME from 0.53±0.3 to 0.7±0.02 [%].

Conclusion: Elimination of motion artefacts significantly reduced artefactual enhancement and increased SNR. Reduced variation in ROI measurements significantly influenced the accuracy of quantitative analysis of inflammation. This supports the use of DCE-MRI augmented by motion reduction algorithms for more robust and valid analysis of synovitis in RA patients.

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Disclosure: M. Boesen, None; **O. Kubassova**, Olga Kubassova, 5 ; **M. A. Cimmino**, None; **M. Ostergaard**, None; **B. Danneskiold-Samsoe**, None; **H. Bliddal**, None.

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F-18 Flurorodeoxyglucose Positron Emission Tomography Can Detect Early Response to Adalimumab in Rheumatoid Arthritis. Denis Mulleman[1], Véronique Eder[2], David Ternant[1], Jean-Camille Méric[2], Maxime Courtehoux[2], François Tranquart[3], Philippe Goupille[4] and Gilles Paintaud[4], [1]Université François Rabelais de Tours; CNRS, UMR 6239; CHRU de Tours, Tours, France, [2]CHRU de Tours, Tours, France, [3]CHRU de Tours; INSERM 806, CIC-IT, Tours, France, [4]Université François Rabelais de Tours, CNRS, UMR 6239; CHRU de Tours, Tours, France

Purpose: To analyse the ability of F-18 flurorodeoxyglucose (FDG) positron emission tomography (PET) to detect an effect of adalimumab on joint inflammation in active rheumatoid arthritis (RA) 2 weeks after treatment initiation.

Method: Patients with a high disease activity score measured on 28 joints (DAS28 > 5.1) were recruited to undergo F-18 FDG PET three consecutive times: before and 2 and 12 weeks after adalimumab initiation. Inflammation was assessed by a semi-quantitative scale and compared to results of clinical and ultrasonography examination of the corresponding joints. A global score was defined by the sum of the

maximal standard unit values (SUV_{max}) of each of the inflammatory joints. **Results:** Six patients participated in the study. Five patients were responders, according to PET assessments, by showing a decrease in median SUV_{max} global score of 62.9% at week 2 and 88.2% at week 12.

Conclusion: F-18 FDG PET is a promising imaging tool able to identify an effect of tumor necrosis factor a antagonists on inflammatory joints as early as 2 weeks

Disclosure: D. Mulleman, Abbott Laboratories, 2 ; **V. Eder**, None; **D. Ternant**, None; **J. C. Méric**, None; **M. Courtehoux**, None; **F. Tranquart**, Bracco Research, 3 ; **P. Goupille**, Abbott Laboratories, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2 ; **G. Paintaud**, Roche Pharmaceuticals, 5, Innate Pharma, 2, Roche Pharmaceutical, 2, LFB, 5 .

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Changes in Patellar Cartilage Morphology and Water Content in Response to An Acute Bout of Loading: A Comparison of Young Females with and without Patellofemoral Pain. Shawn Farrokhi, Patrick M. Colletti and Christopher M. Powers, University of Southern California, Los Angeles, CA

Purpose: Patellofemoral Pain (PFP) is prevalent in a wide range of individuals; however the highest incidence is evident in young, physically active populations. One proposed theory regarding the etiology of PFP may be related to the inability of the patellofemoral joint cartilage to adequately adapt to mechanical loading. An impaired response to loading may result in elevated stress within the cartilage or at the cartilage-bone interface. The purpose of the current study was to compare the adaptive response of articular cartilage following an acute bout of loading between females with PFP and pain-free controls. We hypothesized that females with PFP would demonstrate less cartilage deformation and diminished water content changes post-exercise when compared to control subjects.

Method: Ten females with the diagnosis of PFP and 10 pain-free controls participated. Subjects were matched for gender, age and activity level. Baseline quantitative magnetic resonance imaging of patellar cartilage morphology was performed using an axial plane spoiled gradient recalled echo protocol. In addition, axial transverse relaxation times (T_2) were obtained from a 4-echo sequence with echo times spaced evenly over a range of 20-80 msec. Following the initial imaging session, subjects performed 50 deep knee bends over the course of 90 seconds while wearing a weighted vest equivalent to 25% of their body weight. Subjects were imaged immediately following completion of the exercise protocol (within 2 minutes). Independent sample t-tests were used to evaluate changes in cartilage morphology (volume and thickness) and water content (T_2) pre-post exercise.

Results: Compared to pre-exercise values, post exercise cartilage volume change scores were significantly lower for the PFP group compared to the control group (4% vs. 9%, 4% vs. 14%, and 4% vs. 11% for the lateral, medial, and total patella cartilage, respectively). Similarly, post exercise cartilage thickness change scores for the PFP group were lower compared to the control group (2% vs. 9%, 7% vs. 11%, and 4% vs. 10% for the lateral, medial, and total patella cartilage, respectively). In contrast, post exercise T_2 change scores for the PFP group were less pronounced compared to the control group (0% vs. -8%, 2% vs. -2%, and 1% vs. -5% for the lateral, medial, and total patella cartilage, respectively).

Conclusion: Consistent with our hypothesis, females with PFP demonstrated less cartilage deformation following an acute bout of loading. In addition, females with PFP demonstrated smaller changes in cartilage water content following exercise. This finding suggests an altered interaction between the collagen matrix and the interstitial fluid seen in healthy cartilage. Our findings support the premise that the mechanical response of patella cartilage following an acute bout of loading is impaired in females with PFP.

Disclosure: S. Farrokhi, None; **P. M. Colletti**, None; **C. M. Powers**, None.

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Periarticular Bone Mineral Density Does Not Distinguish Between Healthy Controls, Established RA and Early Arthritis Patients. C. Alves, E. M. Colin, W. J. van Oort, J. Sluimer, J. M. W. Hazes and J. J. Luime, Erasmus Medical Centre, Rotterdam, Netherlands

Background Early recognition of rheumatoid arthritis (RA) is important, but difficult due to lack of a distinct feature. Loss of periarticular bone mineral density (pBMD) in the hand is thought to be an early feature. The difficulties in pBMD measurement are dilution of BMD loss in the whole hand and less precise measurements in small regions of interest (ROI's). Choosing the size of a ROI is a trade-off between area size and precision error.

Purpose: To identify periarticular ROI's relevant to RA with a low precision-error and sufficient interrater reliability and to test the validity of these ROI's.

Methods: Five ROIs were defined around the MCP and/or PIP joints II-V, II-IV and mid-metacarpal to mid-phalangeal. BMD was estimated using a Lunar Prodigy. Precision was estimated by measuring 5 healthy adults 7 times, after repositioning, using the Root-Mean-Square-Coefficient of Variation (RMS-CV). To determine the interrater reliability 20 patients were analyzed on separate occasions by 2 readers using the ICC. Validity of the ROI's was tested using 2 patient groups and healthy controls matched on sex, age and menopausal status. Patients with established RA were recruited from the rheumatology outpatient clinic, patients with early arthritis via the Rotterdam Early Arthritis CoHort (REACH). Simple descriptive analyses, scatter plots, paired t-tests and ROC-curves were done.

Results: The RMS-CV varied from 0.45% to 1.07%. The ICC was 0.99 for all measurements. Between September 2006 and October 2008 44 patients and 33 healthy controls were recruited. Mean BMDs of the ROI's ranged from 0.321 to 0.372 g/cm^2 in established RA, 0.321 to 0.382 g/cm^2 in early arthritis and 0.342 to 0.401 g/cm^2 in controls. The mean differences ranged from 0.011 to 0.032 g/cm^2 for established RA and 0.028 to 0.033 g/cm^2 for early arthritis patients compared to matched controls. For ROI 1 and 3-5 in early arthritis and the whole hand in established RA the mean differences were significant. The ROC-curves indicated low discriminative power of all ROI's, with AUC's from 0.60 to 0.66.

Conclusion: Periarticular BMD seems not to be a useful diagnostic feature due to the wide distribution in BMD values resulting in strong overlap between healthy controls, established RA and early arthritis patients.

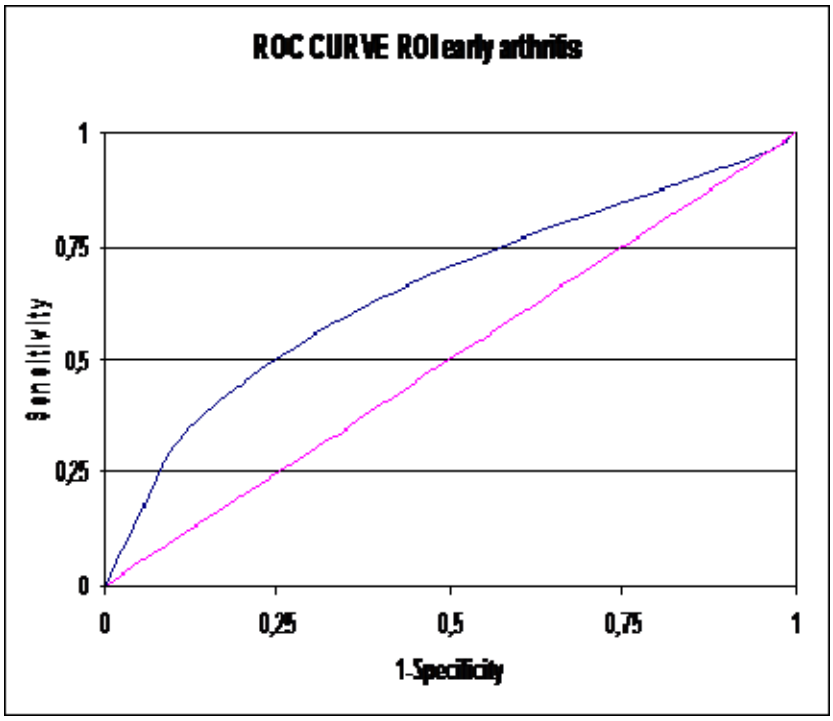
Table 1 One sample T-test on matched differences between BMD patients and controls

	Established RA (n=25)	Early arthritis (n=25)
ROI 1 * (mean diff, sd)	-0.014 (0.062)	-0.028 (0.052) $
ROI 2 * (mean diff, sd)	-0.009 (0.054)	-0.023 (0.055)
ROI 3 * (mean diff, sd)	-0.014 (0.068)	-0.032 (0.058) $
ROI 4 * (mean diff, sd)	-0.013 (0.060)	-0.023 (0.051) $
ROI 5 * (mean diff, sd)	-0.025 (0.066)	-0.030 (0.056) $
Whole hand * (mean diff, sd)	-0.036 (0.078) $ (n=24)	-0.027 (0.082)

* in g/cm^2

$ p-value < 0.05

Figure 1. ROC curve for ROI 1 in early arthritis (AUC=0.62)



Disclosure: C. Alves, None; **E. M. Colin**, None; **W. J. van Oort**, None; **J. Sluimer**, None; **J. M. W. Hazes**, None; **J. J. Luime**, None.

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Reader Reliability of the OMERACT Psoriatic Arthritis Magnetic Resonance Score (PsAMRIS): Results From An OMERACT Workshop. Pernille Bøyesen[1], Frédérique Gandjbakhch[2], Fiona M. McQueen[3], Siri Lillegraven[4], Laura Coates[5], Charlotte Wiell[6], Philip Conaghan[7] and Mikkel Østergaard[8], [1]MD, Oslo, Norway, [2]MD, Paris, France, [3]University of Auckland, Auckland, New Zealand, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]University of Leeds, Leeds, United Kingdom, [6]MD, Hvidovre, Denmark, [7]Leeds, United Kingdom, [8]Hvidovre and Gentofte, Denmark

Purpose: The aim of this study was to test cross-sectional and longitudinal inter- and intra reader reliability of the Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) under standardized conditions.

Methods: The exercise was performed using MRI scans from 12 PsA patients (8 acquired in Copenhagen and 4 in Leeds) before and after 12 months of anti-TNFα therapy. The metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints of the 2nd–5th fingers were examined, using a 0.6 T MRI unit (Copenhagen) and a 0.2T MRI unit (Leeds). Coronal, axial and sagittal T1-weighted pre- and post-gadolinium-contrast images and sagittal and axial pre-contrast STIR images were obtained, anonymized and blinded for time sequence and read twice by FG, FMQ, MØ and PB on identical PACS workstations. For the second reading the images were re-anonymized and re-randomised. The images were scored according to the PsAMRIS: at MCP, PIP and DIP joint-level synovitis was scored 0-3, tenosynovitis 0-3, bone proliferation 0-2, pariarticular inflammation 0-2, bone marrow edema 0-3 per bone and bone erosions 0-10 per bone. Inter-reader reliability was assessed using average measure intraclass correlations coefficient (ICCa) and intra-reader reliability by single measures intraclass correlations coefficient (ICCs).

Results: The median (IQR) average baseline/1-year follow-up synovitis score was 10.8 (8.5-14.3)/ 8.4 (6.7-9.7), tenosynovitis score 5.7 (1.7-8.5)/ 2.0 (0.9-4.4), bone proliferation 2.2 (1.4-3.9)/ 2.2 (1.4-3.9), periarticular inflammation 1.1 (0.1-3.6)/ 0.5 (0.3-0.6), bone marrow

edema 0.3 (0.1-1.4)/ 0.1 (0.0-0.8) and bone erosions 1.8 (0.2-5.1)/ 1.9 (0.1-5.0). The cross-sectional inter-and intra reader reliability as well as the inter-reader reliability for 1-year change are presented in table 1. The inter-reader ICC was high for all measures except moderate for bone proliferation. Poor ICCs for bone proliferation and erosion change scores are explained by minimal change in the 1-year period.

Conclusion: In this multi-reader exercise testing the PsAMRIS under standardized conditions, very high interreader and intrareader reliability for status and change scores for most parameters and readers were found. Inflammatory parameters performed best. These results suggest that PsAMRIS is a reliable tool for MRI assessment of PsA patients.

Table 1. Cross sectional inter- and intra reader reliability

	Inter-reader reliability (ICCa)		Intra-reader reliability (ICCs) (cross-sectional)			
	Cross-sectional	1-year change	Reader 1	Reader 2	Reader 3	Reader 4
PsA synovitis	0.95	0.95	0.97	0.73	0.93	0.90
PsA flexor tenosynovitis	0.97	0.95	0.81	0.74	0.93	0.73
PsA bone proliferation	0.77	0.10	0.20	0.84	0.79	0.44
PsA periarticular inflammation	0.91	0.91	0.39	0.95	0.88	0.91
PsA bone marrow edema	0.87	0.87	0.98	0.97	0.99	0.03
PsA bone erosion	0.97	0.44	0.91	0.93	0.92	0.91

Disclosure: P. Bøyesen, None; **F. Gandjbakhch**, None; **F. M. McQueen**, None; **S. Lillegraven**, None; **L. Coates**, None; **C. Wiell**, None; **P. Conaghan**, None; **M. Østergaard**, None.

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Is STIR Necessary for Evaluating Synovitis and Osteitis in Rheumatoid Arthritis When Using MRI Protocols That Also Include Gadolinium-Enhanced Magnetic Resonance Imaging? C. Peterfy[1], J. DiCarlo[1], J. C. Becker[2] and H.K. Genant[1], [1]SYNARC, Inc, San Francisco, CA, [2]Bristol-Myers Squibb, Princeton, NJ

Purpose: Magnetic resonance imaging (MRI) is increasingly being used in clinical trials of rheumatoid arthritis (RA) to evaluate severity and progression of bone erosion, osteitis and synovitis. We previously showed that coronal short-tau inversion recovery (STIR) and axial fat-suppressed 3D T1-weighted gradient-echo ± intravenous gadolinium contrast (GRE±Gd) performed similarly for scoring synovitis[1] and osteitis[2] in the wrist and, therefore, that MRI protocols need not necessarily include both techniques. However, bone erosion and osteitis are best evaluated in the same plane, so here we compare the performances of coronal GRE±Gd and coronal STIR in a different cohort of RA patients.

Method: As part of a Phase III double-blind, placebo-controlled, multi-site trial of abatacept in RA, the dominant hands/wrists of 39 patients with early RA were scanned using 1.5T whole-body MRI. Scans of the wrist included coronal STIR (0.47mm x 0.63mm x 3.0mm voxels)

requiring 6 mins, and coronal fat-suppressed GRE±Gd (0.23mm x 0.63mm x 1.5mm voxels; 0.1 mmol/kg Gd-DTPA, iv) requiring 15 mins, including the injection. One radiologist experienced with the RA MRI scoring (RAMRIS) method[3] scored baseline GRE±Gd images for osteitis on a scale of 0 to 3 in 15 bones of each wrist, and for synovitis on a scale of 0 to 3 in the distal radioulnar, radiocarpal and intercarpal-carpometacarpal joints in each wrist. Several days later, the same radiologist scored the STIR images without referring to the GRE±Gd images or the previous scores. Agreement between the two methods was determined by intra-class correlation coefficient (ICC).

Results: GRE±Gd and STIR showed identical results for synovitis scoring and very similar results for osteitis scoring (Table 1). Most of the osteitis visible on STIR, but not GRE±Gd, could be attributed to partial-volume averaging and pulsation artifacts on STIR. The ICCs for total synovitis and osteitis between the two methods were 1.00 and 0.98, respectively.

	STIR	**GRE±Gd**
Patients with synovitis, n (%)	11 (28%)	11 (28%)
Mean synovitis score, mean (SD)	1.1 (1.9)	1.1 (1.9)
Joints with synovitis, n (%)	22 (19%)	22 (19%)
Not visible with the other technique	0	0
Patients with osteitis, n, %	13 (33%)	11 (28%)
Osteitis score, mean (SD)	3.8 (8.7)	3.5 (8.2)
Bones with osteitis, n (%)	52 (9%)	48 (8%)
Not visible with the other technique	7 (13%)	5 (10%)
SD=standard deviation		

Conclusion: These findings confirm that coronal STIR and coronal GRE±Gd perform equivalently, and that STIR may not need to be included in a protocol which already has coronal GRE±Gd. STIR can, however, substitute for GRE+Gd if a Gd-free MRI protocol is preferred or if homogeneous spectral fat suppression is difficult to achieve.

References:
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2. Peterfy, et al. *Arthritis Rheum* 2008;**58**(Suppl 9)
3. Østergaard M, et al. *Ann Rheum Dis* 2005;**64**(Suppl 1):i3–7

Disclosure: C. Peterfy, Synarc, Inc., 3 ; **J. DiCarlo**, Synarc, Inc., 3 ; **J. C. Becker**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 9 ; **H. K. Genant**, Synarc, Inc., 1, BMS, 2, Roche, 2, Genentech, 2, Pfizer Inc, 2, Amgen, 2, Merck Pharmaceuticals, 2, Servier, 2, BiogenIdec, 2, Lilly, 2, BMS, 5, Roche Pharmaceuticals, 5, Merck, 5, Genentech, 5, Amgen, 5, Servier, 5, Synarc, 5 .

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Clinical Disease Activity Scores of Knee Joints in Newly Diagnosed JIA Predicts Reduction in Bone Pixel Value Detected by Computed Radiography. Laura Pascoli[1], Aaron Mc Cann[2], Michael Stevenson[3], Catherine Mc Allister[4] and Madeleine E. Rooney[5], [1]Belfast, United Kingdom, [2]Belfast Hospital Trust, Belfast, United Kingdom, [3]Queens University of Belfast, Belfast, [4]BHT, Belfast, United Kingdom, [5]Queen's University Belfast, Belfast, Northern Ireland

Purpose: . Evaluation of joint radiographs in JIA is highly subjective. We wished to evaluate the relationship between CR Pixel values and disease activity scores obtained for the knees of newly diagnosed JIA children. If we can identify reproducible differences between involved and contra lateral non/less involved knees in early disease we may be able to objectively track changes in serial CR images over time.

Methods: Children with newly diagnosed untreated JIA were recruited. Both knees were scored for disease activity on a score of 0-3. Weight-bearing antero-posterior (AP) images of both knees were captured via CR. A hydroxyapatite phantom was fixed to an unobscured region of the phosphor cartridge during all exposures. Pixel values in the phantom region were used to determine the brightness and contrast settings of the CR system allowing conversion of the whole image to values of absolute attenuation. Scattered radiation, whose random nature interferes with measurement of tissue content, was estimated based on Monte Carlo N-particle (MCNP) simulations. Measurements of bone and soft tissue content were taken at a number of repeatably identifiable regions in AP X-rays of both knee joints. The effect of overlying soft tissue in the bone regions was compensated by extracting the residual values of bone vs soft tissue plots over the full data set. Knee joints for all patients were independently assigned clinical scores (none, mild, moderate, severe). Association of clinical score categories with soft tissue and bone residual parameters was characterized by ordinal regression with the individual subject incorporated as a blocking variable.

Results: Results of 35 children and 70 knees are reported (11 had unilateral knee involvement). Mean disease duration 8.1 months (range 1-24 months). Mean age at visit time 8 years (range 1.6-16.6 years).

The analysis showed a highly significant ($p<0.0001$), direct relationship between clinical score and soft tissue, and a significant ($p=0.003$), inverse relationship between clinical score and bone residuals. Therefore, incremental differences in the clinical scores for a subject's knee joints are reflected both in the soft tissue content and reduced bone content. Regression analysis of contra lateral differences between knees indicates a significant inverse relationship between soft tissue difference and bone residual difference ($p<0.001$, $r^2=0.45$) Thus 45% of variation of the differential in bone content can be explained by the differential in soft tissue.**Conclusion:** Following appropriate image registration CR images can be used to measure peri-articular bone loss in JIA. The results obtained from standard X-rays could be of substantial value to the clinician using serial X-rays to determine joint damage over time. We are currently evaluating the CR images obtained over the 2 years of our prospective study and comparing these with disease outcome during the same time period

Disclosure: L. Pascoli, None; **A. Mc Cann**, None; **M. Stevenson**, None; **C. Mc Allister**, None; **M. E. Rooney**, None.

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Defining Spinal Inflammation in Ankylosing Spondylitis-a Correlation of Magnetic Resonance Imaging Findings with Clinical, Radiological and Laboratory Markers. Ismahan Bozbey, Sebnem Ataman, Elif Ozyurek, Atilla Halil Elhan, Derya Oztuna and Ilhan Erden, Ankara University, Ankara, Turkey

Purpose: To detect spinal inflammation by magnetic resonance imaging (MRI) in patients with ankylosing spondylitis (AS) and to investigate whether there is any relationship between MRI findings and validated methods of disease assessment.

Method: A total of 40 patients were included in this observational cross-sectional study (29 men, 11 women). The main outcome measures were Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Radiology Index (BASRI), measurement of serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and MRI of the thoracic and lumbar spine (ASspiMRI-a).

Results: The median ASspiMRI-a scores for the acute lesions were 4.5 (0.0-23.0) for T1/Gd-DTPA MRI images and 5.0 (0.0-21.0) for STIR MRI images. The median BASDAI, BASFI, BASMI and BASRI scores were 3.42 (0.0-8.7), 1.0 (0.0-7.7), 6.0 (5.0-12.0) and 8.0 (5.0-13.0), respectively. The mean ESR and CRP were 14.60±15.15 and 8.87±9.78, respectively. In this study most commonly affected vertebral unit (VU) was found as T11-T12 with both STIR and T1/Gd-DTPA MRI sequences. No singificant difference was found between T1/Gd-DTPA and STIR sequences ASspiMRI-a scores. We found significant correlations between ESR and ASspiMRI-a scores of thoracic spine and total spine, ESR and affected number of VU detected with both T1/Gd-DTPA and STIR MRI sequences. When patients on anti-tumor necrosis (TNF) therapy compared with patients not taking anti-TNF therapy, we found significant relationships with ESR, T1/Gd-DTPA ASspiMRI-a total scores, number of affected VU in thoracic spine and total spine detected with T1/Gd-DTPA MRI sequences. We found significant correlation between BASFI and number of affected VU in total spine with STIR sequences. We also found positive correlation between number of affected VU with T1/Gd-DTPA sequences and BASFI but it was not statistically significant. When we compare patients who have BASDAI ≥ 4 and BASDAI <4, no significant relationship was found between ASspiMRI-a scores.

Conclusion: Our study would suggest that use of MRI techniques in assessment and follow-up uf AS patients along with other validated methods of disease assessment. But there is need for further studies about MRI scoring systems.

Disclosure: I. Bozbey, None; **S. Ataman**, None; **E. Ozyurek**, None; **A. H. Elhan**, None; **D. Oztuna**, None; **I. Erden**, None.

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Repair of Erosions Occurs Preferentially in Patients Treated with Anti-TNF Therapy and in Joints with Clinical Improvement. C. Lukas[1], Désirée M.F.M. van der Heijde[2], Saeed Fatenejad[3] and Robert Landewé[4], [1]Lapeyronie hospital, Montpellier, France, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Wyeth Research, Collegeville, PA, [4]University Hospital Maastricht, Maastricht, Netherlands

Purpose: Negative radiographic change scores obtained under strictly blinded time-sequence conditions have raised the impression that repair of previously damaged joints may indeed occur. It is likely that – if it truly exists – repair is preferentially seen in joints with clinical improvement and in patients treated with TNF-blocking drugs. We tested this hypothesis in the TEMPO trial.

Method: Radiographs from patients of the TEMPO trial were scored twice by two readers using the Sharp/van der Heijde method, blinded to both treatment and true time sequence. Single-joint change scores in erosions were calculated and matched with single joint swelling scores. Factors expected to increase the likelihood of occurrence of both worsening and improvement of erosion over time were tested by GEE modelling (2 different models were built). The independent influence of clinical response in single joints and treatment (methotrexate, etanercept, or combination of both drugs) on 'progression' and 'repair' in single joints was investigated while adjusting for within-reads correlation.

Results: Multivariate analyses showed that worsening of erosion score in a joint was significantly increased if that joint was already damaged at study entry, clinical swelling was still persistent at the end of trial and MTX was used instead of etanercept (or combination) (data not shown), while repair was independently associated with clinical improvement of that joint and treatment with etanercept or combination ($p \leq 0.007$ for all associations).

Likelihood of single joint 'repair' in patients participating in the TEMPO trial

Compared conditions		**OR [95% CI]**	**p**
Treatment	MTX	1 (reference)	
	ETA	1.28 [1.07-1.53]	0.007
	MTX+ETA	1.33 [1.12-1.58]	0.001
Swelling	Worse/Persistent	1 (reference)	
	Improvement/None	1.57 [1.16-2.14]	0.004

Conclusion: Repair of erosions preferentially occurs in joints that show an adequate clinical response on anti-TNF treatment, while progression is seen more frequently in joints with persistent swelling, and in those receiving MTX monotherapy, preferentially if damage is already present.

Disclosure: C. Lukas, None; **D. M. F. M. van der Heijde**, Abbott, Amgen, , Centocor, Schering-Plough, UCB, Wyeth, 5 ; **S. Fatenejad**, Wyeth Pharmaceuticals, 3 ; **R. Landewé**, Abbott, Amgen, Centocor, Schering-Plough, UCB, Wyeth, 5 .

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Comparison of Structural Bone Alterations in Rheumatoid Arthritis and Psoriatic Arthritis by High-Resolution 3D Quantitative Computerized Microtomography. Christian M. Stach[1] and Georg Schett[2], [1]Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: Alterations in bone structure, such as bone erosions and osteophytes are a typical phenomenon of rheumatoid arthritis (RA) and psoriatic arthritis (PsoA) and are closely linked to bad functional outcome. Morphology of bone structure changes can be used as an important criterion for differential diagnosis between RA and PsoA. Modern therapies aim to prevent progression of structural bone changes. Early detection of bone lesions right from their onset is important for diagnosis and monitoring of disease.

Conventional radiographs have a limited sensitivity to detect very small lesions. Other techniques like ultrasound and magnetic resonance imaging (MRI) are optimal in assessing inflammation but not bone structure.

Objectives: We used a recently introduced novel imaging technique, a high resolution peripheral quantitative computed tomography (HR-pQCT) system, which allows a high-resolution assessment of bone structure and a 3 dimensional (3D) reconstruction of the entire joint surface. With this system we assessed bone structure of PsoA patients compared to RA patients and healthy subjects.

Method: MCP joints 2, 3 and 4 as far as the proximal wrist of the dominant hand from 60 patients with RA, 40 patients with PsoA and 30 healthy subjects were scanned at a resolution of 84 micrometer. Subchondral trabecular structure and cortical shell were studied by cut views and 3D reconstructions.

Results: More than 25% of healthy subjects showed structural bone changes like erosions or osteophytes. However estimating results in consideration of size position and morphology allows to distinguish bone alterations in healthy patients from alterations in patients. RA patients could be identified with a sensitivity of 0.75 and a specificity of 0.85 with a recently suggested combined score. Bone changes in especially older healthy controls resembled to those in PsoA patients However PsoA patients could be identified with a sensitivity of 0.72 at a specificity of 0.69 with the suggested combined score. RA patients and PsoA patients showed significant differences in incidence, morphology and localization of erosive lesions and osteophytes allowing distinction of RA patients and PsoA patients.

Conclusion: These data suggest that HR-pQCT is an interesting method for depicting and measuring structural bone changes in RA and PsoA patients with a high sensitivity and specificity. Evaluating these alterations could be used for differential diagnosis between rheumatoid arthritis and psoriatic arthritis. Furthermore the method could be used for monitoring disease specific lesions under therapy. Beyond this an assessment of bone structure in the ultra-distal radial bone is included in the method delivering information about bone density and potential fracture risk of distal bones.

Disclosure: C. M. Stach, None; **G. Schett**, None.

ACR/ARHP Poster Session B

Miscellaneous Rheumatic and Inflammatory Diseases II

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Prevalence of Systemic Autoimmune Rheumatic Diseases(SARDs): Regional Comparisons. S. Bernatsky[1], L. M. Lix[2], J. G. Hanly[3], M. Hudson[4], CA Peschken[5], A. E. Clarke[1], C. A. Pineau[1], P. Belisle[1] and L. Joseph[1], [1]MUHC, Montreal, QC, [2]University of Saskatchewn, Saskatoon, SK, [3]Dalhousie University, Halifax, NS, [4]McGill University, Montreal, QC, [5]University of Manitoba, Winnipeg

Purpose: Decision-makers are looking to administrative databases as a means of chronic disease surveillance, to aid in planning. Our purpose was to determine the prevalence of systemic autoimmune rheumatic diseases (SARDs) using population-based administrative data, and to compare results in three provinces representing central Canada (Quebec), western Canada (Manitoba) and the Maritimes (Nova Scotia).

Method: Cases of SARDs (including systemic lupus, scleroderma, Sjogren's syndrome, and polymyositis/dermatomyositis) were ascertained using physician billing and hospitalization data from these provinces. We based our case ascertainment approach on three different case definition algorithms, combining information from each definition by using hierarchical Bayesian latent class regression models that account for the imperfect sensitivity and specificity of each case definition. Our methods allow us to estimate SARD prevalence and assess differences across patient demographics.

Results: Using methods that account for the imperfect nature of both billing & hospitalization databases, we estimated the prevalence of SARDs to be approximately 2-3 cases per 1,000 residents. Prevalence was marginally higher in Manitoba at 2.8 cases/1,000(95% credible interval, CrI 2.7, 3.0), compared to Quebec at 2.6 cases/1,000(95% CrI 2.5, 2.6). Stratified prevalence estimates suggested similar demographic trends across provinces (i.e. greater prevalence in females-versus-males, and in persons of older age). The prevalence in older females approached or exceeded 1 in 100, which may reflect the high burden of primary Sjogren's syndrome in this group. Though stratified estimates were somewhat imprecise, they suggested a somewhat higher female:male ratio in Manitoba (approximately 8:1) compared to Nova Scotia(4:1) or Quebec(5:1). Adjusting for demographics, there was a greater prevalence in urban-versus-rural settings(less evident in Manitoba). **Conclusion:** Our results suggest that surveillance of some rheumatic diseases using administrative data may indeed be feasible and useful. Our work highlights the usefulness of using multiple data sources, adjusting for the error in each. Using these methods, we estimate that SARDs are as common as inflammatory bowel disease (estimated prevalence of about 2-3 cases/1000) & more common than HIV-related disease(1.8 cases/1000).

Disclosure: S. Bernatsky, None; **L. M. Lix**, None; **J. G. Hanly**, None; **M. Hudson**, None; **C. Peschken**, None; **A. E. Clarke**, None; **C. A. Pineau**, None; **P. Belisle**, None; **L. Joseph**, None.

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Neutrophilic Dermatosis: An Uncommon Side Effect of Azathioprine. Karen M. Sky[1], Jeff Bidinger[2], David W. Bray[2], J. Scott Henning[2] and Daniel F. Battafarano[3], [1]Brooke Army Medical Ctr, Fort Sam Houston, TX, [2]Lackland AFB, TX, [3]Brooke Army Medical Center, San Antonio, TX

Purpose: Neutrophilic dermatoses, such as Sweet's syndrome, pyoderma gangrenosum (PG) and erythema nodosum, are characterized by a reactive, sterile, pustulopapular rash with an intense neutrophilic dermal infiltrate on biopsy. These disorders can be associated with malignancy, infections, autoimmune diseases and can be drug induced. Our purpose was to report and characterize the seldom recognized association of azathioprine with the neutrophilic dermatoses.

Methods: Three patients receiving azathioprine for autoimmune diseases developed a papulopustular rash. Routine investigations including biopsies were performed. The literature was reviewed for similar cases.

Results: Two patients met revised 1982 ACR diagnostic criteria for systemic lupus erythmatosus and one patient had biopsy-proven Crohn's disease. One lupus patient, while taking 300 mg of azathioprine daily, and the patient with Crohn's, who was taking 50 mg of azathioprine daily, developed papulopustular rashes within 3 weeks of medication initiation. Biopsy results were consistent with Sweet's syndrome and Walker and Cohen criteria were met for drug-induced Sweet's syndrome. The other lupus patient developed lower extremity ulcerative lesions after 1 year of azathioprine 100 mg daily. Biopsy demonstrated a mixed infiltrate of neutrophils, lymphocytes and eosinophils. Clinical diagnosis was consistent with PG. All 3 cases met criteria for a probable adverse drug reaction based on the Naranjo algorithm. The neutrophilic dermatoses resolved after discontinuation of the azathioprine, with time to resolution ranging from 5 days for Sweet's syndrome to 5 months for PG. The patient with PG required 3 months of treatment with dapsone in addition to withdrawal of azathioprine. The patient with Crohn's was rechallenged with azathioprine and again developed the rash within 24 hours; the eruption resolved 3 days after medication discontinuation. All 3 patients had normal thiopurine methyltransferase (TPMT) levels.

Conclusion: Azathioprine may cause drug-induced neutrophilic dermatoses. Our patients developed neutrophilic dermatoses at widely varied dosages and duration of exposure to azathioprine. Azathioprine-induced neutrophilic dermatoses appear unrelated to dosage, disease process, TPMT levels or length of treatment. Physician awareness of this potential side-effect is important as the dermatoses often mimic infectious processes such as viral, atypical mycobacterial, deep fungal or disseminated candidal infections in immunosuppressed patients. Biopsy is necessary to differentiate neutrophilic dermatoses from other etiologies of papulopustular rashes and to avoid delays in diagnosis and treatment. Treatment may consist of cessation of azathioprine, supportive care and may require usual treatment for the particular dermatosis.

Disclosure: K. M. Sky, None; **J. Bidinger**, None; **D. W. Bray**, None; **J. S. Henning**, None; **D. F. Battafarano**, None.

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Cytokine Profiles of Macrophage Activation Syndrome Associated with Rheumatic Diseases. Junko Maruyama[1] and Shigeko Inokuma[2], [1]Tokyo Metropolitan Komagome Hospital, Tokyo, Japan, [2]Japanese Red Cross Medical Center, Tokyo, Japan

Purpose: Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic diseases. The aim of this study is to elucidate the cytokine profiles of MAS in relation to underlying diseases and prognosis.

Method: The clinical features and laboratory data of eighteen MAS patients with rheumatic diseases were retrospectively analyzed. Serum levels of macrophage-colony stimulating factor (M-CSF), interleukin-18 (IL-18), tumor necrosis factor-α, interleukin-6, interferon-□, ferritin and □$_2$-microglobulin (□$_2$MG) were obtained. These data were compared between rheumatological conditions and between those with and without a fatal outcome.

Results: Of the 18 MAS patients, 8 had underlying systemic lupus erythematosus (SLE), 7 adult-onset Still disease (AOSD), 1 mixed connective tissue disease (MCTD), 1 rheumatoid arthritis (RA) and 1 antiphospholipid syndrome. Two SLE, 1 MCTD and 1 RA patients had a fatal outcome. The serum M-CSF and IL-18 levels were substantially elevated in all of the patients. In the SLE patients, M-CSF level was higher than IL-18 level (median: 4,224 vs. 1,336 pg/mL, p=0.012), and it was the reverse case in the AOSD patients (5,883 vs. 228,350 pg/mL, p=0.0017). The serum M-CSF and □$_2$MG levels were significantly higher in the patients who died than those who survived (M-CSF: 18,245 vs. 3,404 pg/mL, p=0.019; □$_2$MG: 18.8 vs. 5.4 mg/dL, p=0.0058).

Conclusion: The cytokine profiles associated with MAS differed between SLE and AOSD patients. The SLE patients showed a prominent increase in serum M-CSF level, as did AOSD patients in serum IL-18 level. Patients with a fatal outcome had higher serum M-CSF and □$_2$MG levels. The data suggests that aggressive treatment for patients with MAS and these profiles should be promptly started.

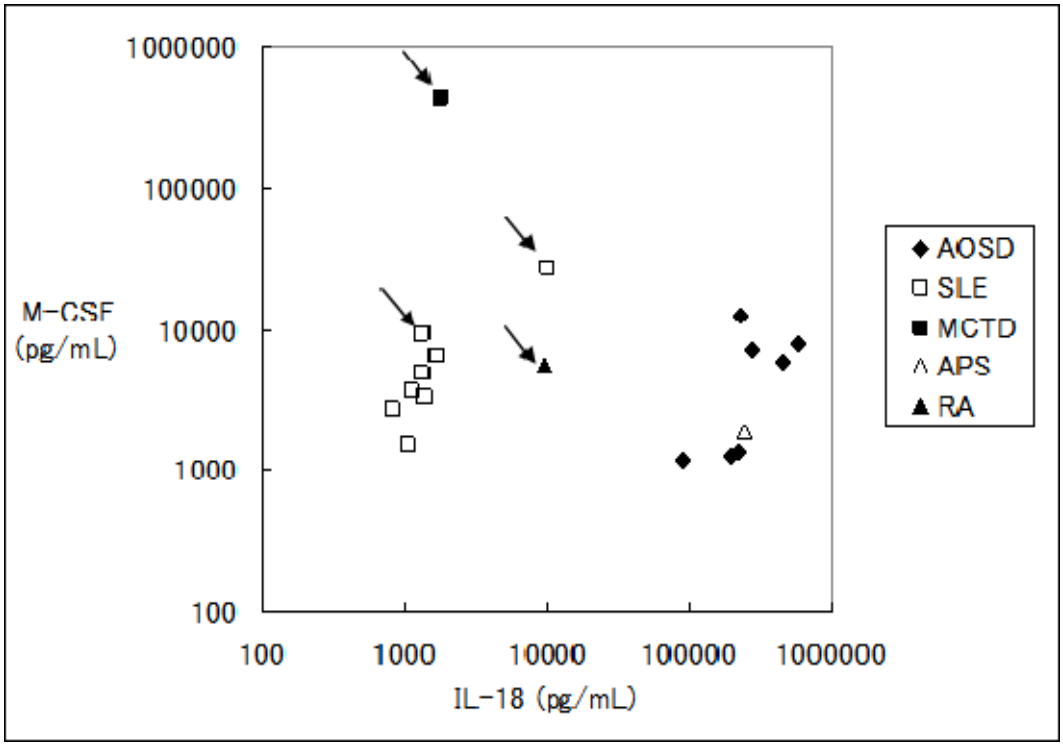

Figure. Serum M-CSF and IL-18 levels in MAS patients with rheumatic diseases. Patients with a fatal outcome (arrows) had higher serum M-CSF levels.

Disclosure: J. Maruyama, None; **S. Inokuma**, None.

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Comparison of Serum Biomarkers Across Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis Patient Populations Prior to and Following Treatment with Golimumab, a Human Anti-TNF Antibody. C. Wagner[1], H. Fan[1], M. U. Rahman[2], A. Beutler[1], B. Hsu[1], M. Elashoff[3] and S. Visvanathan[1], [1]Centocor R&D, Inc, Malvern, PA, [2]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [3]Elashoff Consulting, Redwood City, CA

Purpose: To compare and contrast biomarker profiles prior to and following golimumab (GLM) treatment across 3 populations of pts with rheumatic disease: active rheumatoid arthritis (RA) despite MTX; psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Methods: Sera were collected at wks0, 4 and 14 from a subset (approx. 100) pts from each of the GLM Phase 3 trials: GO-FORWARD (active RA despite MTX), GO-REVEAL (active PsA despite conventional treatment) and GO-RAISE (active AS despite conventional treatment). Across the 3 studies, pts were randomized to either PBO, 50mg or 100mg GLM in the presence or absence of MTX or other conventional medications. Samples were tested for select inflammatory markers (Quintiles Laboratories) and bone and cartilage markers (Pacific Biometrics) and protein profiling using multi-analyte profiles (Rules Based Medicine). Change from baseline in markers was compared between GLM±MTX and PBO+MTX using ANOVA on the van der Waerden normal scores and t-tests. Pathway analysis comparisons were made using Ingenuity software and data were compared using the Fisher Exact test.

Results: Prior to treatment**,** there were no biomarkers that were significantly different between the GLM±MTX and the PBO±MTX treatment groups that were consistently observed across the 3 pt populations. In the GLM±MTX groups at wk4, there were 7 biomarkers (haptoglobin, CRP, serum amyloid P, thyroxine binding globulin, MMP-3, ICAM-1, TNFRII) that showed significant changes from baseline ($p<0.05$) relative to PBO±MTX that were similarly modulated across the 3 populations. At wk4 following GLM±MTX treatment, there were 4 other commonly modulated biomarkers between the AS and PsA populations, 3 more markers similarly modulated between RA and PSA, and one more commonly modulated marker between the AS and RA populations. At wk14, in the GLM±MTX groups there were 9 markers (CRP, MIP1β, haptoglobin, MMP-3, α1anti-trypsin, thyroxine binding globulin, serum amyloid P, PAI-1 and TIMP-1) that were significantly ($p<0.05$) changed from baseline relative to PBO±MTX across all populations. In the PsA and AS populations, 5 other markers were commonly changed from baseline at wk14 compared with only 1 additional marker for each population relative to the RA pts. Signaling pathways significantly impacted in response to treatment with GLM±MTX at wk4 and 14 across the different populations included the acute phase response, TREM1, hepatic fibrosis, coagulation system, and leukocyte extravasation.

Conclusion: GLM impacts multiple proteins and signaling pathways associated with TNFα in the RA, PsA and AS disease processes. Principal component analysis indicates all 3 diseases are notably different from normal individuals, and pts with RA have a somewhat distinct overall profile compared with AS and PsA. Select markers were modulated across all populations of pts treated with GLM±MTX, with some overlap of modulated markers across all diseases.

Disclosure: C. Wagner, Centocor RD, Inc , 3 ; **H. Fan**, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 ; **A. Beutler**, Centocor Research and Development, Inc., 3 ; **B. Hsu**, Centocor Research and Development, Inc, 3 ; **M. Elashoff**, Centocor, Inc., 5 ; **S. Visvanathan**, Centocor Research and Development, Inc, 3 .

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A Nucleolar-Pattern ANA in Patients with Idiopathic Interstitial Pneumonia Suggests Underlying Connective Tissue Disease. Aryeh Fischer, Jeffrey J. Swigris, Roland M. du Bois, Joann Z. Gillis, Marc D. Cohen, Richard T. Meehan and Kevin K. Brown, National Jewish Health, Denver, CO

Background: Interstitial lung disease (ILD) comprises a diverse group of disorders characterized histologically by varying degrees of inflammation and fibrosis. Although ILD may have no identifiable etiology, (i.e. idiopathic interstitial pneumonia [IIP]), ILD is a common finding in patients with known connective tissue disease (CTD) or can be the forme fruste presentation of CTD. Recent data suggest that, CTD-related ILD has a more favorable prognosis than IIP, arguing for the careful evaluation of patients presenting with an idiopathic ILD in an attempt to identify underlying CTD.

Purpose: To examine the significance of a nucleolar-pattern ANA in patients presenting with idiopathic ILD, and specifically, to describe the clinical characteristics of 15 patients presenting with IIP and a nucleolar-pattern ANA over a 12 month period at a tertiary ILD referral center.

Method: Retrospective cohort of 21 patients presenting to a tertiary referral center for evaluation of IIP and found to have a nucleolar-pattern ANA. All patients underwent comprehensive ILD evaluation that included consultation with a board certified rheumatologist. The diagnoses of systemic sclerosis (SSc) and undifferentiated connective tissue disease (UCTD) were rendered by the treating physicians and confirmed on retrospective review based on current or proposed criteria.

Results: Based on collaborative pulmonary and rheumatology evaluations, 17 (81%) were diagnosed with SSc and 4 (19%) with UCTD. As a result of the connective tissue disease (CTD) classification, most patients (81%) were treated with medication regimens containing a cytotoxic agent.

	N=21
Median age (range)	66 (35-86)
Female gender	10 (48%)
Smoking history	12 (57%)
Duration of dyspnea in months (range)	12 (1-60)
Median ANA titer (range)	1:640 (80-5120)
Anti-Scl-70	3 (14%)
Other antibodies	2 anti-Ro, 1 with combined PM-Scl, RF, CCP, dsDNA
Arthritis	7 (33%)
Sclerodactyly	5 (24%)
Telangiectasia	12 (57%)
Raynaud's	13 (62%)
Digital edema	8 (38%)
Esophageal dysmotility (N=18)	14 (67%)
FVC%	59 (30-105)
DLCO%	43 (15-82)
ILD pattern by HRCT	12 NSIP (57%), 7 UIP (33%), 2 NSIP/UIP (10%)
Surgical lung biopsy (N=6)	2 NSIP, 2 UIP, 1 NSIP+OP, 1 OP

Conclusion: Cross-specialty collaboration with rheumatology is helpful to detect occult forms of CTD-related ILD. The presence of a nucleolar-pattern ANA in patients with IIP suggests underlying CTD – and SSc in particular – and should prompt rheumatologic evaluation. Clinicians involved in the evaluation of patients with ILD should ensure that ANA testing includes pattern determination in addition to titer.

More precise ILD classification will allow for studies that determine optimal therapy and prognosis based on specific ILD type.

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Performance of Three Self-Report Measures in Connective Tissue Disease-Associated Interstitial Lung Disease. Jeffrey J. Swigris, David B. Sprunger, Roland M. du Bois and Aryeh Fischer, National Jewish Health, Denver, CO

Background: Interstitial lung disease (ILD) is a common manifestation of connective tissue disease (CTD) and often associated with significant morbidity and mortality. Dyspnea, a ubiquitous symptom in ILD patients, leads to physical inactivity and a number of adverse downstream effects, including deconditioning, loss of independence, and impaired emotional well-being and overall quality of life. Two patient self-report questionnaires, University of California San Diego shortness of breath questionnaire (UCSD-SOBQ) and Dyspnoea-12 questionnaire (D12Q), have been developed and validated to reflect pulmonary impairment in chronic lung disease – yet have not been validated for CTD-related ILD. The multidimensional health assessment questionnaire (MDHAQ) has proven useful in clinical care of CTD patients and assesses function, pain and patient global estimate of status with a composite "RAPID" score.

Purpose: We conducted this study to assess scores from the MDHAQ, UCSD-SOBQ, and D12Q in patients with CTD-related ILD.

Method: The study cohort was comprised of 48 consecutive subjects with CTD-related ILD who completed the MDHAQ, UCSD-SOBQ, and the D12Q, and underwent pulmonary function testing (PFT). Pearson product moment correlation coefficients were used to examine the relationship between different outcomes.

Results: See table.

Conclusion: There was moderately strong correlation between components of the MDHAQ, FVC correlated significantly with day-to-day functioning but with no other component of the MDHAQ, DLCO did not correlate with any MDHAQ component, there was significant correlation between dyspnea and day-to-day functioning, psychological well-being, fatigue, and global status, there was moderately strong correlation between scores from the two dyspnea instruments. Serial self-reporting with the MDHAQ, UCSD-SOBQ, and D12Q helps with ongoing clinical care of CTD-ILD patients and provides valid and reproducible measures of clinical disease activity.

	FNHAQ	PSHAQ	Pain	Fatigue	Global	R30	Stiff	Joint	FVC	DLCO	D12	UCSD
FNHAQ	-	0.6 <.0001	0.45 0.002	0.5 0.0006	0.62 0.0006	0.74 <.0001	0.24 0.3	0.53 0.0002	-0.37 0.04	-0.29 0.13	0.36 0.02	0.58 <.0001
PSHAQ	0.6 <.0001	-	0.44 0.002	0.62 <.0001	0.58 <.0001	0.62 <.0001	0.53 0.01	0.62 <.0001	-0.04 0.8	-0.06 0.8	0.48 0.001	0.53 0.0003
Pain	0.45 0.002	0.44 0.002	-	0.51 0.0003	0.68 <.0001	0.88 <.0001	0.46 0.03	0.67 <.0001	-0.03 0.9	-0.1 0.6	0.22 0.14	0.14 0.4
Fatigue	0.5 0.0006	0.62 <.0001	0.51 0.0003	-	0.6 <.0001	0.63 <.0001	0.7 .0004	0.45 0.002	0.02 0.9	0.1 0.6	0.3 0.04	0.36 0.02
Global	0.62 0.0006	0.58 <.0001	0.68 <.0001	0.6 <.0001	-	0.91 <.0001	0.5 0.02	0.6 <.0001	-0.08 0.7	0.1 0.6	0.43 0.004	0.34 0.03
R30	0.74 <.0001	0.62 <.0001	0.88 <.0001	0.63 <.0001	0.91 <.0001	-	0.51 0.01	0.69 <.0001	-0.15 0.4	-0.09 0.6	0.38 0.01	0.36 0.02
Stiff	0.24 0.3	0.53 0.01	0.46 0.03	0.7 .0004	0.5 0.02	0.51 0.01	-	0.3 0.2	0.17 0.5	0.32 0.2	0.23 0.3	0.17 0.5
Joint	0.53 0.0002	0.62 <.0001	0.67 <.0001	0.45 0.002	0.6 <.0001	0.69 <.0001	0.3 0.2	-	0.01 0.9	0.02 0.9	0.3 0.06	0.35 0.02
FVC	-0.37 0.04	-0.04 0.8	-0.03 0.9	0.02 0.9	-0.08 0.7	-0.15 0.4	0.17 0.5	0.01 0.9	-	0.8 <.0001	-0.26 0.16	-0.6 0.0004
DLCO	-0.29 0.13	-0.06 0.8	-0.1 0.6	0.1 0.6	0.1 0.6	-0.09 0.6	0.32 0.2	0.02 0.9	0.8 <.0001	-	-0.34 0.08	-0.53 0.004
D12	0.36 0.02	0.48 0.001	0.22 0.14	0.3 0.04	0.43 0.004	0.38 0.01	0.23 0.3	0.3 0.06	-0.26 0.16	-0.34 0.08	-	0.4 0.004
UCSD	0.58 <.0001	0.53 .0003	0.14 0.4	0.36 0.02	0.34 0.03	0.36 0.02	0.17 0.5	0.35 0.02	-0.6 0.0004	-0.53 0.004	0.4 0.004	-

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Synovial Sarcoma Presenting as Soft Tissue Rheumatic Syndrome: A Challenge for the Clinician. Leticia C. Baena-Ocampo[1], Federico Bertrand[2], Saul León[1], L. Miguel Linares[1], Genaro Rico[1] and Carlos Pineda[3], [1]Instituto Nacional de Rehabilitacion, Tlalpan D.F, Mexico, [2]Escuela de Medicina Universidad la Salle, Mexico City, Mexico, [3]Instituto Nacional de Rehabilitacion, Mexico City, Mexico

Purpose: Despite of its name, synovial sarcoma (SS) does not have synovial origin; it arises from the primitive mesenchyme of the tendon sheath and fascial aponeurosis. SS is frequently misdiagnosed as a benign soft tissue condition. Will be described clinical and histopathological features of patients with diagnosis of SS, emphasizing those manifestations that may lead to misdiagnosis of soft tissue rheumatism.

Methods: A retrospective chart, imaging and pathological review of consecutive histopathological proved cases of SS, registered between January 2000 to December 2008 at Pathology department.

Results: 27 patients (17 male 63%; 10 female, 37%). The average age at diagnosis was 28 years (11 – 63 years). Anatomical regions involved were, lower limb in 93% (foot 11, 41%; ankle 4, 15%; knee 4, 15%; thigh 4, 15%; inguinal region 2, 7%) and upper limb in 2, 7%; arm and forearm,). Signs and symptoms at presentation were: pain in all cases, palpable deep-seated swelling or periarticular mass in 22 (81%), decrease range of joint motion in 44%, weight loss in 18%, skin color changes in 7%, and muscle weakness in 4%.

Eleven (34%) were initially diagnosed as benign rheumatologic conditions: synovitis in 3 (11%); fasciitis in 2 (7%); Mortonxs neuroma; arthrofibrosis; chronic bursitis, synovial cyst, bunionette, and tarsal tunnel syndrome 1 (4%) instance each. The time elapsed since onset of symptoms to diagnosis was 40 months (1 – 156 months). The more advantageos imaging studies that helped defining the presence of a soft-tissue tumor were MRI, CT-scan, scintigraphy and X-rays. In all cases a biopsy was necessary to confirm diagnosis. Surgical treatment was: amputation in 11 patients (41%), block resection in 6 (22%) and marginal resection in 5 (18.5%). Five patients (18.5%) refused surgical treatment. The size of the tumors ranged from 1-to 12 cm. Histological subtype was identified as monophasic (24/89%) and biphasic (3/11%). Patients were classified according to the TNM system as follows: T1N0M0 19(70%), T2N0M0 2(7%) T2N1M0 1(4%) and T2N1M1 5(19%). They also were categorized according to the IRSG classification as type I in 18 patients (67%), type II in 2 (7%), type III in 6 (22%) and type IV in 1 case (4%). Ten (37%) patients underwent adjuvant chemotherapy and radiotherapy. The average follow-up was 51 months (6-96), local recurrences and metastases were in 7 patients (26%). Fifteen (55.5%) patients were alive and disease free.

Conclusion: It is essential that the Rheumatologist retain awarness of SS, particularly in young male patients presenting with slow growth, palpable, deep-seated soft tissue swelling or mass in close proximity to joints of the lower extremities. SS should be included in the differential diagnosis of soft tissue rheumatic syndromes.

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Safety of Golimumab, A New Human Anti-TNF α Antibody, in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis: An Analysis of Pooled Data From Randomized, Double-Blind, Placebo-Controlled Studies. Jonathan Kay[1], R. M. Fleischmann[2], Edward C. Keystone[3], M. U. Rahman[4], E. C. Hsia[4], M. K. Doyle[4], B. Hsu[4], M. Mack[5], J. Zrubek[5], A. Beutler[5], J. Braun[6] and Arthur Kavanaugh[7], [1]University of Massachusetts Memorial Medical Center, Worcester, MA, [2]Metroplex Clinical Research Center, Dallas, TX, [3]Professor of Medicine/University of Toronto, Toronto, ON, [4]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [5]Centocor R&D, Inc, Malvern, PA, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]U of California San Diego, San Diego, CA

Purpose: To analyze pooled data from 5 GLM Phase 3 trials (and a Phase 2 trial for serious infections, malignancies, and deaths).

Methods: Placebo (PBO) or GLM(50or100mg) was given SC q4wks in the ongoing Phase3 trials. About half of the pts received MTX; smaller proportions received other DMARDs. Analyses included safety data from randomized pts receiving ≥1 dose of study agent. Since pts could crossover from PBO to GLM or increase GLM dose from 50 to 100mg in cases of inadequate response, pts may appear in more than one column.

Results: As of June 2, 2008,639 pts received PBO,1233 GLM50mg, and 1286 GLM100mg. Most pts (75%RA, 90%PsA, 89%AS) had GLM exposure ≥52wks. Duration of f/u was >2-fold longer for GLM vs PBO. The proportions of pts with any adverse event (AE), AE leading to d/c, serious AEs, and clinically important hepatobiliary events were similar across groups (Table). All cases of tuberculosis (6 pts;3 each for GLM 50&100 mg) and histoplasmosis (1 pt,GLM100mg) were in GLM group. Overall occurrence of injection site reactions was low; most were mild, and only 2 cases led to study agent d/c. No GLM-treated pt developed anaphylaxis or serum sickness-like reaction. There was no statistically significant difference in the incidences of serious infection or death per 100pt-yrs of f/u between GLM 50/100 mg and PBO. Malignancies occurring during the 5 Phase 3 plus 1 Phase 2 trials included skin cancers, solid tumors, and lymphoma. In comparison to

Surveillance Epidemiology and End Results (SEER) database for malignancies, the incidence of malignancies in GLM-and PBO-treated pts was similar to that expected in general US population.

Table:

Pooled GLM safety. Values are mean or %pts.

	PBO +/-MTX	**GLM 50mg +/-MTX**	**GLM 100mg +/-MTX**
Pts treated	**639**	**1233**	**1286**
Wks of follow-up/ No of administrations	27.1/6.6	58.9/14.9	67.9/17.2
Any AE / D/C due to AE	73.4% / 4.9%	82.1% / 5.9%	82.3% / 6.8%
Serious AE	8.8%	10.9%	14.0%
Pts with inj site rxn Inj with inj site rxn	2.8%/0.4% (31/8389)	8.2%/0.7%(249/35516)	12.4%/1.1%(469/41777)
Clinically important hepatobiliary AE	1(0.2%)	3(0.2%)	5(0.4%)
Pts with serious infections	18/674 (2.7%)	37/1301 (2.8%)	65/1356 (4.8%)
Total pt-yrs f/u / incidence per100ptyrs	344 / 5.81	1467 / 3.20	1757 / 5.07
95% CI	3.55, 8.97	2.35, 4.26	4.07, 6.23
Deaths	1/674 (0.1%)	4/1301 (0.3%)	7/1356 (0.5%)
Total pt-yrs f/u / incidence per100ptyrs	344 / 0.29	1467 / 0.27	1757 / 0.40
95% CI	(0.01, 1.62)	(0.07, 0.70)	(0.16, 0.82)
Malignancies			
Total pt-yrs f/u / median pt-yrs f/u	343 / 0.5	1459 / 1.2	1747 / 1.5
Observed (incidence per 100 pt-yrs)	2.04	1.37	1.09
95% CI	(0.82, 4.20)	(0.84, 2.12)	(0.65, 1.70)

SIR=standardized incidence ratio (observed/expected)

Conclusion: GLM was generally well tolerated, with overall low rates of d/c due to AEs and injection site reactions. Safety profiles were similar between GLM 50 and 100mg.

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Adult's Onset Still's Disease: a Review of 41 Cases. Anna Moltó[1], Elena Riera[2], Alejandro Olivé[1], Javier Narváez[3], Susana Holgado[1], Maria M. Bianchi[3], Lourdes Mateo[1], Pilar Santos[3], Xavier Tena[1] and Joan Miquel Nolla[3], [1]Hospital Germans Trias i Pujol, Badalona, Spain, [2]Hospital Universitari Mútua de Terrassa, Terrassa, Spain, [3]Hospital Universitari de Bellvitge, Barcelona, Spain

Purpose: To describe the clinical manifestations, treatment, evolution, prognosis and functional class of 41 patients with Adult Onset Still's Disease (AOSD)

Method: Retrospective study (1984-2006). Multicenter study. Setting: Hospital Universitari Germans Trias i Pujol and Hospital Universitari de Bellvitge. All patients fulfilled Yamaguchi et al Classification criteria. (J Rheumatol 1992; 19: 424-430).

Results: Forty one patients were included (15 men and 25 women). Mean age at diagnosis: 38.19 years (SD 15,59). All patients had spiking fever. Typical exanthema was present in 38 patients (92,6%). Symptoms were preceded by sore throat in 37 (90,2%). Forty patients (97,5%) had polyarthralgia and 36 (88%) had arthritis; polyarticular pattern in 29 (80,5%) and oligoarticular in 7 (19,5%). Knees, wrists and ankles were the joints more often involved. Other clinical manifestations were lymphadenopathy in 17 patients (41%), hepato/splenomegaly in 16 (39%), abdominal pain in 5 (12%), pleuritis in 6 (14,6%), pericarditis in 5 (12%) and interstitial pneumopathy in 2 (4,8%). Most of the patients had leucocytosis and neutrophilia and a remarkable elevation of ESR and CRP. Liver function abnormalities were detected in 50% of the patients . Hyperferritinemia was preset in (83%.)

The course of the disease was monocyclic in 44% of the patients and polycyclic/chronic in 56%.

ASA or NSAID controlled the disease in seven patients (17,5%) and prednisone in eleven (27,5%). Immunosupressors were required in 55% of the patients and in seven of them (17,5%) a biological treatment with TNF-a blockers or anakinra had to be added in order to control the disease.

Currently 17 patients (42,4%) are free of disease without treatment (mean duration of disease 114.74 moths. SD: 105,65) and totally asymptomatic (72.55 moths; SD 30,75). Fifteen patients had a monocyclic patterns and a polycyclic-chronic in two.

Twenty-three patients (57,5%) are still on treatment (duration of disease: 110.96 months. SD: 70,22). Three patients treated with ASA, 1 with NSAID and prednisone, 8 with NSAID, prednisone and methotrexate, 4 with methotrexate alone and 7 with NSAID, prednisone, methotrexate and a biological treatment. Four patients had a monocyclic course and 19 a polycyclic-chronic one.

Erosions were present in nine patients (22%). ACR class were as follows: 29 (72,5%) class I, 7 (17,5%) class II, 2 (5%) class III and 2 (5%) class IV.

Conclusion: The clinical manifestations were similar to other series. A fevered polyarthritis was the most frequent clinical presentation. Patient with monocyclic course tend to have a better prognosis. Fifty six percent of the patients had a polycyclic-chronic course and required an aggressive treatment. Radiological bony erosions were present in 22% of patients. Most patients are in functional class I.

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Value of Bone Erosions in Undifferentiated Arthritis. Mohamed M. Thabet, Tom W.J. Huizinga, Désirée M.F.M. van der Heijde and Annette H.M. van der Helm-van Mil, Leiden University Medical Center, Leiden, Netherlands

Purpose: In rheumatoid arthritis (RA) the presence of bone erosions at baseline is the most significant predictor for a severe destructive disease course, while the prognostic importance of erosive joints for disease outcome in undifferentiated arthritis (UA) is unknown. UA has a variable disease course; 40-50% of patients remit spontaneously, while about one third develop RA. Identifying UA patients who will develop RA is essential to initiate early DMARD therapy. This study aims to identify the predictive value of erosive joints for the disease outcome in UA as measured by the development of RA as well as persistent arthritis.

Methods: Baseline radiographs of hands and feet of 518 UA patients were evaluated for erosions using a clinical definition (erosion score of SENSE method) as well as the Sharp-van der Heijde (SHS) method. After 1 year, patients were re-assessed for the fulfilment of the 1987 ACR classification criteria for RA. Persistent arthritis was defined as the absence of sustained remission. The mean follow-up was 8 ± 3 years.

Results: 31% (n= 160) of UA patients fulfilled the 1987 ACR classification criteria for RA within 1 year. During the whole period of follow up 39.6% (n= 205) UA patients achieved clinical remission, while the remaining 60.4% (n= 313) had persistent arthritis (remained UA, developed RA or developed a disease other than RA).

At baseline, 28.6% of UA-patients had erosive joints. The presence of 2 or more erosive joints showed a positive predictive value for RA-development of 53% and for persistent disease of 68%. Patients with erosions that did not develop RA were less often ACPA+, RF+ and had lower CRP, ESR and number of swollen joints compared to those who developed RA. Feet erosions were equally predictive compared to hand erosions. 74% of erosive UA patients who developed RA received DMARDs in their first year compared to 66% in non-erosive UA patients who developed RA, meaning that the presence of erosions didn't affect the physician's decision to start DMARDs. 32.5% of UA patients with two or more erosive joints achieved sustained remission.

Conclusion: Unlike RA, the presence of baseline erosions in UA is not always predictive for an unfavourable disease outcome and are on their own insufficient to establish treatment decisions. Although feet erosions are not part of the 1987 ACR criteria, feet erosions have at least equal predictive performance for RA development and disease persistency.

Table: Predictive value for the progression from UA to RA within 1 year using different cut-off values for erosiveness.

	Nr of Erosive Joints	n	PPV	NPV	Specificity	Sensitivity	LR+	LR-	AUC (SEM)
Hands and/or Feet	≥ 1	148	45	75	77	42	1.8	0.75	0.60 (0.028)
	≥ 2	83	53	73	89	28	2.5	0.81	0.58 (0.028)
	≥ 3	50	54	72	94	17	2.6	0.89	0.55 (0.028)
	≥ 4	24	54	70	97	8	2.6	0.95	0.53 (0.028)
	≥ 5	15	73	70	99	7	6.2	0.94	0.53 (0.028)
Hands	≥ 1	103	44	72	84	28	1.7	0.86	0.56 (0.028)
	≥ 2	38	55	71	95	13	2.8	0.91	0.54 (0.028)
	≥ 3	18	56	70	98	6	2.8	0.96	0.52 (0.028)
	≥ 4	9	67	70	99	4	4.5	0.97	0.52 (0.028)
	≥ 5	7	71	70	99	3	5.6	0.97	0.51 (0.028)
Feet	≥ 1	89	49	73	87	28	2.2	0.83	0.57 (0.028)
	≥ 2	42	60	72	95	16	3.3	0.89	0.55 (0.028)
	≥ 3	18	67	70	98	8	4.5	0.94	0.53 (0.028)
	≥ 4	9	67	70	99	4	4.5	0.97	0.52 (0.028)
	≥ 5	5	80	70	100	3	8.9	0.98	0.51 (0.028)
Erosion Location	Wrist	7	63.6	69.8	98.9	4.4	3.9	0.97	0.52 (0.028)
	MCP	5	38.5	69.3	97.8	3.1	1.4	0.99	0.50 (0.028)
	PIP	5	55.6	69.5	98.9	3.1	2.8	0.98	0.51 (0.028)
	MTP	23	67.6	71.6	96.6	14.4	4.3	0.88	0.56 (0.028)

n= number of UA patients positive for this cutoff
LR+= Positive Likelihood Ratio
LR-= Negative Likelihood Ratio

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Catecholamines Are Produced by Immune Cells During Arthritis: New Aspects of Neuro-Immunological Response. Silvia Capellino, Kristina Weber, Alexander Fassold, Christine Wolff and Rainer H. Straub, University Hospital Regensburg, Regensburg, Germany

Purpose: In our previous study, we demonstrated that synovial cells produce catecholamines during chronic inflammation such as rheumatoid arthritis (RA) and osteoarthritis (OA). The modulation of intracellular catecholamine balance by reserpine or other drugs that influence catecholamine handling reduced TNF release by 60% in primary synovial cells and reduced paw swelling *in vivo* in arthritic DBA/1J mice. The aim of our study was to understand whether catecholamine-producing cells differentiate in the synovial tissue or whether external organs can be the source of these cells. Furthermore, we investigated when these cells start to play a role in the inflammatory process.

Method: Collagen type II induced arthritis was induced in DBA/1J mice. Twenty mice were immunized and 20 mice served as controls. At day 0, 7, 14, 21, 28, 35, 42, 49, 60 and 80 after first immunization, two mice of each group were sacrificed. Lymph nodes, thymus, adrenal glands and spleen were fixed and frozen until use. Paws and bone marrow were fixed, decalcified and then frozen until use. Immunofluorescence staining was performed by using a primary antibody against vesicular monoamine transporter-2 (VMAT-2).

Results: Fourteen days after first immunization, the density of VMAT-2 positive cells in bone marrow started to be significantly higher in arthritic mice compared to controls, and density reached the maximum difference at day 42 after first immunization. In the spleen in arthritic mice compared to control animals, the most marked difference in density of VMAT-2 positive cells was found at day 49. The splenic density of VMAT-2 positive cells was higher in arthritic compared to control mice already at day 21. VMAT-2 positive cell density was very low in the joints of control mice compared to arthritic animals, but a difference was already detected 14 days after first immunization. The maximum density of VMAT-2 positive cells in joints from arthritic mice was reached at day 35, and density subsequently decreased until day 80 but still remained higher than in control animals.

Conclusion: These results demonstrate for the first time that catecholamines are produced and stored by immune cells also in the early asymptomatic phase of arthritis. Moreover, catecholamines are produced by immune cells not only at the site of inflammation but also in bone marrow and spleen.

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A Study of Myelodysplastic Syndrome Patients and Rheumatologic Phenomena. Christopher M. Burns and Daniel A. Albert, Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Purpose: Patients with myelodysplastic syndrome (MDS) frequently have associated rheumatic diseases, including rheumatoid arthritis and polymyalgia rheumatica. In some (and perhaps all) patients, the cytopenias in MDS are immune-mediated. It is theorized that immune activation in the bone marrow in MDS may lead to systemic autoimmunity and rheumatic manifestations. Additionally, with the advent of stimulating factor therapy to reduce transfusion requirements, treatment-related autoimmune conditions are becoming more common in MDS. We reviewed the rheumatologic findings in all the MDS patients in our institution over a 2 year period.

Method: We conducted an IDX (238.75 myelodysplastic syndrome) based search of the records from Dartmouth Hitchcock Medical Center from 2006 to 2008 to identify patients with MDS, and then reviewed each chart for rheumatologic phenomena

Results: We found 7 patients with bone marrow biopsy-proven MDS. All patients were older, 58 to 87 years of age, and 5 of 7 have died. Two patients had necrotizing vasculitis one with a lung nodule and the other with mononeuritis multiplex. One male patient had palmar fasciitis with exudative pleural effusions (non malignant) similar to ovarian carcinoma. One patient had inflammatory arthritis negative for crystal, malignancy or infection. One patient had steroid responsive extremity pain similar to hypertropic osteoarthropathy with no evidence of periarthritis. One patient had nonmalignant mediastinitis with exudative pleural effusions. One patient had typical ANCA+ Wegener's Granulomatosis.

Conclusion: MDS patients had a wide range of rheumatic findings and every patient had some immune-mediated phenomena, but only one patient had a typical rheumatic disease. In some cases, treatment of the rheumatic disease ameliorated the MDS. Immune activation within the bone marrow milieu is a feature of MDS. A subset of patients responds to immunosuppressive agents with reduced transfusion requirements and slower progression to acute myelocytic leukemia. Multiple components of the immune system are involved, including cytolytic CD8 cells directed at tumor neoantigens expressed on hematopoietic cells with the trisomy 8 mutation, cytokines such as TNF-a, and NK cells. It is postulated that local immune activation induces systemic autoimmunity and rheumatic manifestations. We conclude that a host of rheumatic conditions, both classic and atypical, can occur in the setting of MDS or its treatment. Rheumatologists should be vigilant for MDS when diagnosing rheumatic conditions, particularly atypical presentations or in the setting of unexplained cytopenias. We propose an MDS-related Autoimmune Disease Registry as a data-base for these cases with the hope that patterns will emerge to help elucidate the pathogenesis of both MDS and rheumatic diseases.

Disclosure: C. M. Burns, None; **D. A. Albert**, None.

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Ex Vivo Softlaser Treatment Inhibits the Synovial Expression of Vimentin and á-Enolase, Potential Autoantigens in Rheumatoid Arthritis. Geza Balint[1], Klara Barabas[1], Zsuzsanna Zeitler[2], Jozsef Bakos[2], Akos Pethes[3], Erzsebet Nagy[3], Tamas Lakatos[3], Peter Balint[1] and Zoltan Szekanecz[4], [1]National Institute of Rheumatology and Physiotherapy, Budaoest, Hungary, [2]National Frederic Joliot-Curie Research Institute of Radiation Biology, Budapest, Hungary, [3]Polyclinic of the Hospitalier Brothers pf St John Of God, Budapest, Hungary, [4]University of Debrecen medical and Health Sciences Center, Debrecen, Hungary

Purpose: Softlaser therapy has been used to treat rheumatic diseases for almost 30 years. It has been postulated that the major effects of laser treatment may not be dependent on thermic but rather cellular, photochemical mechanisms. Yet, the exact cellular and molecular mechanism of action has not been elucidated. Thus, in this study, we wished to determine the effects of ex vivo laser irradiation of rheumatoid arthritis (RA) synovial tissues on protein expression profile.

Method: Synovial samples of 5 RA patients undergoing knee surgery were irradiated by near-infrared diode laser. A dose of 25 J/cm^2 was applied. Untreated paired synovial samples obtained from the same patient served as negative controls. Synovial protein expression was assessed using two-dimensional polyacrylamide gel electrophoresis followed by mass spectrometry.

Results: Altogether 12 proteins exerted differential expression after laser irradiation in comparison to untreated controls. Laser treatment resulted in decreased expression of α-enolase in 2, vimentin, haptoglobin and complement component 3 (C3) precursors in 4 samples. The expression of other proteins including HSP70, HSP96, lumican, osteoglycin and ferritin increased upon laser therapy.

Conclusion: Both α-enolase and vimentin have been considered as important autoantigens that are readily citrullinated and drive autoimmunity in RA. Other differentially expressed proteins may also be implicated in the pathogenesis of RA. Softlaser therapy may be effective in RA in part by the suppression of the expression of potential autoantigens in RA.

Disclosure: G. Balint, None; **K. Barabas**, None; **Z. Zeitler**, None; **J. Bakos**, None; **A. Pethes**, None; **E. Nagy**, None; **T. Lakatos**, None; **P. Balint**, None; **Z. Szekanecz**, None.

796

Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Antibody Profile in Patients with Morphea. Cristián Vera Kellet and Jan P. Dutz, Univ of BC, Vancouver, BC

Purpose: Systemic autoimmune disease is more common in patients with morphea. Rheumatoid factor (RF) has been reported in a subset of patients with morphea, but the significance of this remains unclear. Anti-cyclic citrullinated peptide antibody (anti-CCP) is a sensitive and specific marker for the diagnosis of rheumatoid arthritis that has not been examined in morphea.The aim of this study was to determine the presence of RF and anti-CCP antibodies in patients with morphea, who attended a Dermatology Connective Tissue Disease Clinic and to assess any association between the presence of RF and anti-CCP, disease activity and clinical manifestations.

Method: This was a retrospective study. We reviewed all the charts of patients with a diagnosis of morphea assessed between January 2006 and December 2008.

Results: 54/72 patients with morphea had at least one RF assessment (43 women and 11 men, mean age 44.3 years). RF was negative (< 10 kU/L) in 48 % (26/54) of patients, and it was positive either at low (>10 kU/L and <30 kU/L) or high (>30 kU/L) titers in 52% (28/54). There was a trend to generalised versus linear morphea in patients with a high positive RF compared to those with a negative RF (9/12 versus 14/26). There was a trend to active disease in those patients with a high positive RF compared to those with a negative RF (12/12 active versus 21/26). In 2 patients, RF reverted from positive to negative when their disease became clinically inactive. Only 7/28 patients with a positive RF had co-morbid diseases previously associated with RF: Hepatitis B or C (3), autoimmune liver disease (1), SLE (1), SLE/ MCTD (2). All patients tested for anti-CCP (including 9/12 with high positive RF and 7/16 with low titre RF) were negative.

Conclusion: RF can be positive in morphea, and it may be used as a marker of disease activity. Anti-CCP was not positive in any of our patients with morphea. RF seropositivity is not a marker of RA in patients with morphea and likely connotes B-cell dysregulation in these patients.

Disclosure: C. Vera Kellet, None; **J. P. Dutz**, None.

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Rheumatic Manifestations in Common Variable Immunodeficiency. Satoko M. Kanahara, Leonard H. Calabrese, David Lang and Eamonn S. Molloy, Cleveland Clinic, Cleveland, OH

Purpose: Common variable immunodeficiency (CVID) is a primary humoral immunodeficiency typified by hypogammaglobulinemia and recurrent sinopulmonary infections. A proportion of CVID patients may develop autoimmune diseases, especially autoimmune cytopenias. CVID has been associated with rheumatic diseases, but these have not been well-characterized to date. This study was conducted to evaluate the prevalence, disease course and treatment of rheumatic manifestations in CVID.

Method: Retrospective chart review of patients with diagnosis of CVID from the Rheumatology and Allergy and Immunology Departments at the Cleveland Clinic.

Results: The cohort of 45 CVID patients consisted of 32 females and 13 males, with median age of 51 years (range 19 - 78). 86% of the patients were Caucasian, 8.8% were African American. The median duration of disease since diagnosis was 5 years (range 1 - 41). 23/45 (52%) of the patients had at least one recorded history of moderate to severe joint pain, 85% of whom had multiple joint involvement. 14 patients were considered to have fibromyalgia, 9 were diagnosed with osteoarthritis and 5 patients had a clearcut inflammatory arthropathy. There were no proven cases of septic arthritis. Of the patients with inflammatory arthropathy, all 5 were treated with low doses of glucocorticoids, 4 with hydroxychloroquine, and 2 patients with methotrexate. One patient, with a concomitant diagnosis of ulcerative colitis, was sequentially treated with infliximab and abatacept. No patients developed radiographic erosions or joint deformity. There were no serious infectious complications associated with immunosuppressive therapy, although 4/5 patients were receiving immunoglobulin replacement therapy. One patient underwent synovectomy. Two patients with osteoarthritis had successful total knee replacement, without infectious complications.

Conclusion: Moderate to severe joint pain was noted in 23/45 (52%) in this cohort of CVID patients. Inflammatory arthritis was noted in 11% of the patients. In general, only modest immunosuppressive therapy was required for control of joint inflammation, and no patients developed destructive arthritis. As CVID patients may present initially with autoimmune phenomena even before onset of recurrent infections, rheumatologists should be cognizant of this disease association to facilitate diagnosis of CVID, and to minimize use of immunosuppressive therapy. Judicious use of immunosuppressive therapy appears to be well tolerated, once patients are established on immunoglobulin replacement therapy.

Disclosure: S. M. Kanahara, None; **L. H. Calabrese**, None; **D. Lang**, None; **E. S. Molloy**, None.

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Do Patients with Elderly Onset Rheumatic Chronic Conditions Receive the Same Treatment as Their Younger Counterparts?

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Purpose: To determine whether there are differences in the therapeutic management of patients with chronic rheumatic conditions according to the age of disease onset

Method: Secondary analysis of five nationwide databases from studies on different chronic rheumatic conditions conducted by the Spanish Society for Rheumatology. The conditions included were osteoarthritis (OA), Paget's disease of bone, gout, and rheumatoid arthritis (RA), this latter with and without exposure to biologics. An elderly onset was considered if patients were ≥ 65 years old at the beginning of symptoms. We used propensity score matching to select 1:1 controls with similar disease duration and disease than cases but with onset before 65 years.

Results: OA (n=373 per group): Analgesics, mainly acetaminophen, were more frequently used in elderly patients (p=0.003). By contrast, NSAIDs were more frequently used in younger patients (p=0.02) but also in two thirds of the elderly. We did not find significant differences between the two age groups in the prescription of SYSADOA or hyaluronic acid. **Paget's** (n=223 per group): No differences in the number or type of pharmacologic treatment were found between both age groups. **Gout** (n=87 per group): Patients with elderly onset gout have different predisposing conditions that younger patients, but the treatment of the acute attack and the chronic hypouricemic therapy was similar in the two groups. **RA** (n=109 patients per group): Although young patients were more frequently positive for RF (p=0.008), and despite a similar disease activity, elderly patients had a worse HAQ (p=0.002) and Larsen score (p=0.02). Patients with elderly onset RA (EORA) received less frequently NSAIDs (p=0.0001) and biologics (p=0.03). **RA exposed to biologics** (n=149 per group) There were no differences in the type and survival time of biologics. However, elderly patients receive more frequently other DMARDs different from MTX in combination with biologics. Total adverse events (AE), especially infections, severe AE, and AE leading to death were more frequent in EORA (p<0.05).

Conclusion: Patients with elderly onset rheumatic chronic conditions receive less NSAIDs than young patients. Despite the same disease activity and worse functional capacity and structural damage, EORA patients receive biologics less frequently. Although the survival time of biologics is similar between both age groups, EORA have more severe AE, especially infections.

Disclosure: I. Villa, None; **L. Carmona**, None; **M. A. Descalzo**, None; **V. M. Martinez-Taboada**, None.

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Therapeutic Potential of Apoptosis Induction by Anti-Fas Antibody in Inflammatory Arthritides. Kazuo Yudoh[1], Rie Karasawa[1], Chika Sawa[1] and Kusuki Nishioka[2], [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]St Marianna University School of Medicine, Kawasaki Kanagawa, Japan

Purpose: We postulated that agents to inhibit synovitis may have a potential as anti-inflammation, pain relief, and also as an anti-arthritis drug to inhibit the bone and cartilage degeneration. Our previous studies demonstrated that the anti-Fas antibody induces cellular apoptosis of synovial fibroblasts in vitro. In the current study, we studied whether or not anti-Fas antibody has a therapeutic potential to protect against the joint destruction in the inflammatory joint disease.

Method: In vitro: To clarify the inhibitory effect of anti-Fas antibody on syovitis, we used the co-culture system with the transwell chamber. Synovial fibroblasts, macrophages and chondrocytes were isolated from synovium and cartilage in patients undergoing arthroplastic knee surgery. In the presence or absence of anti-Fas antibody (CH-11), the cells were incubated with 10 ng/ml TNF-α. Then, catabolic responses were analyzed.

In vivo: We studied whether or not CH-11 reduced bone and cartilage degeneration in the rat model of arthritis. In each rat, the left knee joint was treated by an intra-articular injection of the appropriate CH-11 by 26 gauge needle once weekly over 8 weeks. The right knee joint was also treated by an intra-articular injection of control solution as a control once a week over 8 weeks. The severity of cartilage damage was histologically monitored at 4 and 8 weeks.

Results: 1) To examine the effect of CH-11 on catabolic activity in chondrocytes, the levels of MMPs (MMP-1, -3, -13) in the culture were measured using an enzyme-linked immunosorbent assay kit. TNF-a stimulated the production of MMP-1 and -13 in control cultures. CH-11 significantly decreased the TNF-a-induced excess production of MMP-1 and -13. 2) The effects of CH-11 on chondrocyte apoptosis and production of proteoglycan from chondrocytes were examined in chondrocyte-macrophage co-culture system. Chondrocyte apoptosis was significantly accelerated by treatment with TNF-α. Interestingly, in the presence of CH-11, TNF-α-induced apoptosis was significantly decreased compared with their control counterparts. 3) To study the protective effect of CH-11 on anabolic activity of chondrocytes, the levels of proteoglycan production by chondrocytes were analyzed**.** In the presence of TNF-a, production of proteoglycan was inhibited in the co-culture. Whereas, even in the presence of TNF-α, CH-11 maintained the production of proteoglycan from the cells. 4) In the control right knee of model rat, the joint showed a progression of surface fibrillation of articular cartilage, chondrocyte clustering, abnormal deposition of chondrocytes, a decreased cell density with cartilage thinning and subchondral bone destruction. In contrast, the cartilage in the left knees that had been treated with CH-11 showed less severe bone and cartilage degeneration in comparison with the control knee joint.

Conclusion: Our results indicate that apoptosis induction by anti-Fas antibody may have a therapeutic potential to protect against the progression of bone and cartilage degeneration in inflammatory arthritides.

Disclosure: K. Yudoh, None; **R. Karasawa**, None; **C. Sawa**, None; **K. Nishioka**, None.

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What Percentage of Patients with UIA Will Evolve to a Classifiable Arthritis in One Year? - A Systematic Literature Review. Pooneh S.Akhavan[1], Louis Bessette[2], B. Haraoui[3], J. Pope[4] and Vivian P. Bykerk[5], [1]university of Toronto, Toronto, ON, [2]Groupe de Recherche en Rhumatologie et Maladies Osseuses, Sainte-Foy, QC, [3]Institut de Rhumatolgie de Montreal, Montreal, QC, [4]St Joseph Health Care, London, ON, [5]Mt Sinai Hospital, Toronto, ON

Purpose: Several studies have been conducted to show the role of early treatment in patients with undifferentiated inflammatory arthritis (UIA) and its potential protective role in disease evolution to a differentiated disease such as rheumatoid arthritis. The objective of this study was to determine what percentage of patients with UIA would evolve to a classifiable arthritis in one year.

Methods: We conducted a systematic literature review of all English language prospective studies, which followed a cohort of early inflammatory arthritis for one year. We searched Medline, EMBASE and the Cochrane Library (up to January 2009), as well as abstracts from ACR (2007-2008) and EULAR (2007-2009). Inclusion criteria consisted of adult patients with clinical evidence of UIA that did not fulfill criteria for any definitive inflammatory disease. If, in a study the cohort was a mixed population of undifferentiated and differentiated

arthritis, it was included if the number (or percentage) of patients who had initially presented as an undifferentiated disease and then evolved to differentiated arthritis at one year, was indicated in the paper. Reviews, guidelines and case reports were excluded.

Results: 25 studies were included. The diagnosis of rheumatoid arthritis was reported in 19 studies at one year. 10.7% - 55% of patients presenting with UIA were diagnosed with rheumatoid arthritis at one year. In 9 studies, 28-72% of these undifferentiated cases remained undifferentiated at one year. Remission was reported in 8-32% of these patients in 6 studies.

Conclusion: A significant percentage of patients who present with UIA may still have evidence of inflammatory arthritis at one year, but the range was wide and may be related to the inclusion criteria of each cohort as many selected for probable RA. This further supports the importance of long term follow up and early therapy initiation in these patients.

Disclosure: P. S.Akhavan, Abbott Laboratories, 9 ; **L. Bessette**, None; **B. Haraoui**, None; **J. Pope**, None; **V. P. Bykerk**, Abbott Laboratories, 2 .

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Efficacy of Influenza and Meningococcal Vaccinations in Healthy Subjects Exposed to Canakinumab 300 Mg s.c.: Preliminary Study Results. A. Chioato[1], E. Noseda[1], S. D. Felix[2], M. Stevens[3], G. Del Giudice[4], S. Fitoussi[5] and A. Kleinschmidt[6], [1]Novartis Institutes for Biomedical Research, Basel, Switzerland, [2]Novartis, Basel, Switzerland, [3]EMStat Ltd, Leics, United Kingdom, [4]Novartis Vaccines and Diagnostics, Siena, Italy, [5]Medicis, Poitiers, France, [6]Novartis Vaccines and Diagnostics, Marburg, Germany

Purpose: Interleukin-1β (IL-1β), a key mediator of immune and inflammatory responses, is implicated in the etiology of autoinflammatory diseases. Canakinumab, a fully human anti IL-1β antibody, provides selective, potent, and sustained blockade of IL-1β. Since IL-1β is also involved in the immune response triggered by some vaccines, mainly using aluminum salts adjuvant, the aim of this study was to evaluate the efficacy of influenza and meningococcal vaccinations in healthy subjects exposed to canakinumab.

Method: Open-label, parallel group, randomized, single-center study in healthy subjects (aged 18–45 years; weight ≥50 Kg) with negative tuberculin skin test (PPD 5 TU) (<5 mm induration) or at low environmental tuberculosis (TB) risk. Main exclusion criteria: vaccination during previous year; use of prescription drugs and history of autoimmune or other significant systemic diseases. After measurement of antibody (Ab) titers at baseline, subjects were randomized to a single canakinumab 300 mg s.c. dose or no treatment (control group), followed by inactivated influenza or conjugated meningococcal vaccinations i.m. after 2 weeks. The primary efficacy variable was the response (≥2 fold increase in Ab titer in ≥2/3 serotypes) to influenza vaccination at 4 weeks post-vaccination in subjects treated with canakinumab compared to the control group. Secondary efficacy variables were the response to influenza or meningococcal vaccines at different fold thresholds and time points.

Results: 50 out of 112 subjects screened were randomized (1:1) to canakinumab or control groups. Preliminary results for 38 subjects (19 canakinumab, 18 control [1 withdrew, lost to follow up]) are presented. Response to influenza vaccination (≥2 fold in ≥2/3 serotypes) at 4 weeks was shown in 18/19 subjects in the canakinumab group compared to 18/18 subjects in the control group; a response of ≥4 fold increase at 4 weeks was produced in 17/19 subjects and 17/18 subjects in the two groups, respectively. A response of ≥2 fold increase at 6 weeks was produced in 100% of subjects in both groups. Both treatments induced a comparable response to meningococcal vaccine (Table 1). A formal statistical analysis will be completed when the final results are available.

Conclusion: Blockade of IL-1β by canakinumab does not appear to interfere with the efficacy of influenza and meningococcal vaccinations, as measured by the Ab titers, despite the fact that the adjuvant property of aluminum salts is mediated by IL-1β. A protective (more than 4 fold) immune response to influenza and meningococcal vaccinations at 4 weeks has been achieved in 73.7–89.5% of subjects treated with canakinumab. Further studies are needed to replicate the results in patients with autoinflammatory conditions treated with canakinumab.

Table 1. Antibodies titer increase in vaccination groups vs. controls at different time points

Vaccine	Fold increase in titer	Time post-vaccination (weeks)	Canakinumab (%)	Control (%)
Influenza (≥2/3 serotypes)	≥2	4	94.7	100.0
	≥2	6	100.0	100.0
	≥4	4	89.5	94.4
Meningococcal	≥4	4	73.7	72.2
	≥4	6	73.7	72.2

Disclosure: A. Chioato, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **E. Noseda**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **S. D. Felix**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **M. Stevens**, Novartis Pharmaceutical Corporation, 5 ; **G. Del Giudice**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **S. Fitoussi**, None; **A. Kleinschmidt**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 .

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Rheumatoid Arthritis Patient Self Assessment of Disease Activity as Determined by Joint Count Compared to Clinical Joint Count Assessment by Trained Master's Student. Juliana Tricta, Maggie J. Larché, Karen A. Beattie, Andy KO Wong, William G. Bensen, Viktoria Pavlova, George Ioannidis and Jonathan D. Adachi, McMaster University, Hamilton, ON

Purpose: To assess the correlation between rheumatoid arthritis (RA) patients' self assessment of swollen and tender joint count and clinical joint count performed by a trained Master's student in order to better understand patients' awareness of disease activity.

Methods: In a cross-sectional study, 126 rheumatoid arthritis patients were asked to perform a 28 joint count assessment on themselves. These patients were not given any instructions on how to perform the joint count. They were simply asked to indicate which of the 28 joints they thought were swollen and/or tender upon performing a self examination. Once the RA patients had completed the self assessment a Master's student performed the joint count. The Master's student received training on completing a 28 joint count assessment from a Registered Nurse Specialist, with close agreement in their findings.

Results: The mean (SD) age and symptom duration of the 126 patients was 56.9 (14.5) years and 11.3 (12.2) years, respectively. On the self assessment of 28 joint count the median (range) swollen joint count and tender joint count was 2 (0-25) and 6 (0-28) respectively. For the trained Master's student the results were 5 (0-19) swollen and 5 (0-28) tender. There were high levels of correlation between patients' self assessment and trained Master's student for tender joint counts (0.72, $p<0.01$) and lower correlation for swollen joint counts (0.43, $p<0.01$) (Spearman's).

Conclusion: Patients' self assessment shows significant correlations with trained assessor's joint count, with higher levels of correlation for tender than swollen joint counts. However, at the moment, it is not known if there is an agreement regarding which joints assessed as swollen and/or tender by the patient and the Master's student.

Disclosure: J. Tricta, None; **M. J. Larché**, None; **K. A. Beattie**, None; **A. K. Wong**, None; **W. G. Bensen**, Wynne Tech, 4 ; **V. Pavlova**, None; **G. Ioannidis**, None; **J. D. Adachi**, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, Procter and Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, Bristol-Myers Squibb, 5, Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter and Gamble, Roche, Sanofi-Aventis, Wyeth, Bristol-Myers Squibb, 8 .

ACR/ARHP Poster Session B

Muscle Biology in Rheumatic Diseases

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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The Microvasculature in the Vicinity of the Fascia as the Primary Target in Myopathy of Dermatomyositis: Detection of Fasciitis and Analysis of the Process of Inflammatory Progression by En Bloc Biopsy and Magnetic Resonance Imaging. Ken Yoshida, Maimi Yanagimachi, Eigo Takahashi, Kenichiro Hirai, Kentaro Noda, Kazuhiro Furuya, Taro Ukichi, Isamu Kingetsu, Daitaro Kurosaka and Akio Yamada, Jikei University School of Medicine, Tokyo, Japan

Background: It is generally known that inflammatory cells are concentrated around the intramuscular blood vessels in dermatomyositis (DM). However, in some cases, muscle biopsies reveal no inflammatory cells in the muscle. In such cases, short tau inversion recovery (STIR) magnetic resonance imaging (MRI) occasionally shows the abnormal hyperintensity of the fascia and perimuscular sites. Although in DM, histological findings of intramuscular inflammation have been well documented, those of inflammation in the vicinity of the fascia have hardly been reported.

Purpose: To investigate whether the fascia is a common site of inflammation, and to analyze the process of inflammatory progression.

Method: STIR MRI and en bloc muscle biopsy, which involves resection of muscle, fascia, subcutaneous tissue, and skin altogether, were performed on ten patients with newly diagnosed adult onset DM. Paraffin sections from the biopsy specimens were stained with hematoxylin-eosin. Immunohistochemistry was performed to identify T lymphocytes (CD3, CD4, CD8), B cells (CD20, CD79a), and macrophages (CD68). Severity of inflammatory cell infiltration around the small blood vessels in the vicinity of the fascia and in the muscle (vascular inflammation score: VIS) was evaluated using a four-grade scoring system.

Results: In all cases, STIR MRI revealed abnormal hyperintensity in predominantly peripheral sites of the muscle compared with central sites. En bloc biopsy showed no inflammatory cell infiltration around the small blood vessels in the muscle in three cases, but in all cases, it showed inflammatory infiltrates in the vicinity of the fascia (i.e. fasciitis). Immunohistochemistry showed that CD4+ T and CD20+ B cells were mainly present among inflammatory cells. In cases where the period from muscle symptom appearance to en block biopsy on the site was less than eight weeks (“early group”), VIS of the fascia was significantly higher than that of the muscle. On the other hand, in cases where en block biopsy was performed more than eight weeks after appearance of muscle symptoms (“late group”), VIS of the fascia did not differ significantly compared with that of the muscle.

Conclusion: Fasciitis was histologically observed in all of ten patients with adult onset DM. Our study showed that microvasculature in the vicinity of the fascia is a favorite site of inflammation in similarity with intramuscular microvasculature and likely to be the primary target in myopathy of DM. These results suggest that the inflammatory cell infiltration around the small blood vessels originates from the vicinity of the fascia into the muscle in myopathy of DM.

Disclosure: K. Yoshida, None; **M. Yanagimachi**, None; **E. Takahashi**, None; **K. Hirai**, None; **K. Noda**, None; **K. Furuya**, None; **T. Ukichi**, None; **I. Kingetsu**, None; **D. Kurosaka**, None; **A. Yamada**, None.

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Increased Ferritin Predicts Development and Severity of Acute Interstitial Lung Disease as Complication of Dermatomyositis. Takahisa Gono, Yasushi Kawaguchi, Kae Takagi, Yasuhiro Katsumata, Ikuko Masuda, Akiko Tochimoto, Yuko Ota, Masako Hara and Hisashi Yamanaka, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Dermatomyositis (DM) is characterized by the inflammation of skin and muscle, occasionally complicated with interstitial lung disease (ILD), which is classified into two subsets, acute/subacute interstitial pneumonia (A/SIP) and chronic interstitial pneumonia (CIP). A/SIP is of prime importance in the clinical management of patients with DM because it is an intractable and a life-threatening complication. It is imperative to establish a novel strategy for the diagnosis of early-stage A/SIP as a complication of DM. The aim of this study is to determine whether serum ferritin is a potential predictive indicator of the occurrence of A/SIP in DM.

Method: Sixty-four patients with DM were enrolled, including 19 with A/SIP, 24 with CIP and 21 without ILD. The study also enrolled 35 patients with polymyositis (PM), including 3 with A/SIP, 14 with CIP and 18 without ILD. Clinical manifestations and laboratory data were obtained from medical records.

Results: Serum ferritin on admission was significantly higher in DM than that in PM (median 269 ng/mL versus 73.6 ng/mL, $P = 0.0003$ by Mann-Whitney U test). Particularly, it was extremely high in DM with A/SIP (median: 790 ng/mL, range: 121-8330 ng/mL), which was the highest value among those in all subsets of patients with DM/PM ($P < 0.0001$ versus DM with CIP; $P = 0.0002$ versus DM without ILD; $P < 0.0001$ versus DM without A/SIP; $P < 0.0001$ versus PM; $P < 0.0001$ versus PM with ILD). Moreover, we evaluated the association of patients with high concentrations of serum ferritin with the complication of A/SIP. High level of serum ferritin was defined as □ 500 ng/mL according to diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis 2004. As the result of the comparison in the occurrence of A/SIP between the groups with high and low concentrations of serum ferritin in DM patients, the frequency of A/SIP was significantly higher in the group with high concentrations of serum ferritin ($P = 0.0009$, odds ratio = 6.9 and 95% confidence interval = 2.1-22.4). The cumulative survival rate for 6 months was 62.7% in patients with DM with A/SIP. Moreover, the cumulative survival rate was significantly lower in the group with ferritin levels □1500 ng/mL than the rate in the group with ferritin levels <1500 ng/mL ($P = 0.016$).

Conclusion: Serum ferritin can be useful as a predictor of the occurrence of A/SIP and correlates with the prognosis of A/SIP in DM. Because elevated ferritin levels can be associated with macrophage activation, we speculate that alveolar macrophage activation may be involved in the pathogenesis of AIP/SIP with DM.

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The Relationship Between the Vitamin D Receptor Gene and Anti-155/140 Antibodies in UK Caucasians with Idiopathic Inflammatory Myositis. Sabrina Kapoor[1], Robert G. Cooper[2], Hector Chinoy[2], William Ollier[3], L. R. Wedderburn[4], Neil J. McHugh[5] and Chester V. Oddis[6], [1]Russells Hall Hospital, Dudley, England, [2]Hope Hospital, Salford, [3]University of Manchester, Manchester, United Kingdom, [4]UCL, London, United Kingdom, [5]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [6]University of Pittsburgh, Pittsburgh, PA

Purpose: Idiopathic inflammatory myopathy (IIM) is a complex disease and is due to the interaction of environmental and genetic risk factors. A latitudinal gradient exists for IIM, whereby increasing ultraviolet (UV) exposure is associated with the preferential development of dermatomyositis (DM), rather than polymyositis (PM). IIM also displays seasonal variation which may be related to UV exposure. A further DM-specific antibody, anti-155/140, has recently been described in adult and juvenile DM. VDR and other single nucleotide polymorphisms (SNPs) putatively related to UV susceptibility are associated with other conditions where UV exposure is an aetiological risk factor, including prostate cancer and multiple sclerosis. We hypothesise that such polymorphisms are associated with the development of IIM.

Method: 362 UK Caucasian adult and juvenile onset cases were recruited from the UK Adult Onset Myositis Immunogenetic Collaboration and the Juvenile Dermatomyositis (JDM) National Registry and Repository. They were compared to 287 matched Caucasian controls: PM, n=112; DM, n=98; myositis/overlap, n=64; JDM, n=88, females 71%, mean age of disease onset adults 49+/-14 years, juveniles 6+/-3.6 years. SNPs were selected from the following genes: VDR, glutathione S-transferase pi 1, melanocortin 1 receptor and tyrosinase due to their putative functional role or because they had been used in previous studies. SNPs were removed from further analysis where the assay success rate was <90% and sample success <80%. **Results:** were thus available for 38 SNPs. Circulating antibodies (anti-Jo-1, PL-7, PL-12, EJ, OJ, KS, Mi-2, SRP, U1/U3-RNP, Ku, PM-Scl, 155/140) were detected using immunoprecipitation.

Results: All 38 SNPs conformed to Hardy Weinberg equilibrium in controls. No SNP was associated in the overall or traditional clinical sub-groups. Anti-155/140 antibodies were detected in 29 patients, all of whom had DM. Possession of the A allele in a VDR haplotype tagging SNP (rs2254210) was associated with possession of anti-155/140 antibodies (51%), compared to both controls (33%) (odds ratio 2.1, 95% confidence interval 1.2-3.8, p=0.006) and anti-155/140 antibody negative cases (36%) (1.9, 1.1-3.4, p=0.01). Associations for this SNP were observed independently in the juvenile and adult 155/140 (+) sub-groups. No other significant associations were observed in any of the remaining serologically-defined sub-groups.

Conclusion: The rs2254210 polymorphism in the VDR gene is a possible risk factor in juvenile and adult anti-155/140 positive DM patients.

Disclosure: S. Kapoor, None; **R. G. Cooper**, None; **H. Chinoy**, None; **W. Ollier**, None; **L. R. Wedderburn**, None; **N. J. McHugh**, None; **C. V. Oddis**, Genentech and Biogen IDEC Inc., 9 .

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High Burden of Cardiovascular Risk in Patients with Inflammatory Myositis. Irene Z. Whitt and Steven R. Ytterberg, Mayo Clinic, Rochester, MN

Purpose: To determine cardiovascular (CV) risk and its predictors in patients with inflammatory myositis.

Methods: We performed a cross-section, observational study of adult patients seen in our clinic in the past year with probable or definite dermatomyositis, polymyositis, or connective tissue disease associated myositis based on Bohan and Peter criteria. Patients with inclusion body myositis and cancer-associated myositis were excluded. Standard CV risk factors were assessed and a determination was made of low, moderate, or high CV risk based on the current guidelines outlined by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III-revised or ATP III R). Univariate relationships between each potential predictor and each risk group were examined. A multivariable linear regression model was then developed for each significant ($p < 0.05$) risk marker.

Results: 63 patients met the inclusion criteria and had CV risk assessment. The distribution of CV risk is tabulated below.

	Framingham Risk of CV Event in 10 years		
Patients	Low Risk (<10%)	Moderate Risk (10-20%)	High Risk (>20%)
Total, n (%)	19 (30.2)	24 (38.1)	20 (31.8)
Candidates for lipid-lowering agent, %	11	54	89
With hypertension, %	6	67	63
With SBP < 130, %	74	58	50

Across all risk levels, 51% of patients would be placed on a lipid-lowering agent according to the current ATP III R guidelines.

Several variables were assessed in univariate analysis with ordered logit regression. Significant correlations were found for: hypertension (HTN) ($p=0.001$) and age ($p=0.005$). Nonsignificant correlations were observed for: gender, hyperlipidemia, BMI, disease duration, current prednisone dose, current smoking status, chronic renal insufficiency, and family history of coronary heart disease. In a multivariate analysis, HTN was the only independent predictor of higher CV risk ($p=0.004$, $R^2=0.155$).

Conclusion: Patients with inflammatory myositis have a high burden of CV risk. HTN was the only independent predictor of CV risk. However, only about 50% of high-risk hypertensive patients achieved the recommended goal of SBP<130. Although 51% of patients in this cohort would be candidates for a lipid-lowering agent, there is concern for worsening myositis with lipid lowering therapy. Further research is needed to determine the safety of using statins in patients with inflammatory myositis.

Disclosure: I. Z. Whitt, None; **S. R. Ytterberg**, None.

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Development of the Novel Assay System for Detecting Anti-SRP Autoantibodies: The Clinical, Histopathological, and Immunogenetic Features in Japanese Patients. Michito Hirakata[1], Tetsuya Takada[1], Yuko Kaneko[1] and John A. Hardin[2], [1]Keio University School of Medicine, Tokyo, Japan, [2]Albert Einstein College of Medicine, New York, NY

Purpose: The signal recognition particle (SRP) is a cytoplasmic ribonucleoprotein consisting of the 7SL RNA and six associated polypeptides (72, 68, 54, 19, 14 and 9 kDa) which mediates the translocation of newly synthesized proteins across the endoplasmic reticulum. Autoantibodies to the SRP are known to be associated with a distinct clinical subset of refractory myositis characterized histologically by "necrotizing myopathy". Definitive detection of anti-SRP autoantibodies requires imunoprecipitation of HeLa cell extracts, a complicated technique not available in clinical laboratories. Previous studies have shown that anti-SRP antibodies recognize predominantly the SRP-54 kDa subunit on immunoblots. For this reason, we examined the usefulness of a new enzyme-immunoassay method using the human recombinant SRP-54 kDa protein as the test substrate.

Method: We developed a fluoroenzyme-immunoassay (Elia: Phadia, Germany) for detecting antibodies against the biotinylated human SRP-54 kDa protein expressed by recombinant baculovirus (AcMNPV) infection of Sf9 insect cells (Diarect AG, Germany). We studied18 Japanese patients identified among 1,500 patients with polymyositis /dermatomyositis and various other connective tissue diseases whose sera immunoprecipitated the 7SL RNA. These sera were tested in the Elia system and results were correlated with clinical, immunogenetic, and myopathic histopathological features in the patient donors.

Results: All 18 sera that immunoprecipitated 7SL RNA, strongly recognized the recombinant SRP-54 kDa in Elia. This result was confirmed by immunoblots, while none of 50 anti-SRP-negative sera whose sera contained other myositis–specific antibodies including anti-synthetase, and anti-U1 RNP antibodies, showed any reactivity. Sixteen of 18 (89%) patients with anti-SRP antibodies had myositis. Among them, 9 of 14 (64%) showed refractory myositis resistant to corticosteroid therapy, and all 8 patients whose muscle biopsy specimen were studied histologically in detail, showed muscle fiber necrosis and regeneration without inflammatory infiltration. It should be noted that two patients (11%) had rheumatoid arthritis without any features of myositis. Eight of 18 patients (44%) with anti-SRP had DR 8 (DRB1*0802/08032), compared to 20% of healthy controls.

Conclusion: These studies indicate that the novel Elia assay is a useful tool for detecting anti-SRP autoantibodies. Patients who are positive in this assay system have a clinical profile that is consistent with the features of myositis, and identify a subgroup of patients with necrotizing myopathy resistant to corticosteroid therapy, consistent with the patient group identified by the classical immunopreicpitation assay.

Disclosure: M. Hirakata, None; **T. Takada**, None; **Y. Kaneko**, None; **J. A. Hardin**, None.

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Peripheral Immunological Biomarkers and Laser Doppler Imaging in Idiopathic Inflammatory Myopathy. Nora Anna Szabo[1], Peter Szodoray[2], Szilveszter Lukacs[3], Sandor Sipka[4], Margit Zeher[1] and Katalin Danko[1], [1]Division of Clinical Immunology, 3rd Department of Internal Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary, [2]University of Oslo, Oslo, Norway, [3]East Surrey Hospital, Redhill, United Kingdom, [4]Laboratory of Immunology, 3rd Department of Internal Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary

Purpose: Polymyositis (PM), dermatomyositis (DM) and antisynthetase-syndrome (aSS) are members of Idiopathic Inflammatory Myopathies (IIM). In the pathogenesis of IIMs microvasculature abnormalities often present, partly driven by autoimmune processes.

Method: Evaluation of immunological parameters from blood samples, as well as laser Doppler imaging was carried out in 28 PM, 12 DM and 12 aSS patients and 20 age and sex-matched healthy individuals. Comprehensive analysis was performed between IIM patients and healthy control group; also subgroup analysis was carried out among the three different group of IIM patients. Peripheral blood samples were measured and assessed for number and percentage of CD4+ and CD8+ T cells, activated T-cells, naïve- and memory T-and B cells, intracellular and solubile IFN-g, IL-4, and IL-10 levels. Laser Doppler imaging was performed in every case, by assessing the steady state cutaneous perfusion (SSCP) of the non-dominant hand.

Results: Regarding CD3+, CD4+, CD8+ T lymphocytes there was no significant difference in the cell numbers and percentage between IIM and healthy control group. Among subgroup analysis CD4+ T cells were increased in DM compared to PM ($p=0.032$). There was a predominance of CD8+ T cells in PM patients compared to results of DM patients ($p=0.012$). Elevated percentage of CD4+ and CD8+ CD45RA+/CD62L- (terminally differentiated effector memory) T cells was found in IIM ($p<0.0001$), while in the control group the percentage of CD4+ and CD8+ CD45RA-/CD62L+ (central memory) T lymphocytes were significantly higher ($p<0.0001$). The comparison of LDI values of IIM patients with the control group indicated that all subgroups of IIM had decreased SSCP ($p<0.05$). Within subgroup analysis, SSCP was non-significantly decreased in PM and DM compared to aSS.

Conclusion: Our findings support the idea that patients with IIMs have microcirculation abnormalities, reflected by decreased SSCP detected by LDI and specific peripheral immunological defects. We believe that the therapeutical modulation of these immunological irregularities might be an important element in the future management of microcirculation abnormalities in IIMs.

Disclosure: N. A. Szabo, None; **P. Szodoray**, None; **S. Lukacs**, None; **S. Sipka**, None; **M. Zeher**, None; **K. Danko**, None.

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Anti-p155/140 (anti-TIF1γ) Autoantibodies in Patients with Cancer Associated Myositis Detected in a Single Centre. Jiri Vencovsky[1], Herman Mann[2], Ivana Putova[1], Zoe Betteridge[3], Harsha Gunawardena[3] and Neil J. McHugh[3], [1]Institute of Rheumatology and Department of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic, [2]Institute of Rheumatology, Prague 2, Czech Republic, [3]Royal National Hospital, Bath, United Kingdom

Purpose: Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory diseases of striated muscles. About 10-20% cases are associated with various forms of cancer (CAM). No specific signs and symptoms can distinguish between patients with CAM from patients without malignancy. Recently described autoantibodies to p155/140 antigen (Anti-TIF1γ = transcriptional intermediary factor 1-γ) have been associated with an increased frequency of cancer in patients with DM. The aim of this study was to determine the frequency of anti-p155/140 antibodies in the cohort of patients with PM/DM and relate the presence of these antibodies to an occurrence of cancer.

Method: Patients with definite or probable diagnosis of PM/DM (n=153) from a single centre were investigated for the presence of a cancer. CAM was defined as any cancer occuring within the timeframe of 3 years of the onset of myositis. Sera were mixed with protein-A-sepharose beads and immunoprecipitated with [^{35}S]-methionine-labelled K562 cell extract. Proteins were fractionated by SDS-PAGE and analysed by autoradiography.

Results: Seventeen patients (11%) were diagnosed with CAM. Sixteen patients (10.5%) had anti-p155/140 antibodies. In patients with CAM, 7 (41%) had anti-p155/140, whereas in non-cancer patients the frequency of anti-p155/140 was 6.6% ($p<0.0001$; OR=9.9). Testing for anti-155/140 antibodies was 41% sensitive for the detection of CAM with a 44% PPV; and 93% specific for non-CAM with high NPV 93%. Four out of 17 CAM patients had polymyositis; however, none of these had anti-p155/140 antibodies. Only 1 patient from anti-p155/140+ group had PM and this patient was non-CAM. There was no apparent difference in the type of cancer between anti-p155/140 positive and negative patients, although data are somewhat suggestive to a more disseminated process in positives.

Conclusion: Possession of anti-p155/140 (anti-TIF1γ) antibodies represented a significant risk for cancer associated dermatomyositis. This fact may provide a strong argument for thorough search of malignancy in patients diagnosed with DM and anti-p155/140 antibodies. Routinely available testing is needed since it will have significant clinical implications.

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Modification of the Myositis-Specific Jo-1 Autoantigen by Reactive Oxygen/Nitrogen Species. Sander H.J. van Dooren[1], Reinout Raijmakers[2], Angelique M.C. Lokate[1], Tom Koemans[1], Walther J. van Venrooij[1] and Ger J.M. Pruijn[1], [1]Nijmegen Center for Molecular Life Sciences, Institute for Molecules and Materials, Radboud University Nijmegen, Nijmegen, Netherlands, [2]Bijvoet Center for Biomolecular Research and Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands

Purpose: The idiopathic inflammatory myopathies are a heterogeneous group of chronic skeletal muscle diseases often characterized by muscle weakness and inflammatory muscle damage. The etiology and pathogenesis of this group of diseases, also called myositis, remain unknown. Myositis can be classified into three main subgroups, polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) all with distinct clinical and histopathological features that are important for diagnosis, prognosis and treatment. Autoantibodies are found in up to 80% of PM and DM patients and are directed against a variety of cellular components. They can be divided into myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA), of which the latter are also found in other rheumatic diseases. In approximately 25% of myositis patients MSAs are found that are directed against the Jo-1 (histidyl-tRNA synthetase) protein. The aim of

our research is to unravel the mechanism by which immunological tolerance to Jo-1 is broken in myositis patients. We investigate whether protein modifications, e.g. resulting from (inflammation-associated) cell death, affect the autoantigenicity of Jo-1.

Method: The effect of cell death on Jo-1 protein function, localization and modification in cultured cells as well as myositis patient materials was investigated and compared with healthy controls. Western blotting, mass spectrometry and ELISA were used to determine specific cell death-induced Jo-1 modifications in apoptotic and necrotic Jurkat cells.

Results: Necrosis resulted in retarded Jo-1 migration in SDS-PAGE, which is due to the oxidation of several amino acids as well as enhanced dimerization. Five oxidized residues in the amino acid sequence of Jo-1 were mapped by mass spectrometry. Enhanced Jo-1 dimerization was also observed in cells treated with SIN-1, an inducer of reactive oxygen/nitrogen species. Up to now, no autoantibodies specifically targeting oxidatively modified Jo-1 were detected in established myositis sera.

Conclusion: The Jo-1 protein is oxidatively modified under necrotic conditions. Elevated levels of reactive oxygen and/or nitrogen species in the muscle microenvironment might result in the modification of the Jo-1 protein. In predisposed individuals the resulting neo-epitopes might trigger the initial immune response in the early stages of myositis. Further investigations using especially early patient sera are required to elucidate the existence of modification-specific autoantibodies and to study their role in the development of myositis.

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Rituximab Is An Effective Therapy for Anti-Signal Recognition Particle (Anti-SRP) Myopathy. Ritu Valiyil, Livia Casciola-Rosen, Grace Hong, Andrew Mammen and Lisa Christopher-Stine, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: The myopathy associated with anti-signal recognition peptide (SRP) is a severe necrotizing immune-mediated disease characterized by rapidly progressive proximal muscle weakness, markedly elevated serum creatine kinase (CK) levels, and poor responsiveness to traditional immunosuppressive therapies. Currently, reports on the efficacy of B cell depletion therapy for anti-SRP associated myopathy are mixed. We describe eight patients with anti-SRP associated myopathy and their clinical response to treatment with the anti-CD20 monoclonal antibody rituximab.

Method: We identified eight patients with myopathy who tested positive for anti-SRP antibodies by immunoprecipitation and had been treated with rituximab as part of clinical care between 2006 and 2009. We reviewed their medical records to assess clinical, serologic, and histologic characteristics of their muscle disease and response to therapy. In five of the eight patients, serum samples were also collected before and after rituximab treatment. In those patients, autoantibodies were detected by immunoprecipitation and quantitated by densitometry, and the percent decreases in anti-SRP autoantibody levels were calculated.

Results: In our cohort, the mean age was 37 years, 75% were female, and 50% were African-American. All patients presented with severe, rapidly progressive proximal muscle weakness with myalgias, dysphagia, and high CK levels with a mean maximum CK of 18,900 IU/l (3,148-56,000 IU/L). Six of the eight patients refractory to standard immunosuppressive therapy demonstrated improved manual muscle strength and/or decline in CK levels as early as two months after receiving two doses of rituximab. Three patients sustained the response for twelve to eighteen months after initial dosing. All patients were continued on adjunctive corticosteroids, but dosages were substantially reduced after rituximab. In four of the five patients tested, quantitative levels of serum anti-SRP antibodies also decreased after rituximab treatment.

Conclusion: B cell depletion therapy with rituximab is an effective therapy for patients with anti-SRP myopathy. The substantial decrease in anti-SRP antibody levels after rituximab treatment also suggests that B cells and anti-SRP antibodies may play a role in the pathogenesis of this myopathy.

Patient	CK prior to therapy	Highest prednisone dose (mg/day)	Prior treatments	Lowest prednisone dose post-therapy	Lowest CK post-therapy	Outcome post B cell depletion, duration of remission
1	2710	60	AZA, MTX	20	622	CK decline, improved strength, 10 months

2	1000	160	AZA, MTX, IVIg, plasma exchange	5	163	Normalized CK, improved strength, 18 months
3	550	40	AZA, MTX, IVIg, MMF	15	126	Normalized CK, improved strength, 19 months
4	1063	80	IVIg, plasma exchange	50	22	Died 1 month later from pneumonia
5	2900	80	MTX, IVIg	10	963	CK decline for 12 months, then re-dosed for increased CK
6	2100	60	MTX, MMF, IVIg	30	1144	CK decline, improved strength, 9 months
7	1250	60	MTX, MMF	N/A	1080	CK decline, 5 months
8	3110	60	AZA, MTX, IVIg, plasma exchange	15	2100	CK decline for 6 months, persistent weakness

Disclosure: R. Valiyil, None; **L. Casciola-Rosen**, None; **G. Hong**, None; **A. Mammen**, None; **L. Christopher-Stine**, None.

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Classification Criteria for Idiopathic Inflammatory Myopathy: Comparison of the Performance of Accepted Criteria. Helen Linklater[1], Nicolo N. Pipitone[2], Michael R. Rose[1], Fiona Norwood[1], David L. Scott[1] and Patrick A. Gordon[1], [1]Kings College Hospital, London, United Kingdom, [2]Arcispedale Santa Maria Nuova, Bari, Italy

Purpose: A large number of classification criteria have been proposed for the inflammatory myositides (IIMs) polymyositis (PM) and dermatomyositis (DM). However, none have received universal acceptance and clinical trials have used a variety of classification criteria. Recently the European Neuromuscular Diseases Collaboration (ENMC) has begun the process of developing international and multidisciplinary criteria with the publication of a set of preliminary criteria. This study aimed to assess the the performance of the ENMC criteria against the main previously published criteria [Bohan and Peter(1975), Dalakas (1991, 2003), Tanimoto (1995) and Targoff (1997)] using specialist consultant diagnosis as the gold standard.

Method: Patients attending Kings College Hospital (KCH) or the Rheumatology Unit, Reggio Emilia Hospital (REH) since 1990 with a diagnosis of IIM or non-inflammatory myopathy, were identified, and their records and laboratory investigations were retrospectively reviewed. Patients without complete data available were excluded. The project received ethics committee approval. Data were analysed using SPSS (version 15.0). Agreement between specialist consultant diagnosis and classification criteria was measured using Cohen's kappa statistic. Cohen's kappa values of 0.41 – 0.60 indicate moderate agreement.

Results: 44 patients had a complete set of investigations available, and a specialist diagnosis of IIM (PM, DM, IBM) or non-inflammatory myopathy.

Classification Criteria	**Cohen's kappa**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Tanimoto (1995)	0.16	90% (73-97%)	23% (6.0-54%)
Bohan & Peter	0.20	94% (77-99%)	23% (6.0-54%)

(1975)			
ENMC (2004)	0.44	68% (49-83%)	85% (54-97%)
Dalakas (1991)	0.48*	100% (84-100%)	58% (29-84%)
Dalakas (2003)	0.54	90% (73- 97%)	62% (32-85%)
Targoff (1997)	0.59	94% (77-99%)	62% (32-85%)

* Analysis of subset of 38 patients

The Targoff criteria had moderate agreement with specialist diagnosis, but other criteria performed less well.

Conclusion: Older classification criteria are sensitive but not specific for IIM, although they are still used predominantly in clinical studies. There is therefore a potential risk that these study populations may contain cases of non-inflammatory myopathy.

One of the strengths of the Targoff criteria is that they require disease specific findings (either positive muscle biopsy, cutaneous DM, myositis-specific antibody) to be present in order to make a diagnosis.

Consensus in the use of classification criteria for the purposes of clinical trials would lead to improvements in knowledge of prognosis and treatment in IIM. This analysis demonstrates the limitations of retrospective studies and the need for a multi-centre prospective myositis cohort. The International Myositis Assessment and Clinical Studies group (IMACs) is currently studying a prospective cohort of patients with IIM and non-inflammatory myopathy in order to examine the performance characteristics of commonly used classification criteria.

Disclosure: H. Linklater, None; **N. N. Pipitone**, None; **M. R. Rose**, None; **F. Norwood**, None; **D. L. Scott**, None; **P. A. Gordon**, None.

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Muscle Interstitial Levels of Pro- and Anti-Inflammatory Cytokines in Polymyalgia Rheumatica: Impact of Short-Term Prednisolone Treatment. Frederik Kreiner, Henning Langberg and Henrik Galbo, Bispebjerg Hospital, Copenhagen, Denmark

Purpose: The pathophysiology of symptomatic muscle in polymyalgia rheumatica (PMR) is disputed. In this study, interstitial levels of pro- and anti-inflammatory cytokines in symptomatic muscle were measured before and after short-term prednisolone treatment.

Methods: Twenty patients (12 females and 8 men; age 74±9 years, BMI 24±5 kg/m^2) with PMR just diagnosed according to the Chuang criteria (Ann Intern Med 1982;97:672-80) and 20 controls (11 females and 9 men; age 73±5 years; BMI 25±6 kg/m^2) were included. Subjects were studied before and after treatment for 14 days with 20 mg prednisolone/day. Interstitial concentrations of various interleukins (IL), IL-1 receptor antagonist (IL-1Ra), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein 1 (MCP-1) were measured in aching quadriceps and trapezius muscles using the microdialysis technique. Plasma levels were measured too.

Results: Prednisolone treatment abolished symptoms in all patients within a few days; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normalized at day 14. Controls had normal ESR and CRP before and after treatment. In both patients and controls, the interstitial levels (table) of most cytokines were markedly higher ($p<0.05$) than in plasma; exceptions were IL-1α, which was lower in both groups, and TNF-α, which did not differ. However, in both studied muscles interstitial concentrations of all cytokines were significantly higher in patients than in controls (table). Furthermore, in patients concentrations were considerably reduced by prednisolone treatment (table).

	Patients		Controls	
	Untreated	Treated	Untreated	Treated
IL-1α (pg/ml)				
Quadriceps	*16.0±6.1	#2.05±1.21	2.31±0.87	3.78±1.82
Trapezius	*36.5±7.05	#5.85±1.38	3.64±1.28	10.38±4.33
IL-1β (pg/ml)				
Quadriceps	*2.18±0.79	#0.29±0.24	0.29±0.07	0.18±0.06
Trapezius	*4.65±0.92	#0.70±0.24	0.56±0.12	0.40±0.15
IL-1Ra (pg/ml)				
Quadriceps	*2133.7±392.0	#1575.6±408.2	980.3±283.5	853.7±211.2
Trapezius	*1795.7±366.3	#1188.9±235.3	580.5±120.8	623.1±126.1
IL-6 (pg/ml)				
Quadriceps	*2473.1±934.1	#1245.7±399.3	597.2±108.7	441.3±82.5
Trapezius	*3747.0±1052.2	#1635.5±686.2	802.9±122.2	717.1±111.4
IL-8 (pg/ml)				
Quadriceps	*141.1±21.8	#94.6±33.3	67.1±17.1	50.8±8.37
Trapezius	*290.2±67.9	254.9±92.0	74.0±17.8	63.8±9.01
TNF-α (pg/ml)				
Quadriceps	*0.98±0.16	#0.59±0.12	0.76±0.18	0.44±0.10
Trapezius	*1.40±0.26	#0.74±0.11	0.49±0.11	0.56±0.08
MCP-1 (pg/ml)				
Quadriceps	*1601.7±310.4	*#1342.5±297.9	891.5±153.2	622.3±88.9
Trapezius	*2687.7±411.9	*#1600.3±344.7	853.7±187.1	637.3±71.9

*$p<0.05$ vs. corresponding controls; #$p<0.05$ vs. untreated patients. Data are mean±SE.

Conclusion: The present study has provided evidence that skeletal muscle contributes to the pathophysiology of PMR, pro- and anti-inflammatory cytokines being produced locally in the aching muscle.

Disclosure: F. Kreiner, None; **H. Langberg**, None; **H. Galbo**, None.

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Elevated Circulating CD40L Levels in Patients with Dermatomyositis. Shintaro Maeda, Kanazawa University School of Medical Science, Kanazawa, Japan

Purpose: Dermatomyositis (DM) is a connective tissue disorder characterized by muscle weakness, myalgias, vascular changes in skin and other internal organs, and autoimmunity. CD40L /CD40 interactions play a role in the regulation of autoimmunity and vascular function. A recent study revealed that myoblasts and muscle cells in DM patients highly expressed CD40, suggesting that increased CD40/CD40L interactions contribute to muscle inflammation in patients with DM.

Method: Serum sCD40L levels were examined by enzyme-linked immunosorbent assay of serum samples in 75 Japanese patients with DM, in 52 control patients with systemic sclerosis (SSc), and in 16 healthy control (CTL). A retrospective longitudinal study was also performed in 30 serum samples from 9 DM patients.

Results: Serum sCD40L levels were significantly elevated in DM patients compared with normal controls (3.0 ± 3.8 ng/ml vs. 0.5 ± 6.7 ng/ml, $p<0.01$). Serum sCD40L levels were similar for patients with DM and those with SSc (2.7 ± 1.3 ng/ml, $p > 0.05$). The DM patient sample was divided into two groups with sCD40L levels of greater than 2.5 ng/ml (the mean + 3SD of the control serum samples) and 2.5 ng/ml or less. Forty % (30/75) of DM patients were thus classified as having elevated levels of sCD40L. In comparison between the two

groups, the frequency of elevated erythrocyte sedimentation rates (ESR) in DM patients with elevated sCD40L levels was higher than those with normal sCD40L levels (43% vs. 13%, $p < 0.05$). Moreover, patients with an ESR that was greater than 25mm/hr had higher sCD40L compared to those patients with an ESR less than 25mm/hr ($p < 0.05$). In longitudinal studies, patients with elevated ESR levels had higher levels of sCD40L compared to those patients with normal ESR levels ($p < 0.05$). The serum sCD40L levels in DM patients paralleled the ESR levels during the follow up period.

Conclusion: The results of the current study demonstrate that serum sCD40L levels are elevated in patients with DM, and the sCD40L levels correlate with ESR levels at both the initial and the follow up visits. The serum sCD40L levels in this study may reflect the disease activity in the DM patients. In addition, interactions of CD40/CD40L were previously shown to be a therapeutic target in connective tissue diseases with low risk in preclinical studies and clinical trials. Therefore, our results suggest that CD40/CD40L interactions may be potential therapeutic targets in DM.

Disclosure: S. Maeda, None.

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Autoantibodies to the p140 Autoantigen NXP-2 in Adult Dermatomyositis. Zoe E. Betteridge[1], Harsha Gunawardena[1], Hector Chinoy[2], Jiri Vencovsky[3], Simon Allard[4], Patrick A. Gordon[5], Robert G. Cooper[2] and Neil J. McHugh[1], [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Hope Hospital, Salford, [3]Institute of Rheumatology and Department of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic, [4]West Middlesex University Hospital, Middlesex, United Kingdom, [5]Kings College Hospital, London, United Kingdom

Purpose: Myositis-specific autoantibodies (MSAs) define dermatomyositis (DM) and polymyositis (PM) into more homogeneous clinical subsets. Recently, anti-p140 has been demonstrated to form a major autoantibody subset in juvenile DM (JDM) [1-2]. The aim of this study was to investigate if autoantibodies to the same p140 autoantigen, nuclear matrix protein NXP-2, are present in adult myositis sera.

Methods: Sera from 393 adults with myositis based on the Bohan and Peter diagnostic criteria recruited to Adult Onset Myositis Immunogenetic Collaboration (UK) and Institute of Rheumatology, Prague were autoantibody typed by immunoprecipitation using ^{35}S-labelled K562 cells. Serum samples immunoprecipiating a 140-kd protein band were immunodepeleted with reference adult and JDM anti-p140 sera. Disease and normal control sera were screened using the above method. Clinical data was collated using standardised proformas. Probabilities were calculated using Fisher's exact test.

Results: Sera from 11 (3%) of 393 patients with myositis were positive for anti-p140 autoantibodies, which were detected exclusively in 6% of DM. No anti-p140 antibody-positive patients were positive for other recognized autoantibodies. Immunodepletion using reference sera suggested that the identity of p140 was consistent with NXP-2. The major clinical features of anti-p140-positive patients were heliotrope rash (73%), Gottron's lesions (82%), periungal erythema (91%) and systemic involvement including weight loss or fever (78%). In particular, the frequency of interstitial lung disease (ILD) in anti-p140-positive DM patients was 64% in comparison to 28% in anti-p140-negative DM patients ($p=0.018$), and 30% in anti-p140-negative group overall ($p=0.04$). There was no cancer-associated myositis in the adult anti-p140 positive subset. In contrast to anti-p140-positive JDM patients where calcinosis is a significant feature, this was only present in one patient (9%).

Conclusion: Anti-p140 autoantibodies form a further serological subset in adult DM, although the frequency of this MSA is much lower than observed in JDM [1]. In addition, our preliminary data suggests that the clinical associations of anti-p140 autoantibodies in adults differ from JDM. In particular, ILD appears to be a major feature of anti-p140-positive adult DM associated with hallmark cutaneous disease.

References: [1] Gunawardena *et al*, Arthritis Rheum 2009 60(6): 1807-14, [2] Targoff *et al*, Arthritis Rheum 2007 56:S787

Disclosure: Z. E. Betteridge, None; **H. Gunawardena**, None; **H. Chinoy**, None; **J. Vencovsky**, None; **S. Allard**, None; **P. A. Gordon**, None; **R. G. Cooper**, None; **N. J. McHugh**, None.

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Positive Correlations Between Serum Levels of B-Cell Activating Factor of the TNF Family / BLyS (BAFF), Anti-Jo-1 Autoantibodies and Muscle Enzymes in Patients with Polymyositis or Dermatomyositis. Olga Krystufkova[1], Marta Modra[1], Herman Mann[1], Ivana Putova[1], Ingrid E. Lundberg[2] and Jiri Vencovsky[1], [1]Institute of Rheumatology and Department of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic, [2]Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden

Purpose: Anti-histidyl-tRNA synthetase (anti-Jo-1) is a myositis specific autoantibody. A correlation between serum levels of anti-Jo-1 autoantibodies and disease activity has been reported in patients with myositis. BAFF is crucial for B-cell maturation and survival and plays a role in autoantibody production.

We have reported elevated serum levels of BAFF in patients with dermatomyositis (DM) and in anti-Jo-1 positive, polymyositis (PM) patients and a correlation between levels of BAFF and serum creatine kinase (CK).

The aim of this study was to find out if serum levels of BAFF correlated with anti-Jo-1 antibody levels and if serum levels of BAFF and anti-Jo-1 antibody levels correlated to laboratory and clinical markers of disease activity in patients with myositis.

Method: BAFF and anti-Jo-1 autoantibody levels were detected by ELISA in 70 anti-Jo-1 autoantibody positive serum samples from 21 patients with DM and 28 with PM. Longitudinal follow-up paired samples from 11 DM and 10 PM patients were also included. The anti Jo-1 positivity was confirmed by line-blot and western blot assays. Serum levels of CK, myoglobin, lactate dehydrogenase (LDH) and CRP serum were retrieved from patients' records or measured in the same sera. Clinical disease activity was assessed by the IMACS core set measures.

Results: A significant correlation between serum levels of anti-Jo-1 antibodies and BAFF ($rs=0.42$; $p<0.0005$) was found. Both BAFF and anti-Jo-1 serum levels correlated with CK ($rs=0.4$ and $rs=0.39$; $p=0.001$), myoglobin ($rs=0.28$ and $rs=0.29$; $p<0.05$) and CRP ($rs=0.48$; $rs=0.4$; $p<0.001$). Serum levels of CK, LDH and myoglobin correlated with each other, but no correlation was found with CRP except a weak correlation with myoglobin.

In paired longitudinal samples there was a weak correlation between the changes of BAFF and anti-Jo-1 levels ($rs= 0.44$; $p<0.05$). Apart from a correlation between BAFF levels and activity of cutaneous involvement ($rs=0.34$; $p<0.02$), no association was found between BAFF or anti-Jo-1 antibodies and activity of clinical symptoms.

Conclusion: The correlation between serum levels of BAFF and anti-Jo-1 antibodies could indicate that BAFF may be involved in the production of anti-Jo-1 autoantibodies. Another interpretation is that anti-Jo-1 could cause elevation of serum levels of BAFF eg via its type I interferon inducing capacity. The correlation between serum levels of BAFF and anti-Jo-1 antibodies and markers of muscle involvement (CK and myoglobin) might indicate a relationship between these two proteins and pathways implicated in the pathogenesis of myositis with anti-Jo-1 autoantibodies.

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Disclosure: O. Krystufkova, None; **M. Modra**, None; **H. Mann**, None; **I. Putova**, None; **I. E. Lundberg**, None; **J. Vencovsky**, None.

817

Gene Expression Analysis of Proteasomal Catalytic Subunits Allows the Definition of a Specific Profile in Patients with Inflammatory Myopathies. Lorena Martinez Gamboa[1], Marie Fettke[1], Sabine Krause[2], Khetam Ghannam[1], Lydia Naumann[1], Ulrike Kuckelkorn[1], Gerd R. Burmester[1] and Eugen Feist[1], [1]Charite University Hospital, Berlin, Germany, [2]Ludwig Maximilians Universität, Munich, Germany

Purpose: Idiopathic inflammatory myopathies (e.g. polymyositis PM, dermatomyositis DM, inclusion body myositis IBM) are diseases with unknown etiology, probably autoimmune. Expression of components of the ubiquitin proteasome system (UPS) is altered in PM and other autoimmune disorders. UPS is a crucial catalytic system involved in antigen presentation, cell cycle and apoptosis. A simultaneous analysis of constitutive and inducible proteasomal catalytic subunits in inflammatory and non-inflammatory myopathies has not been done yet. Thus, we analysed gene expression of these subunits in muscle samples from patients with PM, DM, IBM and control patients with non-inflammatory myopathies (e.g. mitochondrial myopathy, deficiency of myoadenylat desaminase).

Method: Inflammation degree was estimated in histological stainings. RNA from muscle biopsies was used for relative quantification of gene expression by real time PCR. Transcript levels of proteasomal constitutive catalytic beta subunits b1 (Delta), b2 (Z), b5 (MB1) and corresponding inducible subunits b1i (LMP2), b2i (MECL) and b5i (LMP7) were measured by comparison with the house keeping genes beta actin and GAPDH. For statistic analysis, the non-parametric Mann-Whitney test and P values <0.005 were applied. Ratios were calculated using values of expression of corresponding constitutive:inducible subunits.

Results: In inflammatory myopathies, DM patients showed the strongest significant differences in the expression of all constitutive and inducible proteasome subunits when compared to non-inflammatory controls. PM patients showed differences especially in expression of b1 and b5i. In general, gene expression of constitutive proteasome subunits was significantly higher than of inducible ones, especially for b1:b1i and b5:b5i. Notably, the magnitude of this relation calculated as ratio of expression of corresponding constitutive:inducible subunits showed a typical pattern according to the inflammatory degree (e.g. inflammatory, weak inflammatory or non-inflammatory). In detail, ratio for b1:b1i was 70.7 in non-inflammatory, 17.2 in weak inflammatory and 6.6 in inflammatory cases; for b5:b5i it was 5.3, 1.5 and 0.5, respectively. Ratio of expression of b2:b2i showed no differences between the different inflammatory cases (5.8, 5.9 and 6.0, respectively).

Conclusion: Our results show that gene expression of b1:b1i and b5:b5i proteasome subunits is altered in inflammatory myopathies. Calculation of expression ratios of constitutive vs inducible subunits allowed a clear differentiation between non-, weak- or inflammatory states in the analyzed myopathies and therefore, could be a useful tool for monitoring of disease development. Further implications of these alterations for the disease, including expression at protein level, should be analysed.

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The Holster Sign: A Specific but Under Recognized Skin Finding in Dermatomyositis. Dean H. Stephens[1], Kathryn Schwarzenberger[2] and Sheldon M. Cooper[1], [1]Fletcher Allen Health Care, Burlington, VT, [2]Fletcher Allen Health Care

Purpose: Characteristic skin findings in dermatomyositis (DM) include Gottron's papules (Gp), heliotrope rash (He) and shawl and V (S/V) sign. An erythematous and violaceous rash over the lateral hip, called the "Holster sign," has been noted occasionally in the dermatology literature, but is absent from rheumatology publications. The objective of this study was to evaluate the incidence of the holster sign (HS) in DM patients, to determine the sensitivity and specificity of this and other classic skin findings by comparing DM patients with polymyositis (PM), mixed connective tissue disease (MCTD), and scleroderma (SS) patients.

Method: We identified patients seen by our rheumatology and dermatology services from January 2003 to December 2008 with ICD-9 codes for DM, PM, MCTD and SS. Patients were mailed a survey that included separate pictures of He, Gp, S/V and HS, and were asked to check if they "had any of the following skin findings?" Patients who completed the survey and signed the informed consent were enrolled. Chart reviews were performed to confirm the diagnosis and to look for any description of the above cutaneous findings in the provider's notes. The incidence rate for each skin sign was calculated by diagnosis, and the sensitivity and specificity of each sign for DM was calculated.

Results: Out of a total of 315 surveys mailed, 117 were returned. Positive self-reporting of the HS was 22/28 in DM, 2/13 in PM, 0/21 in MCTD, and 6/55 in SS. Positive reporting of 78.5% for the HS in DM was comparable to S/V (75%), Gp (85%), and He (71%). In the PM, MCTD and SS patient groups, HS self-reporting was lowest (0-15%), with higher responses for Gp (22-33%), S/V (15-33%), and He (5-23%). Of all the skin findings, the HS had the highest specificity for DM at 91% (range 75-91% for all signs). Sensitivity of the HS was 79%, and comparable to other signs (71-85%). Chart review of the patients seen by both a rheumatologist and dermatologist suggested that dermatologists noted the HS more frequently than the rheumatologist, whereas other skin findings were recorded equally.

Conclusion: This patient survey and chart review indicates that the Holster sign has a comparable incidence to the more established cutaneous findings in DM. Description of the HS is not mentioned in rheumatology texts and reviews, suggesting a low recognition of the HS by rheumatologists. Looking for the distinctive HS should be part of the exam in all patients with suspected DM.

Disclosure: D. H. Stephens, None; **K. Schwarzenberger**, None; **S. M. Cooper**, None.

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Isolated Elevation of Aldolase in the Serum of Myositis Patients: A Biomarker of Damaged Early Regenerating Muscle Cells. Livia Casciola-Rosen, Lisa Christopher-Stine, Andrea Corse, Grace Hong, John Hall and Antony Rosen, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Increased serum aldolase levels in the absence of increased serum creatine kinase (CK) levels occurs in patients with myositis, but the mechanism underlying this phenomenon is unclear. Recent studies have demonstrated that regenerating muscle cells express the highest concentrations of myositis autoantigens, and are likely major targets of immune attack in this disease. We therefore examined the gene and protein expression of aldolase and CK in differentiating muscle cells.

Methods: Cultured human myoblasts were induced to differentiate into myotubes over 10 days *in vitro*. Total RNA was isolated on each day of culture and microarray analysis was performed using human Illumina Refseq8 beadchip arrays. Present genes were Z-transformed and normalized, and significant changes in gene expression were calculated by performing Z tests. Gene expression data for aldolase and CK was verified by performing QPCR using the TaqMan assay system. Detergent containing lysates, prepared at various times during differentiation, were immunoblotted with antibodies against aldolase, CK, vinculin and other differentiation markers. Muscle paraffin sections from patients with elevated aldolase levels and normal CK levels were stained with a polyclonal antibody against aldolase.

Results: Gene expression analysis performed on differentiated human myoblasts demonstrated that aldolase expression was highest in myoblasts, and decreased slightly during differentiation into myotubes; however, levels remained robust. In contrast, CK mRNA is expressed at very low levels in undifferentiated myoblasts, but is strikingly upregulated by day 2 of culture, with expression levels peaking by day 3. A marker of muscle differentiation, embryonic myosin heavy chain (MYH3), displayed a similar expression pattern. Consistent with this, we showed by immunoblotting that aldolase protein expression is highest in myoblasts, and, although it decreases during differentiation, it is prominent throughout. In contrast, CK expression is absent in myoblasts and during the early stages of differentiation (the period of highest aldolase expression), and is only detected from day 4 onwards. Immunohistochemical staining confirmed that muscle cells with the highest levels of aldolase have features consistent with regeneration.

Conclusion: In undifferentiated muscle cells, and those early in the differentiation process, aldolase is expressed in the absence of CK. This is a period in muscle cell differentiation in which autoantigen expression is also highest. Thereafter, both aldolase and CK are expressed. We propose that isolated serum aldolase elevation in myositis patients reflects preferential immune-mediated damage of early regenerating muscle cells. Such targeted damage may have important implications in terms of prognosis and therapy.

Disclosure: L. Casciola-Rosen, None; **L. Christopher-Stine**, None; **A. Corse**, None; **G. Hong**, None; **J. Hall**, None; **A. Rosen**, None.

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Increased Mast Cells in Untreated JDM Skin Compared to Paired JDM Muscle: Association with Mature Plasmacytoid Dendritic Cells. Sheela Shrestha[1], Barry Wershil[2], John F. Sarwark[2] and Lauren M. Pachman[1], [1]Children Memorial Research Center, Chicago, IL, [2]Children's Memorial Hospital, Chicago, IL

Purpose: To investigate mast cell distribution in association with dendritic cell subsets in muscle and skin (lesional and non-lesional) pairs from untreated juvenile dermatomyositis (JDM) patients.

Methods: Seven untreated patients diagnosed as probable/definite JDM (Bohan-Peter criteria) (mean age=4.91 ± 2.58 yrs, 1 male, 6 female) were enrolled. MRI directed muscle and skin biopsies (4/7 from active JDM rash) were obtained from each patient. Otherwise healthy children with idiopathic scoliosis donated thoracic skeletal muscle, n=4 and skin, n=6 with their consent (mean age=10.77 ± 5.70 yrs, 6 male, 4 female). Mast cell distribution and number were assessed by staining with toluidine blue. Student's t-test was performed with $p<0.05$ as significant. Using immunohistochemistry, the presence of dendritic cells (myeloid [mDC] or plasmacytoid [pDC]) and their maturation state were examined using antibody to BDCA-1, BDCA-2 and DC-LAMP respectively. MxA staining was used as an indicator of type I interferon (IFN) signaling. The expression of these markers was scored semi-quantitatively (0 = none; 1 = weak; 2 = moderate; 3 = strong expressions). Mann-Whitney U-test was used for statistical analysis. Probabilities <0.05 were considered significant and $p<0.01$ as highly significant.

Results: Mast cell infiltrations in JDM skin ($43.16\pm39.90/mm^2$) were significantly elevated compared to skin from control children ($7.90\pm3.63/mm^2$), $p=0.029$ and did not differ between lesional and non-lesional skin rash, $p=0.40$. No significant difference was seen in the number of mast cell infiltrating JDM muscle ($0.35\pm0.21/mm^2$) and control muscle ($0.28\pm0.26/mm^2$), $p=0.341$. Within the JDM group, the

number of mast cells in skin was significantly higher than in the corresponding muscles, p=0.014. pDC were localized mainly in the perivascular and perifascicular area in JDM muscle as compared to control muscle, p=0.042 and were predominantly mature, p=0.006. MxA protein was preferentially expressed by myofibers in JDM muscle and significantly different from control muscle, p=0.042. In JDM skin, the staining for DC-LAMP, BDCA-2 and MxA was present throughout the epidermal and dermal layers, including perivascular area as compared to control skin, p = 0.001. Both JDM and control muscle were negative for mDC, but a few were sparsely scattered in the dermis of JDM and control skin.

Conclusion: The increased numbers of mast cells in the skin, but not in the muscle, from untreated children with JDM suggests that the pathophysiology of the disease in skin and muscle are distinct, as we have suggested previously (Smith et al 2004). The lack of association between the number of mast cell and the degree of rash severity indicates that immune activation may precede the clinical dermal manifestation of JDM. The predominance of pDC along with type I IFN induced proteins suggests a selective influence on T-cell differentiation and subsequent effector functions. Support: RO-1 AR48289 and Cure-JM (to LMP).

Disclosure: S. Shrestha, None; **B. Wershil**, Prometheus Laboratories, 8, Children's Digestive Health and Nutrition Foundation, 6, American Partnership for Eosinophilic Diseases, 6 ; **J. F. Sarwark**, None; **L. M. Pachman**, None.

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The Expression of IL-23and IL-23R Are Increased in Patients with Dermatomyositis. Park Young-Eun[1], Baek Seung-Hoon[1], Kim Ju-In[1], Kim Jeong-Hee[1], Lee Joung-Wook[2], Kim Geun-Tae[3], Lee Jun-Hee[4] and Kim Sung-Il[1], [1]Pusan National University Hospital, Busan, South Korea, [2]Busan St. Marys center, Busan, South Korea, [3]Kosin University Gospel Hospital, Busan, South Korea, [4]Choonhae Hospital, Busan, South Korea

Purpose: Dermatomyositis (DM) is chronic autoimmune muscle disorders characterized by inflammatory infiltrate in muscle tissues. IL-23, promotes Th17 cell differentiation and induces proinflammatory cytokines, has key roles in autoimmune disease. IL-23R is unique receptor of IL-23 and plays roles on autoimmune disease.

Method: We measured the IL-23 and IL-23R mRNA level of muscle tissues from 9 patients with DM by real-time RT-PCR and compared with controls. We also performed immunofluorescence stain with confocal micoscope to detect IL-23R expression.

Results: In 9 patients with DM (6 male and 3 female patients), mean age was 42±15 years and clinical and laboratory characteristics are in table 1. The relative expression levels of IL-23 (12.2±14.7 in DM, 1 in control) and IL-23R (6.0±6.0 in DM, 1 in control) were significantly enhanced in DM than controls. In immunofluorescence stain with confocal microscope, IL-23R was expressed in vessel walls, infiltrating inflammatory cells and muscle tissues of DM (figure 1).

Conclusion: These results suggest IL-23 and IL-23R play a role in the immunopathogenesis of DM.

Table 1. Clinical and laboratory characteristics, and the expression levels of IL-23R in 9 patients with dermatomyositis

Age(year) /sex	Disease durations (months)	CK (U/L)	Aldolase (U/L)	ESR (mm/h)	CRP (mg/dl)	Relative expression levels compared to controls	
						IL-23	IL-23R
66/F	1	3012	10.1	54	3.41	5.4	2.5
36/M	3	2815	46.1	75	0.9	31.6	19.5
39//M	2	1163	NA	85	0.47	2	1.9
37/M	12	70	5.7	78	0.489	1.7	2.2
58//M	1	3006	NA	13	0.519	4.4	1.3
37/M	2	14139	36.7	73	2.81	42.6	3.1
55/M	1	3034	21.9	24	NA	4	4.6
30/F	6	>6000	54.3	14	0.1	6.4	11.3
18/F	3	668	16.5	52	0.144	11.6	7.5
42±15 M/F 6/3	3.4±3.6					12.2±14.7	6.0±6.0

CK : creatinine kinase (normal < 160 units/liter)

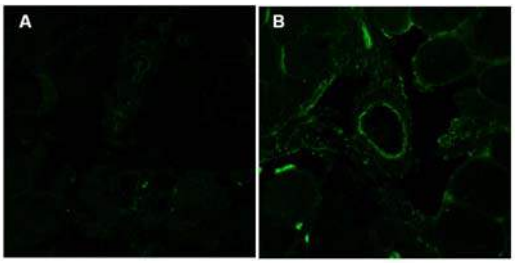

Figure 1. In immunofluorescence stain with confocal microscope in control (A) and patient with dermatomyositis (DM) (B). IL-23R was expressed in vessel walls, infiltrating inflammatory cells and muscle tissues of DM (×400).

Disclosure: P. Young-Eun, None; **B. Seung-Hoon**, None; **K. Ju-In**, None; **K. Jeong-Hee**, None; **L. Joung-Wook**, None; **K. Geun-Tae**, None; **L. Jun-Hee**, None; **K. Sung-Il**, None.

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Early Employed Exercise in Recent Onset Polymyositis or Dermatomyositis – A Randomized, Controlled 2-Year Follow Up Study.

Helene Alexanderson[1], Anne-Marie Noren[2], Li Alemo Munters[1], Christina H. Opava[3] and Ingrid E. Lundberg[4], [1]Rheumatology Unit, Department of Medicine and Department of Physical Therapy, Karolinska Institutet, Stockholm, Sweden, [2]Health Care Department, Stockholm City Council, Stockholm, Sweden, [3]Karolinska Institutet, Huddinge, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Purpose: To evaluate the safety and the benefits of a resistive home exercise program in patients with recent onset polymyositis (PM) or dermatomyositis (DM).

Method: Nineteen patients with recent onset PM/DM (median age of 56 Q1-Q3 (45-65) years) were included. A muscle biopsy from the vastus lateralis was performed and all patients were given 0.75 mg/kg body weight, md 40 (30-40) mg of Prednisone together with Methotrexate or Azathioprine. Measures of muscle endurance (Functional Index), aerobic capacity (treadmill test), perceived health (Nottingham Health Profile)(NHP) and CPK-levels were performed at baseline and after 12, 24, 36, 52, 64, 76 and 104 weeks. Four weeks after diagnosis patients were randomized to an exercise group (EG, n=10) performing a resistive home exercise program five days/week for 12 weeks or to a control group (CG, n=9) performing a range of motion program five days/week for 24 weeks. A second muscle biopsy was performed after 24 weeks. Patients in the CG without inflammatory infiltrates in the second biopsy were then instructed in the resistive home exercise program for 12 weeks. Patients filled out an exercise diary and telephone support was provided weekly during the 12-week exercise. All patients were encouraged to keep on exercising twice a week throughout the 2-year follow-up. The Kruskal-Wallis ANOVA was used for between-group analysis and the Friedman's ANOVA and the Wilcoxon Signed Rank test were used for within-group analysis.

Results: The exercise program was well tolerated. There was no difference between the groups at baseline, except for the EG rating poorer health in three NHP domains compared to the CG ($p<0.05$). A within-group improvement was revealed for both groups in muscle endurance and aerobic capacity at 12-64 weeks compared to baseline ($p<0.01 – p< 0.05$). In the EG, this improvement lasted up to the 104-week follow-up ($p<0.05$), but not in the CG. The EG improved in the NHP domain Energy at 12 and 104 weeks compared to baseline ($p<0.05$) while the CG improved in the domain Sleep at 24 weeks compared to baseline ($p<0.05$). There was no between-group difference in any measures at any follow-up and the number of responders (>20% improvement) was equal in both groups at all follow-ups. No signs of increased muscle inflammation were revealed.

Conclusion: Our study further supports the safety of resistive exercise in patients with active PM/DM but could not reveal any difference in treatment effects between the two groups. As improvements lasted up to the 2 year follow-up in the EG, but not in the CG, our results indicate that early employed exercise might be more effective in a longer perspective than medical treatment alone. There is a need for larger multicenter RCT trials are needed to establish exercise effects in these patients.

Disclosure: H. Alexanderson, None; **A. M. Noren**, None; **L. Alemo Munters**, None; **C. H. Opava**, None; **I. E. Lundberg**, None.

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Patients with Idiopathic Inflammatory Myopathies Have Low Muscle Endurance Rather Than Low Muscle Strength. Helene Alexanderson[1], Jenny Bergegård[2], Li Alemo Munters[1], Maryam Dastmalchi[3] and Ingrid E. Lundberg[3], [1]Rheumatology Unit, Department of Medicine and Department of Physical Therapy, Karolinska Institutet, Stockholm, Sweden, [2]Department of Physical Therapy, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Purpose: To investigate degree of muscle strength and muscle endurance in patients with active, recent onset and chronic idiopathic inflammatory myopathies.

Method: Two cohorts of patients with diagnosis polymyositis (PM), dermatomyositis (DM) or inclusion body myositis (IBM), registered at the Rheumatology clinic at Karolinska University Hospital, were included in this study. Cohort 1 (n=32) is all adult patients that were newly diagnosed with PM, DM or IBM during 2004-2008 who performed both the Manual Muscle test (MMT) (maximal isometric strength) and the Functional Index 2 (FI-2) (muscle endurance assessed as maximal number of repetitions) at the time of diagnosis with no more than two weeks apart. Fourteen patients had PM, 16 DM, and two had IBM and their median diagnosis duration was 0 range (0-3) month. They had median 0 (0-70) mg of Prednisone per day (18 patients were assessed before introduction of medical treatment). Cohort 2 (n=49) is all patients with chronic disease registered at the clinic who performed both the MMT and FI-2 with no more than two weeks apart at a yearly check-up visit during 2004. Twenty-two patients had PM, 24 DM, and three had IBM, with median diagnosis duration of 9 (1-36) years and median 5 (0-20) mg of Prednisone per day. The MMT was conducted by either of two experienced and trained physicians and the FI-2 was performed by either of 4 experienced and trained physical therapists. Comparisons between the MMT and the FI-2 measures were analyzed using the non-parametric Mann Whitney Test.

Results: Patients in cohort 1 with active, recent onset disease had statistically significant and clinically relevant lower muscle endurance with a median of 26 (0.5-86) % of maximal score of the FI-2 compared to a median of 87 (0-100) % of maximal score of the MMT ($p<0.001$). Patients in cohort 2 with chronic disease had statistically significant and clinically relevant lower muscle endurance with a median value of 26 (0-100) % of maximal score of the FI-2 compared to a median value of 94 (46-100) % of the maximal score of the MMT ($p<0.001$). The lowest scores of the MMT and the FI-2 represented the patients with IBM in cohorts 1 and 2.

Conclusion: Patients with inflammatory myopathies with active, recent onset as well as chronic disease have a larger degree of impairment regarding muscle endurance than muscle strength. These results indicate that it is very important to also assess muscle endurance to better capture impairment in these patients in clinical practice and research.

Disclosure: H. Alexanderson, None; **J. Bergegård**, None; **L. Alemo Munters**, None; **M. Dastmalchi**, None; **I. E. Lundberg**, None.

ACR/ARHP Poster Session B

Osteoarthritis Therapeutics & Clinical Aspects

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Analysis of a Broad Spectrum of Urinary and Serum Biomarkers in a Large Cohort of Patients with Early Osteoarthritis of Hip and/or Knee (CHECK): The First Results. Willem E. van Spil, Floris P.J.G. Lafeber and Nathalie W.D. Jansen, University Medical Center Utrecht, Utrecht, Netherlands

Purpose: Biomarkers to diagnose OA in an early stage and/or to predict its course would be of great value. Therefore, we selected a broad spectrum of serum and urinary biomarkers representative of cartilage, bone and synovium turnover for evaluation in CHECK (Cohort Hip & Cohort Knee). This multi-centre cohort consists of 1002 participants with pain and/or stiffness of knee and/or hip, aged 45-65 yrs, and who had never or no longer than 6 months before visited their physician for these symptoms for the first time. Hip and knee radiographs as well as clinical parameters and multiple questionnaires are evaluated at regular intervals. Furthermore, serum (s) and urine (u) samples are collected at 0, 2, 5, 8, and 10 yrs. Baseline biomarker measurement has recently been completed and would provide a unique opportunity to study the diagnostic and prognostic properties of biomarkers in early-stage OA. This abstract covers quality aspects of this large biomarker set.

Method: Baseline samples were thawed for the first time. Commercially available ELISA assays were performed to measure uCTX-II, uCTX-I (ImmunoDiagnostic Systems Ltd.), uNTX-I (Wampole Laboratories), sCOMP (Anamar Med AB), sOC (IDS), sHA (Corgenix Inc.), sPIIANP (Millipore Corp.), sCS846, and sC1,2C (IBEX) and RIA assays for sPINP and sPIIINP (Orion Diagnostica). There was no commercial involvement and kits were from the same badge for each biomarker. Each biomarker was measured in all samples by the same technician in 8 days in a period of 6 wks using 14 kits.

Results: Quality of the assays, checked by using a randomly distributed pooled reference sample, controls as supplied by manufacturers, and blank samples in-between patient samples, was acceptable, except for the COMP assay. The COMP assay showed a remarkably variable biomarker concentration within and between assay plates.

When biomarker concentrations of all patient samples were plotted in chronological order of assaying, it appeared that there was a sufficient window of variation within a positively skewed distribution. There was no evident variation over time and between serial kits of the same assay, except for two remarkable observations: part of the sCOMP kits showed biomarker concentrations that were a 10-fold higher and showed significantly more variation than the other kits. For the sC1,2C and sCS846 assays, there was a relationship between measured biomarker concentration and sample position within assay plates. It appeared that the variation in the COMP assays was due to the coating procedure and the assay will be run again with new kits. For the C1,2C and CS846 assays there is still ongoing research to specify the problem.

Conclusion: Reliable measurement seems possible for the majority of the studied biomarkers in this large sample set. However, there remain some challenges for some of the assays before actual correlations with clinical and radiographic data can be made.

Disclosure: W. E. van Spil, None; **F. P. J. G. Lafeber**, None; **N. W. D. Jansen**, None.

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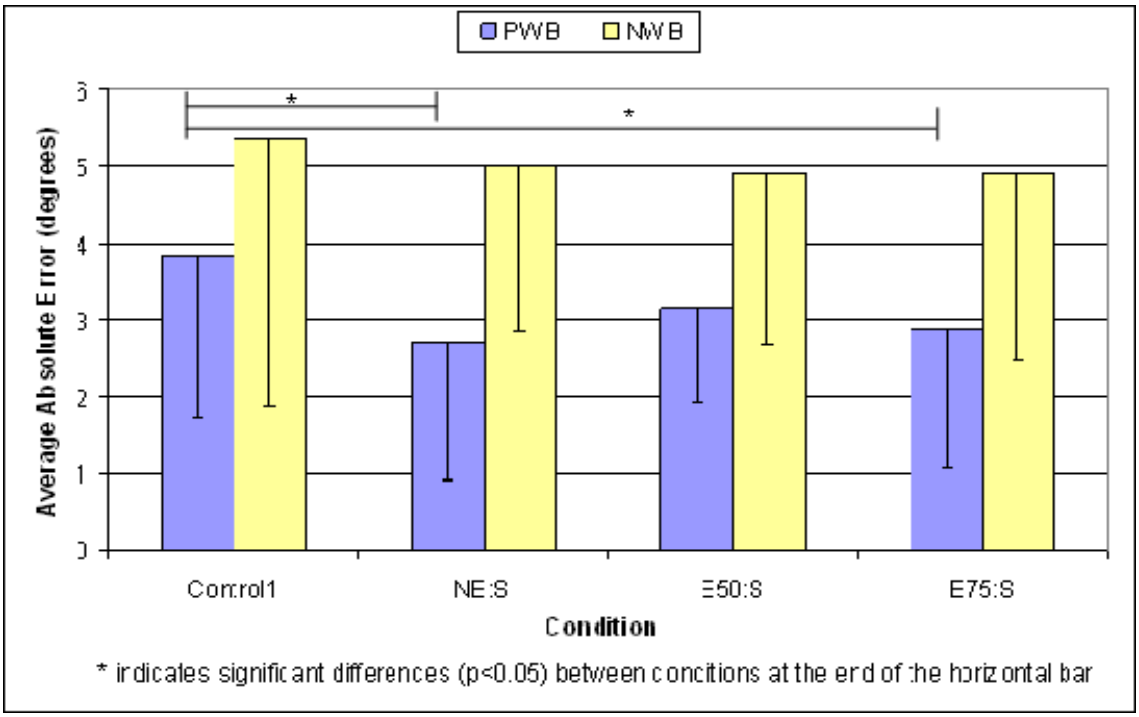
Stochastic Resonance Electrical Stimulation to Improve Proprioception in the Osteoarthritic Knee. A. Collins, T. Blackburn, C. Olcott, J. Miles, J. Jordan, D. Dirschl and P. Weinhold, UNC Chapel Hill, Chapel Hill, NC

Purpose: Proprioception deficits are known to occur with knee osteoarthritis (OA) and it has been proposed that correction of these deficits may help to slow disease progression. While knee sleeves have shown some evidence to improve proprioception in the nonweightbearing knee, a novel means to enhance such effects may be by incorporating a type of electrical stimulation (stochastic resonance) that has been demonstrated to enhance the sensitivity of mechanoreceptors. The purpose of this research was to determine whether proprioception measured by joint position sense (JPS) is improved through the use of electrical stimulation and a neoprene knee sleeve in a population with mild to moderate medial knee OA.

Method: JPS was measured in 24 subjects (18 females, 6 males) with mild to moderate (KL grade 1-3) knee OA under four conditions (control, 50μA stimulation/sleeve E50/S, 75μA stimulation/sleeve E75/S, and no stimulation/sleeve NE/S) during both a partial weight bearing (PWB) and a non-weight bearing (NWB) task using a counterbalanced design. Electrical stimulation consisted of either a 50μA or 75μA Gaussian white noise signal (zero mean, s.d. = 0.05mA, 0-1000Hz bandwidth) applied at superior and inferior electrode pairs placed about the knee. During both tasks the absolute difference (error) between the target knee angle and the reproduction angle was calculated and averaged across the 5 trials within each condition. One-way repeated measures analysis of variance followed by Tukey's post-hoc analysis was used to determine differences between conditions ($p<0.05$). Regression analysis was used to assess correlations between the control condition error and the improvements in proprioception with the treatment conditions or the subject's WOMAC score.

Results: Proprioception was found to be improved ($p<0.05$) relative to the control condition for both the sleeve alone (NE/S) and E75/S conditions in the PWB task (see figure). No significant differences were found in the NWB task. Regression analysis revealed a modest correlation between the improvement of the absolute error of the NE/S and E75/S conditions and that of the control condition in PWB task. No correlation was found between the error of the control condition and the subject's WOMAC score.



Conclusion: Electrical stimulation combined with a knee sleeve (E75/S) as well as the sleeve alone (NE/S) condition improved proprioception compared to a control condition during the physiologically relevant PWB task. The correlation observed between the improvement in proprioception with the E75/S and NE/S treatment conditions and the error of the control condition are suggestive that subjects with larger proprioceptive deficits may benefit most from these therapies.

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Gait Variability Across the Spectrum of Knee Osteoarthritis. Kharma Foucher[1], George Kannankeril[1], Joel A. Block[1], Najia Shakoor[1], Markus Wimmer[1] and Laura E. Thorp[2], [1]Rush University Medical Center, Chicago, IL, [2]Rush University Hospital, Chicago, IL

Purpose: The etiology of knee OA has biomechanical and neuromuscular components. The knee adduction moment (KAddM) during gait is a biomechanical marker of knee OA. The magnitude of gait variability may be a marker of neural control with important consequences on load history; and thus be related to disease severity. Here we evaluated variability in gait parameters across the spectrum of OA severity.

Method: Data from three IRB approved studies were examined: 1) 52 subjects (39 F/13M, age 52.4±6.0 yrs) with no clinical evidence of OA at the knee or hip; 2) 34 pre-OA subjects (18F/18M, age 63.8±9.9 yrs) at high risk for knee OA due to existing contralateral hip OA; 3) 86 subjects (65F/21M, age 57.9±10.2 yrs) with mild/moderate symptomatic radiographic medial knee OA. Walking speed, peak KAddM, and dynamic knee range of motion (KROM) from 3 gait trials at self-selected normal speeds were analyzed for each subject. Intra-subject coefficients of variation (CV=100* standard deviation / mean) were calculated for these variables. Kruskal-Wallis and Mann-Whitney tests were used to detect group differences.

Results: Average walking speed (m/s) for groups 1 through 3 were: 1.3±0.22 (normal), 1.17±0.15 (pre-OA), 1.18±0.23 (OA) (p=0.002); both the pre-OA and the OA groups were slower than normal (p=0.002). CVs for speed were 4.3±2.9% normal, 2.5±1.8% pre-OA, 3.2±2.5% OA (p=0.004); pre-OA and OA groups' CVs (p=0.215) both were reduced compared to normal (p= 0.002 and p= 0.014, respectively). Although there were no differences in KROM among the groups (p=0.234) the CV showed group differences (p=0.012). Variability was significantly less in the OA group than among normals (2.3±1.9% v. 3.6±2.6%, p=0.003). KAddM was 2.27±0.58 %BW*Ht in the normal group,

2.44±0.72 %BW*Ht in the pre-OA group, and 2.84±0.68 %BW*Ht in the OA group ($p<0.001$). The OA group had significantly higher KAddM than both the pre-OA ($p=0.006$) and the normal group ($p<0.001$). The variability decreased from 9.5±6.5% in the normal group to 7.5±4.6% in the pre-OA group to 6.2±4.1% in the OA group ($p=0.003$). KAddM CV was significantly lower in the OA group than the normal group ($p=0.001$) but was not significantly different from the pre-OA ($p=0.129$).

Conclusion: Variability in both loading and motion variables decreased incrementally with knee OA risk and definitive evidence of knee OA, suggesting that a more restricted walking strategy is adopted in response to increased pain, stiffness, or changes in alignment. Decreased variability could potentially exacerbate local cartilage degeneration, as the same areas of cartilage are consistently subjected to abnormally high loads. While decreased step-to-step variability has been documented in knee OA, the reduced trial-to-trial variability of several gait markers in this study suggests a detrimental, neuromuscular adaptation.

Disclosure: K. Foucher, None; **G. Kannankeril**, None; **J. A. Block**, NIH SCOR 1P50 AR048941, 2 ; **N. Shakoor**, None; **M. Wimmer**, None; **L. E. Thorp**, Foundation for Physical Therapy, 2 .

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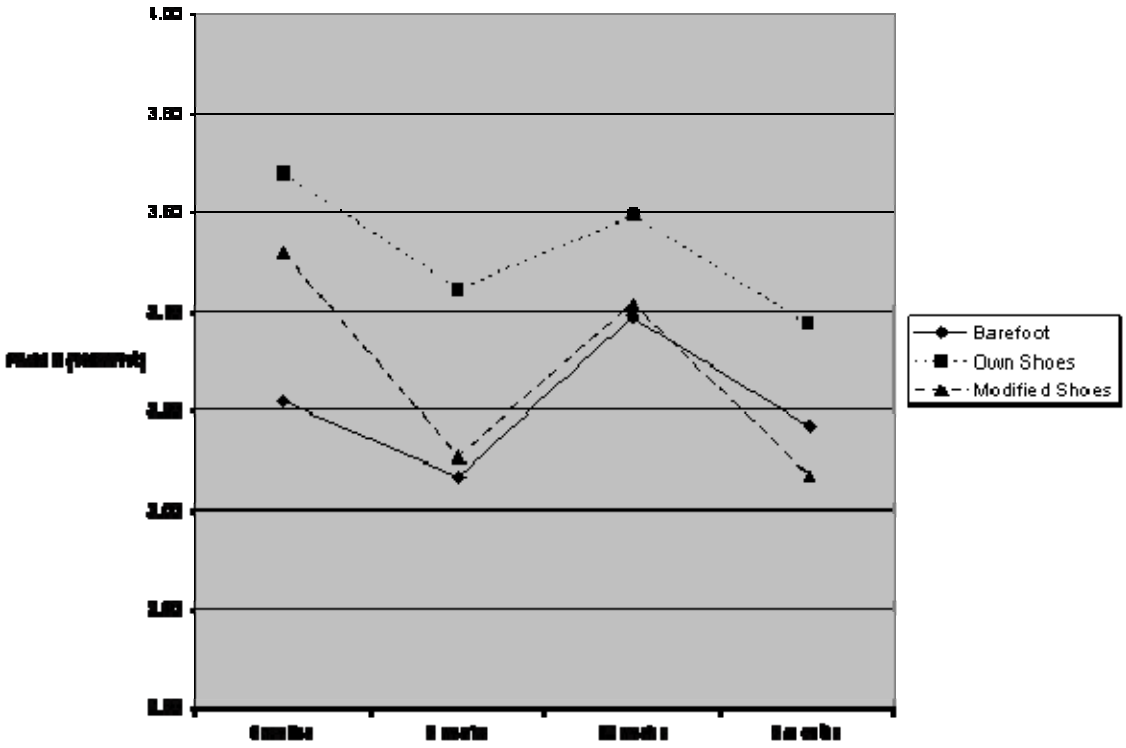
The Effects of Specialized Footwear in OA of the Knee: Clinical and Biomechanical Results of a 6-Month Pilot Study. Najia Shakoor, Roy Lidtke, Rachel Mikolaitis, Robert Trombley, Louis Fogg and Joel A. Block, Rush University Medical Center, Chicago, IL

Purpose: The onset and progression of knee OA are mediated by high dynamic loading of the knee. We recently demonstrated that in knee OA, footwear has a significant effect on knee loads, and that use of a novel "mobility" shoe substantially reduced dynamic joint loads during walking compared to conventional shoes (*Arthritis Rheum* '08). Here, we performed a pilot investigation to test the effects at 6 months of chronic use of "mobility shoes" on pain and dynamic knee loads in symptomatic knee OA.

Methods: Subjects with radiographic (Kellgren Lawrence grades ≥ 2) and symptomatic (at least 30mm pain on a 100mm scale while ambulating on a flat surface) medial compartment knee OA were recruited. At baseline, subjects: 1) had AP standing knee radiographs 2)completed site-directed WOMAC evaluations of their hips, knees and ankles and 3) underwent gait analyses using an optoelectronic camera system and multi-component force plate while wearing their own shoes, "mobility shoes", and barefoot. Subjects were instructed to wear the mobility shoes for a minimum of 6 hours daily for at least 6 days each week. Pain and gait evaluations were performed at baseline, 6 weeks, 12 weeks, and 6 months. WOMAC pain and peak knee adduction moment (PAddM) represented the primary endpoints. An intent to treat analysis (ITT) was performed using repeated measures analyses of variance, $p<0.05$ was considered significant.

Results: Complete data are available for 9 subjects. Three terminated early: two due to lack of efficacy (one each at 6 and 12 weeks), and one was unable to return for study visits and terminated at 8 weeks. All data were carried forward for the ITT analysis. In comparison to the subjects' own shoes, the "mobility" shoes induced significantly decreased loads during gait at all time points ($p=0.012$)(Figure 1), with an overall reduction in PAddM of 17% with "mobility shoes" at 6 months compared to conventional shoes at baseline. There were no significant differences between the mobility shoes and barefoot walking at any time point ($p=0.603$)(Figure 1). Concomitant with the load reductions, there were significant and durable improvements in pain at all study time points compared to baseline, with an overall 46% reduction at 6 months (245±109 vs 137±131 vs 161±126 vs 132±127, $p=0.001$).

Conclusion: This pilot study demonstrates that use of novel "mobility" footwear results in durable reductions in both dynamic knee loading and in pain during 6 months of use by subjects with medial knee OA. Footwear design may be an important therapeutic strategy for OA of the knees.



Disclosure: N. Shakoor, None; **R. Lidtke**, None; **R. Mikolaitis**, None; **R. Trombley**, None; **L. Fogg**, None; **J. A. Block**, None.

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A Randomized Trial of Realignment Therapy for Treatment of Medial Tibiofemoral Osteoarthritis. David J. Hunter[1], K. Gross[2], Paula I. McCree[1], Ling Li[1], Kelly Hirko[1], Bin Zhang[3] and William Harvey[1], [1]New England Baptist Hospital, Boston, MA, [2]MGH Inst Health Prof, Boston, MA, [3]Boston Univ School Medicine, Boston, MA

Purpose: Biomechanical studies of persons with medial tibiofemoral OA demonstrate that even with appropriate valgus knee bracing, large medial forces remain, suggesting that the addition of other interventions to further improve limb alignment may be of therapeutic value. The objective of this 30-week randomized crossover trial was to determine whether a multi-modal realignment therapy (consisting of *valgus knee brace + motion control shoes + neutral foot orthoses*) would be successful in relieving pain and improving function among persons with medial tibiofemoral OA.

Method: We conducted a double blind, *randomized crossover trial* of a multi-modal realignment therapy for persons with medial tibiofemoral OA. Trial participants met ACR criteria for OA with knee pain, aching or stiffness on most of the past month and radiographic evidence of a definite osteophyte. We tested two different treatments: A) CONTROL TREATMENT consisting of a neutral knee brace (no valgus angulation), flat unsupportive foot orthoses, and shoes with a flexible midsole; and B) ACTIVE TREATMENT consisting of a valgus knee brace, customized neutral foot orthoses, and shoes designed for motion control. For each subject, the *trial lasted 30 weeks*, including 12 weeks each of active and control treatment separated by a 6-week washout period. The primary outcome was change in knee pain and function as assessed by the WOMAC Osteoarthritis Index (VAS version). An unstructured correlation matrix for observations within subjects was used in generalized estimating equation fitting. The final linear regression model was conducted with exclusion of the differential carryover effect.

Results: 80 participants with medial tibiofemoral OA were randomized. 63% were female. Their mean age was 62 years, mean BMI was 34 kg/m^2 and mean WOMAC pain score was 8.9 (0-20 scale). The main effects are depicted in the table below. There was no evidence of a

carryover effect in the initial analyses. After removing the potential for carryover effect, the model demonstrated that the mean difference in pain between the active and control treatments was -0.86 units (95% confidence interval 1.74, 0.01 [p=0.05]) on the WOMAC pain scale (range 0-20), indicating a small decrease in pain in association with the multi-modal active treatment.

Predictor	B coefficient for end of treatment WOMAC pain (negative values indicating a decrease in pain)
Active treatment (control as reference)	-0.86
(95% confidence interval)	(-1.74, 0.01)
p-value	0.05
Baseline WOMAC pain score	0.38
(95% confidence interval)	(0.19, 0.57)
p-value	0.0002
Treatment, period 1 vs. period 2	-0.04
(95% confidence interval)	(-0.92, 0.84)
p-value	0.93

Conclusion: The effects of multi-modal realignment therapy on pain and function in persons with medial tibiofemoral OA are small and of equivocal clinical and statistical significance.

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Varus Malalignment Diminishes the Structure-Modifying Effects of Doxycycline (Doxy) in Patients with Knee Osteoarthritis. Rafael Chakr[1], Kenneth D. Brandt[2], Dennis C. Ang[1] and Steven A. Mazzuca[1], [1]Indiana University, Indianapolis, IN, [2]Kansas Univ Medical Center, Fairway, KS

Purpose: The inconsistent results of clinical trials of structure-modifying osteoarthritis drugs (SMOADs) may be due to the presence of abnormal intra-articular stresses that preclude potential benefit from pharmacotherapy. Because varus malalignment increases loading of the medial tibiofemoral compartment and, hence, the risk of OA progression, it may attenuate the benefit of a SMOAD aimed at slowing joint damage. Herein we describe results of a recent subgroup analysis of our previously published randomized clinical trial (Arthritis Rheum 2005;52:2015) asking whether varus malalignment reduced the structure-modifying effect of doxy in OA.

Method: In this placebo-controlled trial, 379 subjects underwent an interim (16-mo) and/or close-out (30-mo) x-ray exam. All were obese, 45-64 year old women who had unilateral Kellgren and Lawrence grade 2-3 knee OA at baseline. The primary outcome was medial compartment joint space narrowing (JSN) measured manually in semiflexed anteroposterior radiographs acquired with standardized fluoroscopic positioning. The anatomic-axis angle (AAA) was measured in each baseline radiograph by one of two readers (inter-reader ICC = 0.95) and transformed to an estimate of the mechanical-axis angle (MAA) using a validated regression equation (MAA=0.915*AAA+13.895, R^2=0.77) (Arthritis Care Res 2006;55:306). Knees with MAA<178° were classified as varus. Treatment group comparisons were performed using a mixed-effect linear model and adjusted for age, BMI, visit (16- or 30-month), clinical center and baseline joint space width.

Results: In our published comparison with placebo, doxy slowed the annualized rate of medial JSN in index (OA) knees by 39% at 16 months (0.11 vs. 0.18 mm/yr, P=0.027) and by 33% at 30 months (0.12 vs. 0.18 mm/yr, P=0.017). Our current subgroup analyses of non-annualized JSN (table) indicated, however, that among varus OA knees, JSN occurred at similarly rapid rates in both treatment groups over both intervals (0.20 - 0.27 mm/yr). In contrast, among non-varus knees, 16-mo JSN in the doxy group was 43% slower than in the placebo group (0.09 vs. 0.16 mm/yr, P=0.080), and 30-mo JSN was 38% slower (0.10 vs. 0.17 mm/yr, P=0.026).

Non-annualized medial compartment JSN (*Mean* ± *SD*, mm) by treatment group: results in varus and non-varus OA knees						
	Varus OA Knees			**Non-varus OA Knees**		
	Doxycycline	**Placebo**	***P***	**Doxycycline**	**Placebo**	***P***
16-mo JSN	0.26 ± 0.39	0.36 ± 0.57	0.230	0.12 ± 0.42	0.21 ± 0.52	0.080
N of knees	37	45		151	146	
30-mo JSN	0.49 ± 0.64	0.55 ± 0.62	0.448	0.26 ± 0.58	0.42 ± 0.73	0.026
N of knees	37	42		146	138	

Conclusion: These *post hoc* analyses show that varus malalignment negated the slowing of structural progression of medial compartment OA by doxy. Given the prime importance of abnormal intra-articular stress in the etiopathogenesis of common, garden-variety OA (Brandt et al. Seminars Arthritis Rheum. In press), it is likely that other conditions which, like malalignment, increase joint loading (e.g., genetic or developmental abnormalities in joint shape, neuromuscular abnormalities that impair micro-coordination [sarcopenia, proprioceptive defects]) can also render SMOADs ineffective.

Disclosure: R. Chakr, None; **K. D. Brandt**, None; **D. C. Ang**, None; **S. A. Mazzuca**, None.

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Effect of Cane Use On Lower Limb Biomechanics and Pain in Knee Osteoarthritis. Sarah M. Lee[1], Constance Heiney[2], Karen L. Perell[3], Sulabha Masih[2], Nancy D. Harada[2], Jennifer M. Yentes[2] and Meika A. Fang[2], [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [3]California State University, Fullerton, CA

Purpose: Dynamic loading of the medial knee is associated with progression of knee osteoarthritis (OA). Therefore interventions that lessen the load of the medial knee may minimize the risk of disease progression. Previous studies have shown that walking with a cane has an immediate effect of reducing the peak knee adduction moment and peak vertical force in people with knee OA. The objective of the current study is to determine whether short-term cane use will lead to persistent alterations in gait biomechanics and improve pain and physical activity in individuals with painful knee osteoarthritis.

Method: Twenty-one overweight or obese participants with symptomatic knee OA were given a single point cane to use contra-lateral to the painful limb for eight weeks. All participants underwent gait assessment with and without a cane at baseline and at 8 weeks by using a three-dimensional motion capture system and an in-shoe dynamic pressure distribution system. The peak vertical force and mean lateral deviation of the center of pressure (COP) of the painful limb were measured. OA-related pain was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and physical activity level was measured with the Physical Activity Scale for Elderly (PASE).

Results: Twenty-one participants (mean age 62.6 ± 7.9 years, male) completed the study. Cane users who used the cane frequently (≥ 4 days per week) had greater pain at baseline than those who used the cane less frequently and 50% of the frequent cane users demonstrated a 20% or greater decrease in pain. The frequent cane users also had a 22% increase in the mean lateral deviation of COP for the painful limb when walking with a cane compared to walking unaided during the baseline visit (P=0.002). After 8 weeks of walking with a cane, the frequent cane users maintained this increase in mean lateral COP deviation when walking with and without a cane. Peak vertical force decreased 11.9% on the painful limb with cane use after eight weeks of walking with a cane. There were no significant changes in physical activity level as measured with the PASE.

Conclusion: To our knowledge, this is the first study to demonstrate that frequent cane use in people with painful knee OA display an immediate lateral shift in the center of pressure; this effect is maintained in frequent cane users after walking with a cane for 8 weeks. Furthermore, we show that frequent cane use may reduce pain and decrease peak vertical force in the painful limb. These findings suggest that regular cane use may be potential cost-effective and noninvasive interventions for knee OA by unloading the medial compartment of the knee and decreasing pain.

Disclosure: S. M. Lee, None; **C. Heiney**, None; **K. L. Perell**, None; **S. Masih**, None; **N. D. Harada**, None; **J. M. Yentes**, None; **M. A. Fang**, None.

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Varus Thrust Is Associated with Pain in Knee Osteoarthritis. Grace H. Lo, Timothy McAlindon, Kimberly A. Carr, Melanie A. Ripley, Melynn Nuite and William F. Harvey, Tufts Medical Center, Boston, MA

Purpose: With its lack of effective treatment and high prevalence, the public health impact of osteoarthritis (OA) is substantial. Varus thrust (VT) is the rapid lateral bowing of the knee visualized during ambulation. VT is predictive of longitudinal medial joint space narrowing in knee OA; however, there are no data on its relationship with pain. We hypothesized that those with VT would have more pain, especially with weight-bearing activities, as compared to those without VT.

Method: This is a cross-sectional study of a convenience sample selected from participants of a randomized controlled trial of vitamin D for symptomatic radiographic knee OA. The parent study is currently still blinded to treatment allocation. All those in the RCT were eligible to participate in this study. Those using ambulatory devices were excluded. Participants were video recorded using a standard digital video camera (60 Hz) walking at a self-selected speed. These videos were viewed at separate reading sessions by two rheumatologists trained to evaluate VT. Videos were scored for VT definitely present, possibly present, or absent. Disagreements were adjudicated by consensus of both evaluators. At the same visit, weight, and height, and the WOMAC pain questionnaire (Likert) was administered evaluating the study knee.

For analytic purposes, VT was dichotomized (VT-d) as either definitely present or (possibly present or absent). We calculated LSMEANS for the total WOMAC pain score by VT-d adjusting for age, sex, height, and weight. We performed ordinal logistic regressions with *individual WOMAC pain questions* as the outcomes and VT-d as the predictor, subsequently adjusting for age, sex, height, and weight.

Results: Participants (N=82) (age 63.0 (±8.5), BMI 30.2 (±5.4), 60% female, 31% with definite VT, 18% with possible VT, and 51% with absent VT. Those with versus without definite VT had a mean total WOMAC pain score (0-20) of 6.3 versus 3.9, p = 0.007. Shorter participants had more pain. Heavier and male participants had a higher prevalence of definite VT. The table shows the proportional odds ratios for each WOMAC pain question.

Individual WOMAC pain questions		***Unadjusted Proportional Odds Ratio for Pain with v. without definite VT***	****Adjusted Proportional Odds Ratio for Pain with v. without definite VT***
Weight-bearing Questions	Pain with walking	5.0 (1.9 – 12.8)	5.5 (2.0 – 15.1)
	Pain standing upright	5.5 (2.2 – 13.9)	6.0 (2.2 – 16.2)
	Pain with stairs	1.9 (0.8 – 4.6)	2.0 (0.8 – 5.2)
Non-weight-bearing Questions	Pain at night in bed	2.0 (0.8 – 4.9)	3.0 (1.1 – 8.3)
	Pain sitting or lying	1.5 (0.5 – 3.8)	1.8 (0.7 – 4.9)

*adjusted for age, sex, height and weight

Conclusion: In those with symptomatic knee OA, the presence of definite VT was associated with greater overall knee pain, but specifically during weight-bearing activities. The evaluation of individual WOMAC pain questions allows for better characterization of the heterogenous pain that occurs in knee OA. These findings suggest that direct treatment of VT (e.g. via bracing or gait modification) may lead to improvement of symptoms.

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Acute Meniscal Injury Is Associated with Synovial Inflammation: Cellular and Molecular Characterization of Synovitis. Carla R. Scanzello[1], Brian P. McKeon[2], Eva Umoh[3], Bryan Swaim[2], Edward F. DiCarlo[3], David J. Hunter[2], John C. Richmond[2], Jeffrey N. Katz[4], Mary K. Crow[3] and Steven R. Goldring[3], [1]Rush University Med Ctr, Chicago, IL, [2]New England Baptist Hospital, Boston, MA, [3]Hospital for Special Surgery, New York, NY, [4]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Purpose: Synovitis is related to pain in patients with osteoarthritis (OA), but little is known regarding synovial responses in patients with acute meniscal injury, which predisposes to development of OA. A prospective study was designed to examine histological and molecular changes in synovium (SM) in patients with acute meniscal injury presenting for menisectomy.

Method: 24 patients (16 M/8F, median age 47, range 21-60) with acute meniscal tears without clinical or radiographic evidence of pre-existent OA underwent arthroscopy. SM biopsies were obtained from the medial and lateral gutters and suprapatellar pouch. Biopsies were processed for histology and RNA analysis. On H&E staining, six histopathologic features were scored: perivascular inflammation, vascularity, detritis, fibrosis, perivascular edema and SM hyperplasia. Scores were compared to patients with pre-existing OA (n=18) from an additional study sample. RNA was prepared for microarray analysis from a subset of patients. Affymetrix U133 + 2.0 chips were used, data analyzed using Genespring software, and pathway over-representation analysis carried out with a focus on innate immune responses.

Results: 23 biopsies at each location (n = 69) were analyzed. Of the histologic features evaluated, synovial hyperplasia (40/69, 58%) was most common, and perivascular inflammation was observed in 32% of biopsies. The spectrum of histologic change was similar to OA, though inflammatory scores were lower in the acute meniscal injury group. From histology, we identified patients with or without inflammation and performed microarray analysis on 8 representative samples. Comparative analysis of gene expression in inflammatory vs. noninflammatory samples demonstrated 260 genes differentially expressed ≥ 2.0 fold, $p<0.05$. Molecular signatures consistent with lymphocyte activation and recruitment were observed. Of note, chemokines involved in cellular trafficking and common-gamma chain cytokine signaling components were enriched in the inflammatory biopsies.

Conclusion: Comparison of expression patterns in patients with or without histologic inflammation revealed enrichment of chemokine and cytokine signaling pathways associated with lymphocyte recruitment and activation in the inflammatory SM biopsies. These patients are being followed longitudinally to determine whether SM inflammation patterns are predictive of post-operative clinical course. Characterization of the cellular and molecular processes associated with joint injury could lead to novel therapeutic approaches for reducing the risk of post-traumatic OA.

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Comparative Clinical Trial of S-Adenosylmethionine Versus Nabumetone in the Treatment of Knee Osteoarthritis: An 8-Week, Multicenter, Randomized, Double-Blinded Study. Jin Hyun Kim[1], Eun Young Lee[1], Eun-Mi Koh[2], Hoon-Suk Cha[2], Bin Yoo[3], Chang Keun Lee[4], Yun Jong Lee[5], Heejung Ryu[5], Ki Hoon Lee[6] and Yeong Wook Song[1], [1]Seoul National University Hospital, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [4]University of Ulsan Collage of Medicine, Asan Medical Center, Seoul, South Korea, [5]Seoul National University Bundang Hospital, Seongnam, South Korea, [6]Jeonju University, Jeonju, South Korea

Purpose: S-adenosylmethionine (SAMe) has an anti-inflammatory and analgesic effect, and was reported to ameliorate pain and dysfunction of knee oteoarthritis (OA). We compared the efficacies and safeties of SAMe and nabumetone in Korean patients with knee osteoarthritis.

Method: This study was a multicenter, 8-week, randomized, double-blinded, double-dummy, phase IV clinical trial. Symptomatic OA patients were randomized to receive SAMe 400 mg three times a day or nabumetone 1000 mg once a day with dummy placebo for 8 weeks. The primary end point was patient assessment of pain intensity using a visual analog scale (VAS) and the secondary end points were an improvement of functional class, patient's global assessment of disease status, physician's global assessment of response to therapy, and WOMAC index. Efficacies after 4 and 8 weeks of treatment were evaluated between two groups, and all patients were evaluated for adverse events.

Results: One hundred and thirty four patients were randomly allocated to receive SAMe 400 mg (n=67) three times a day or nabumetone 1000 mg (n=67) once a day for 8 weeks. Twenty three patients in SAMe group and 14 patients in nabumetone group withdrew during the study. An analysis of changes in pain intensity between week 0 and week 8 demonstrated that SAMe and nabumetone were effective to decrease pain intensity in each group (mean ± SD, SAMe, 13.0 ± 20.8, p<0.001; nabumetone, 15.7 ± 20.9, p <0.001) and the difference in efficacy between two groups was not significant (p=0.451). The secondary end points showed the significant improvement between week 0 and week 8. The differences of efficacies in secondary endpoints between two groups were not significant (patient's general assessment of disease, p=0.276; physician's assessment of treatment response, p=0.140; WOMAC index, p=0.459). No significant differences between the incidences of drug-related clinical or laboratory adverse events were observed.

Conclusion: SAMe was found to be as effective as nabumetone and well tolerated by knee OA patients in Korea.

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Alanine Aminotransferase (ALT) Activity During Early Acetaminophen Therapy in Patients with Osteoarthritis. Edwin Kuffner, Kimberly Cooper, Jeffrey Baggish, Joseph M. Lynch, Brenda Zimmerman and Anthony Temple, McNeil Consumer Healthcare, Fort Washington, PA

Purpose: Acetaminophen (APAP) is a first-line analgesic for the management of OA pain, recommended in the OA Guidelines of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). Over-the-counter (OTC) analgesic labels instruct patients not to use these medications for pain for more than 10 days without consulting a doctor.

Some healthy volunteers given APAP 4000 mg/d for up to 2 wks were reported to have ALT elevations ›3 times upper limit of reference range (ULRR) which continued for several days after stopping therapy but then decreased. To determine whether this phenomenon was transient or persistent with the continued use of APAP, we retrospectively analyzed ALT data collected within approximately 2 wks of initiating therapy with the maximum recommended daily dose (MRDD) of APAP (3900-4000 mg/d) and determined elevated ALT and rates of resolution while the patients remained on APAP therapy.

Methods: 3 McNeil-sponsored, controlled OA trials included ALT measurements within approximately 2 wks of initiating APAP monotherapy. Patients with elevated ALT at screening or baseline were excluded from the analysis. Maximum ALT for each patient was stratified by degree of elevation: >ULRR, >1.5X ULRR, >3X ULRR, >5X ULRR, or ALT >3X ULRR and bilirubin ≥2X ULRR. Resolution of ALT elevation was defined as an ALT ≤ULRR after the last dose of study drug. If ALT at study completion was lower than the maximum ALT observed during the trial but >ULRR, the ALT elevation was considered to be decreasing.

Results: All trials had double-blind study designs and were at least 12 wks in duration. Patients in 2 placebo-controlled trials received extended-release APAP 3900mg/d; patients in the active-controlled trial received extra-strength APAP 4000mg/d. ALT remained within the normal range throughout the 2 wk analysis period for 376 (80.7%) of 466 patients. At some point during the 2 wk analysis period, 90 (19.3%) patients had an ALT >ULRR; 21 (4.5%) patients had an ALT >1.5X ULRR; and 4 (0.9%) patients had an ALT >3X ULRR. No patient had ALT >5X ULRR, or >3X ULRR with bilirubin ≥2X ULRR. No patient exhibited signs or symptoms of hepatotoxicity or hepatic failure. ALT resolution was observed for 62 (68.9%) of 90 patients with elevations and decreasing ALT was observed for 19 (21.1%) patients. Incidence of adverse events possibly of hepatic origin was similar between patients without and with elevated ALT during the 2 wk analysis period.

Conclusion: Fewer than 5% of OA patients taking the MRDD of APAP for 2 wks had elevated ALT (>1.5X ULRR). These elevated values resolved or were decreasing during continued APAP therapy in >95% of patients and were not accompanied by signs or symptoms suggestive of liver toxicity. These data show that while some individuals who take APAP may experience increased ALT during treatment that is consistent with OTC labeling, nearly all of these elevations resolved with continued APAP use.

Disclosure: E. Kuffner, McNeil Consumer Healthcare, 3 ; **K. Cooper**, McNeil Consumer Healthcare, 3 ; **J. Baggish**, McNeil Consumer Healthcare, 3 ; **J. M. Lynch**, McNeil Consumer Healthcare, 3 ; **B. Zimmerman**, McNeil Consumer Healthcare, 3 ; **A. Temple**, McNeil Consumer Healthcare, 5 .

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A Walking Model of Osteoarthritis (OA) Knee Pain: A Double-Blind, Placebo-Controlled, 3-Period Crossover Study to Evaluate the Analgesic Effects of Naproxen and Tramadol/Acetaminophen in Patients with OA of the Knee. Elena Peeva[1], CR Beals[1], JA Bolognese[2], A. Kivitz[3], L. Taber[4], A. Harman[1], H. Chung[1], Steven S. Smugar[1] and Roland W. Moskowitz[5], [1]Merck & Co., Inc., Rahway, NJ, [2]Cytel, Inc., MA, [3]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [4]Pivotal Research Ctrs, Peoria, AZ, [5]University Hospitals, Beachwood, OH

Purpose: New clinical trial designs for OA pain that can be conducted faster and with fewer patients would speed the testing of novel therapeutic agents. We developed a walking model of OA that takes advantage of the clinical observation that patients frequently report an increase in OA pain during and following exertion. The model is based on standardized series of controlled walks over a short period of time that are used to reproducibly elicit specific knee pain in patients with OA. The objective of this study was to validate the walking model in OA by evaluating the acute efficacy of an NSAID and a weak opiate in patients with OA.

Methods: Randomized, placebo-controlled, 3-period balanced cross-over study comparing naproxen 500 mg bid and tramadol/acetaminophen 37.5/325 mg per tablet in titration over a three day period to full dose (75/650 mg/mg) in patients ≥45 years with OA of the knee (N=21). Patients performed a set of standardized 20-minute treadmill walks at 2, 4, 5 and 6 hours post-drug administration on Day 1, and at 4, 5 and 6 hours post-dose on Day 3. The 2, 4 and 6-hour walks were identically paced at a speed set by the patient (self-pace) at pre-study; the 5-hour walks were at a pace 10-30% faster than the self-pace (high-pace). The primary endpoint was change from baseline in time-weighted average pain intensity (TWA PI), on a numerical scale from 0-10, for tramadol/acetaminophen and naproxen vs. placebo for the self-paced walks on Day 3. Time to moderate pain was also evaluated.

Results: Results are shown in the **Table**. For the primary endpoint of TWA PI change from baseline for self-paced walks on Day 3, the comparison was statistically significant for tramadol/acetaminophen ($p<0.05$), but not for naproxen ($p=0.089$). When excluding an outlier patient with PI increase >3 standard deviations above the mean PI, both tramadol/acetaminophen ($p<0.001$) and naproxen ($p<0.01$) were significantly more effective than placebo for the primary endpoint.

Conclusion: The walking model is a promising method for identifying acute treatment effects of drugs for OA pain.

Endpoint	**Tramadol/ acetaminophen**	**Naproxen**	**Placebo**
TWA PI change from baseline, self-paced walks Day 1	-1.5***	-1.0*	-0.4
TWA PI change from baseline, self-paced walks Day 3	-1.7*	-1.5	-0.9
TWA PI change from baseline, self-paced walks Day 3 (outlier excluded)	-2.0***	-1.7**	-0.7
TWA PI change from baseline, high-paced walks Day 1	-1.0**	-0.5	0.2
TWA PI change from baseline, high-paced walks Day 3	-1.3**	-1.1*	-0.2
Time to moderate pain, Day 1, self-paced walks	17.8 min***	16.4 min*	14.2 min
Time to moderate pain, Day 3, self-paced walks	18.0 min**	18.4 min***	14.6 min
All values are least squares means TWA PI: time-weighted average pain intensity *p<0.05; **p<0.01; ***p<0.001 vs. placebo			

Disclosure: E. Peeva, Merck Pharmaceuticals, 3 ; **C. Beals**, Merck Pharmaceuticals, 3 ; **J. Bolognese**, Merck Pharmaceuticals, 3 ; **A. Kivitz**, None; **L. Taber**, None; **A. Harman**, Merck Pharmaceuticals, 3 ; **H. Chung**, None; **S. S. Smugar**, Merck Pharmaceuticals, 3 ; **R. W. Moskowitz**, Merck Pharmaceuticals, 2, Merck Pharmaceuticals, 5 .

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Long-Term Tanezumab Use for Treatment of Moderate to Severe Osteoarthritic Knee Pain: An Open-Label Extension Study. Nancy E. Lane[1], Thomas J. Schnitzer[2], Charles A. Birbara[3], Michael D. Smith[4], Sue Simpson[4], Mark T. Brown[4] and Christina J. McManus[5], [1]Univ of California at Davis, Sacramento, CA, [2]Northwestern Univ, Chicago, IL, [3]Univ of Massachusetts, Worcester, MA, [4]Pfizer Inc., New London, CT, [5]UBC Scientific Solutions, Southport, CT

Purpose: Elevated nerve growth factor (NGF) levels in injured or inflamed tissue are associated with increased pain perception. Tanezumab, a humanized monoclonal antibody, inhibits NGF with high specificity and affinity. This open-label extension study (1009) following a Phase II, placebo-controlled, multiple-dose study (1008), was conducted to evaluate long-term use of tanezumab in patients with osteoarthritis (OA) of the knee. **Method:** Patients from 1008 who had received 2 infusions of tanezumab or placebo and were followed for ≥8 weeks after last infusion were eligible to enroll in 1009 at Week 16 of 1008. In 1009, all patients received tanezumab 50 µg/kg (IV) at Weeks 0 and 8 and subsequent 8-week intervals at the discretion of the investigator. Analyses included change from 1008 baseline in overall pain intensity in index knee, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales, and Subject Global Assessment (SGA) all on 100 mm VAS scales, and Short-Form 36 (SF-36) general health status measure. **Results:** Similar numbers of patients from each of the 1008 treatment groups (placebo, tanezumab 10, 25, 50, 100, and 200 µg/kg) were enrolled in 1009 (n=281; 39% male, 89% white, mean age 59 [SD±8] years). Median duration of treatment was 198 days. Few patients (11%) discontinued due to lack of efficacy indicating that treatment had a persistent beneficial effect. Patients from 1008 placebo, 10 or 25 µg/kg groups reported improvement in overall pain intensity after switching to 50 µg/kg tanezumab (Table). In contrast, patients switched from higher doses of tanezumab (100 or 200 µg/kg) reported slightly decreased efficacy at Week 4, consistent with a reduction in tanezumab dose from 1008 to 1009. Mean pain scores between Wks 8-32 were similar regardless of treatment received in 1008. Similar trends were observed for SGA and WOMAC scores. No notable changes in SF-36 were found in 1009. The most frequently reported treatment-related AEs for 1009 were hypoesthesia, paraesthesia, dizziness, and peripheral edema. AEs of abnormal peripheral sensation, reported by 6% of subjects in 1009, were mostly rated as mild and were transient. Allodynia and dysesthesia were not reported. **Conclusion:** Repeated doses of 50 µg/kg tanezumab were generally safe and well tolerated. Persistent beneficial efficacy similar to that observed in study 1008 was demonstrated and maintained in OA patients over the long term.

	1008 Treatment					
	Placebo	**Tanezumab (µg/kg)**				
		10	**25**	**50**	**100**	**200**
Baseline knee pain	69±10	71±8	70±11	67±11	70±10	71±10
1008 endpoint	-18±27	-20±26	-24±29	-26±30	-39±24	-43±25
Wk 4	-40±22	-41±23	-37±27	-34±25	-33±23	-38±30
Wk 8	-32±28	-40±28	-36±27	-28±29	-36±28	-32±29
Wk 32	-21±28	-34±30	-33±29	-35±27	-31±31	-27±33

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Effect of Hypertensive Status and Antihypertensive Treatment-On Cardiovascular Outcomes in Patients Receiving Etoricoxib or Diclofenac: An Analysis of the MEDAL Program. A. Gammaitoni, Sean P. Curtis, A. Kaur, H. Wang, Q. Dong, Steven S. Smugar and Paul Peloso, Merck & Co., Inc., Rahway, NJ

Purpose: It has been postulated that excess CV events observed in patients receiving NSAIDs may be related to COX-2 mediated effects on blood pressure. In the MEDAL program, the rate of thrombotic CV events was similar between etoricoxib and diclofenac despite an ~2 mm Hg average increase in systolic BP (SBP) on etoricoxib. We previously found that CV events were significantly related to baseline SBP but not on-treatment change in SBP. ~26% of those assigned to etoricoxib and 20% of those on diclofenac had changes in BP treatment (new or added therapy) during the trial. Here we explore the effect of investigator management of hypertension (HTN) on confirmed thrombotic CV serious adverse experiences.

Method: Patients receiving etoricoxib or diclofenac were pooled (N=34,699) and classified by baseline HTN status (SBP≥140mmHg or DBP ≥90mmHg), baseline antihypertensive (antiHTN) drug use, and new antiHTN use or adjustment during the trial. Hazard ratios (HR) for the 8 possible categories of patients were calculated using a Cox proportional hazard model with terms for treatment, patient category, and stratification factors baseline aspirin use, protocol/disease status for confirmed thrombotic CV events within 14 days of therapy discontinuation.

Results: Results are shown in the Table. HRs for CV events were largest in patients with a diagnosis of pre-existing HTN, who used baseline antiHTN drugs and who also needed further BP medication adjustments during the trial. Patients who did not require on-treatment antiHTN adjustment had relatively lower HRs.

Conclusion: HTN at the baseline visit, or need for management of HTN throughout the trial was associated with higher CV event rates. Given our previous finding that short term changes in BP associated with therapy was a less relevant predictor, these data emphasize the need for close monitoring of blood pressure and adequate HTN management for patients receiving traditional NSAIDs or COX-2 inhibitors.

Table. Effect of baseline and on-treatment hypertensive status and antihypertensive use or adjustment on thrombotic CV events

Covariate			Relative Risk ‡	95% CI for Relative Risk	p-Value
Etoricoxib vs. Diclofenac			0.94	(0.81, 1.09)	0.402
Baseline hypertension*	Baseline antihypertensive use	On-treatment antihypertensive adjustment			
N	N	N	1.00 (reference)	NA	NA
N	Y	N	1.52	(1.20, 1.93)	<0.001
N	Y	Y	2.52	(2.00, 3.18)	<0.001
Y	N	N	1.54	(1.10, 2.17)	0.013
Y	N	Y	1.77	(1.19, 2.62)	0.005
Y	Y	N	1.74	(1.27, 2.39)	<0.001
Y	Y	Y	2.83	(2.19, 3.66)	<0.001
N	N	Y	1.86	(1.36, 2.53)	<0.001

n/N=the number of patients with events/total number of patients, CI=Confidence Interval

† Number of events per 100 patient-years.

*Baseline hypertension is defined as measured SBP≥140mmHg or DBP ≥90mmHg, not defined as a history of hypertension.

‡ Relative risk is estimated from Cox proportional hazard model with terms for 2-level treatment, 8-level strata and stratification factors of baseline aspirin use, protocol/disease status

Disclosure: A. Gammaitoni, Merck Pharmaceuticals, 3 ; **S. P. Curtis**, Merck Pharmaceuticals, 3 ; **A. Kaur**, Merck Pharmaceuticals, 3 ; **H. Wang**, Merck Pharmaceuticals, 3 ; **Q. Dong**, Merck Pharmaceuticals, 3 ; **S. S. Smugar**, Merck Pharmaceuticals, 3 ; **P. Peloso**, Merck Pharmaceuticals, 3 .

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The Comparative Safety of Analgesics in Older Adults with Arthritis. Daniel H. Solomon[1], Jeremy Rassen[2], Robert Glynn[2], Joy Lee[2], Raisa Levin[2] and Sebastian Schneeweiss[2], [1]Brigham & Women's Hospital, Boston, MA, [2]Pharmacoepidemiology, Boston, MA

Purpose: The safety of analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids has recently been called into question. However, there is little information on their comparative safety across a broad range of clinically morbid adverse events. We examined the comparative safety of non-selective (ns) NSAIDs, COX-2 selective NSAIDs (coxibs), and opioids.

Methods: We assembled a cohort of Medicare beneficiaries with diagnoses of osteoarthritis (OA) or rheumatoid arthritis (RA) who initiated an nsNSAID, coxib, or opioid. Participants were matched on a comprehensive propensity score, and hazard ratios (HRs) were calculated among propensity-matched cohorts. These analyses focused on morbid adverse events (AEs) commonly related to analgesics, including cardiovascular (CV) events (MI, stroke, HF, re-vascularization or cardiac death), gastrointestinal (GI) bleeding, and fractures (hip, wrist, humerus, and pelvis). Several global safety measures were assessed, including AE leading to hospitalization, AE leading to hospitalization and death, and all-cause mortality. Finally, the numbers needed to harm (NNH) with a coxib or opioid compared with an nsNSAID were calculated to observe one of these AEs at 30, 180, and 365 days.

Results: The average age of participants was 80 years, 84% were female, 89% had OA and the rest RA. After propensity score matching, the three analgesic cohorts were very well balanced on baseline covariates. Compared with nsNSAIDs, coxibs and opioids both exhibited elevated HRs for CV events (see **Table**). GI bleeding risk was similar for coxibs compared with nsNSAIDs and for opioids compared with nsNSAIDs. Coxib use had a similar risk for fracture as nsNSAIDs, however the HR was elevated with opioid use. Both coxibs and opioids increased the HR of AEs requiring hospitalization compared with nsNSAIDs. The HR for all-cause mortality was elevated for both coxibs and opioids compared with nsNSAIDs. At 30 days, the NNH to observe an excess fracture for treating with an opioid compared with nsNSAIDs was 43 (95% 35 – 54). The NNH at 30 days to observe an excess death was 114 (95% CI 78 – 212) for an opioid versus an nsNSAID. At 365 days, the NNH to observe an excess AE leading to hospitalization was 31 (95% CI 18 – 122) for an opioid and 35 (95% CI 20 – 135) for a coxib compared with nsNSAID.

Conclusion: In this non-randomized analysis, the comparative safety of analgesics varies depending on the specific AE. On balance, coxibs and opioids exhibit an increased hazard ratio for many AEs and for several global measures of safety as compared with nsNSAIDs. The NNH suggest that the risks observed are clinically relevant.

Table: Hazard Ratios (95% CIs) for Major Adverse Events Among Propensity Matched Cohorts

	nsNSAIDs	Coxibs	Opioids
Any cardiac	1.00	1.32 (1.06-1.66)	1.50 (1.19-1.91)
Any GI bleed	1.00	0.92 (0.58-1.45)	0.89 (0.53-1.47)
Any fracture	1.00	0.98 (0.64-1.49)	4.91 (3.47-6.96)
Any hospitalized AE	1.00	1.22 (1.00-1.49)	1.48 (1.21-1.82)
Hospitalized AE leading to death	1.00	1.59 (0.92-2.77)	1.43 (0.78-2.62)
All-cause mortality	1.00	1.37 (1.03-1.83)	2.12 (1.58-2.83)

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Biochemical Markers of Bone and Cartilage Remodelling: Interest in the Prediction of Lumbar Disc Degeneration Progression and Effects of Strontium Ranelate Over a 3-Year Period. Olivier Bruyere[1], Julien Collette[1], Rita Deroisy[1], Véronique Rabenda[2], Audrey Neuprez[1], Mickaël Hiligsmann[2] and Jean Y. Reginster[1], [1]University of Liege, Liege, Belgium, [2]University of Liège, Liège, Belgium

Purpose: We previously reported that strontium ranelate could prevent lumbar spinal osteoarthritis (OA) progression in postmenopausal osteoporotic women with prevalent lumbar disc degeneration (LDD). The aim of the present analysis is to assess (1) the effect of strontium ranelate on biochemical markers of bone and cartilage remodelling in patients with prevalent LDD and (2) if the baseline value or the short-term changes in these markers were associated with the progression of LDD.

Method: This study is a post-hoc analysis of the SOTI and TROPOS trials including osteoporotic women with prevalent LDD treated for 3 years with strontium ranelate or placebo. Four biochemical markers were assessed at baseline, after 3, 6, 12, 24 and 36 months of follow-up: serum CTX I, urinary CTX II, serum COMP, and serum YKL-40. At baseline and 3 years, four lumbar inter-vertebral spaces were evaluated for the presence and severity of osteophytes, disc space narrowing and sclerosis, leading to the calculation of a global LDD score for each intervertebral space.

Results: 1105 patients completed the study. In the placebo group (n=539), the level of u-CTX II was highest in women with prevalent LDD compared to women without LDD (p=0.0003). However, the levels of s-CTX I, COMP and YKL-40 were not significantly different between patients with prevalent LDD compared to patients without LDD. Out of these 539 placebo-treated patients, 17.1% experienced a disease progression (i.e. the global LDD score increased by at least one grade of severity (in one or more intervertebral spaces) during the 3-year follow-up period). There were no significant differences in the baseline level of the biochemical markers between patients with and without LDD progression. However, patients with a progression of the disease experienced a decrease in COMP of 1.6 (10.5) % after 3 months compared to an increase of 1.9 (12.7) % in patients without LDD progression (p=0.04). The 3-month changes in the other biochemical markers were not predictive of the progression of the disease in the placebo group. After 3 months of treatment, strontium ranelate was able to significantly decrease, compared to placebo, the level of s-CTX I (p<0.001) and u-CTX II (p<0.001). Strontium ranelate also increases, compared to placebo, the level of COMP (p<0.001). However, no significant effect on YKL-40 was observed. During the 3 years of follow-up, the same trends were observed.

Conclusion: The positive effect of strontium ranelate on LDD progression could be partly explained by the observed decrease in bone (s-CTX I) and cartilage (u-CTX II) resorption. The exact clinical interest of COMP change must be further evaluated as a recent study has shown that a decrease of COMP, previously suggested as being a markers of cartilage destruction, was associated with an increased risk of OA progression.

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Safety and Efficacy of Diclofenac Sodium Gel for Knee Osteoarthritis in Patients Aged <65 Years Versus ≥65 Years. Roy Altman[1], F. Michael Gloth[2], Morris S. Gold[3] and Richard Petruschke[3], [1]University of California, Los Angeles, CA, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Novartis Consumer Health, Inc., Parsippany, NJ

Purpose: Evaluate the efficacy and safety of topical diclofenac sodium 1% gel (DSG) vs vehicle (placebo) in subjects with knee osteoarthritis (OA) aged <65 years vs subjects aged ≥65 years.

Method: This was an analysis of pooled data from three 12-week, randomized, double-blind, parallel-group, multicenter trials comparing DSG with vehicle in patients (aged ≥35 y) with mild to moderate (Kellgren-Lawrence grade 1–3) knee OA. After a 1-week analgesic washout, patients applied DSG 4 g or vehicle 4 times daily to 1 knee. Rescue acetaminophen ≤4 g/d was allowed. Efficacy outcomes common to the 3 trials were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (0–20) and physical function subscale (0–68), a global rating of disease (GRD; 100-mm Visual Analog Scale [VAS]), and pain on movement (POM; 100-mm VAS). Analysis of variance (ANOVA) was used to compare efficacy outcome differences by age (<65 y vs ≥65 y). All adverse events (AEs) were recorded.

Results: A total of 602 subjects aged <65 y and 374 subjects ≥65 y were randomized. Among patients <65 y, at 12 weeks, all efficacy outcome scores were significantly superior (lower) with DSG (LS mean DSG [SE]) versus vehicle (LS mean vehicle [SE]): WOMAC pain (6.4 [0.3] vs 7.4 [0.3], *P*=0.007), WOMAC physical function (22.1 [0.9] vs 25.9 [0.9], *P*=0.002), GRD (33.0 [1.6] vs 38.7 [1.7], *P*=0.01), and POM (37.5 [1.8] vs 45.8 [1.8], *P*<0.001). Among subjects aged ≥65 y, most efficacy outcome scores were significantly superior (lower) with DSG versus vehicle: WOMAC pain (6.9 [0.3] vs 8.0 [0.4], *P*=0.02), WOMAC physical function (24.5 [1.1] vs 29.1 [1.1], *P*=0.004), and POM (41.1 [2.2] vs 48.4 [2.2], *P*=0.02), but the difference in GRD (38.8 [2.0] vs 43.8 [2.1]) was not statistically significant (*P*=0.07). Efficacy of DSG did not differ significantly between patients aged ≥65 y and <65 y: WOMAC pain (*P*=0.85), WOMAC physical function (*P*=0.70), GRD *P*=0.86), (POM (*P*=0.81). In both younger and older groups, more subjects treated with DSG (56.6% and 55.8%, respectively) than placebo (50.8% and 43.9%) had ≥1 AE. Application site reactions were more common with DSG compared with vehicle in both younger (5.6% vs 1.8%) and older (8.8% vs 1.1%) subjects. Gastrointestinal AEs were infrequent and similar to placebo in both age groups. 1 serious AE (deep vein thrombosis/pulmonary embolism) in an 80-year-old woman was considered possibly related to treatment. The event was mild and managed successfully with medication. Patients in each age group applied >90% of scheduled doses.

Conclusion: DSG was effective and generally well tolerated regardless of age. These data support the topical application of DSG for relief of arthritic knee pain in seniors and younger patients.

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The Effect of Intraarticular Injection Devices On Outcomes of Osteoarthritis of the Knee: A Pilot Study. Suzanne Delea[1], Kye S. Park[1], Natalia Chavez[1], Philip A. Band[2], Wilmer L. Sibbitt Jr.[1] and Arthur D. Bankhurst[3], [1]University of New Mexico, Albuquerque, NM, [2]New York University Medical Center, New York, NY, New York, NY, [3]University of NM Med Ctr, Albuquerque, NM

Purpose: True intraarticular positioning of the needle tip is considered important for outcome of intraarticular injections; however, there are few studies demonstrating that technologies that improve needle positioning actually improve injection. The present pilot study investigated whether devices that facilitate accurate placement of the needle affect the outcomes of intraarticular injections of the osteoarthritic knee.

Method: 128 subjects with primary osteoarthritis of the knee were randomized to intraarticular corticosteroid injection (triamcinolone acetonide) with standard syringe or the reciprocating procedure device (RPD), a new safety procedure syringe. Primary outcome measures included baseline pain, procedural pain, and pain at outcome (2 weeks post-injection and 6 months post-injection) as measured by the 0 to 10 cm Visual Analogue Pain Scale (VAS) and well as secondary outcome measures.

Results: Significant reductions in pain scores following intraarticular injection occurred with both devices at 2 weeks (Syringe: 63.7±38.2% VAS reduction from baseline, $p < 0.0001$; RPD: 80.0±30.4%, $p < 0.0001$) and 6 months (Syringe: 16.7±49.4% VAS reduction from baseline, $p < 0.004$; RPD: 30.5±58.8%, $p < 0.0001$). However, relative to the conventional syringe, the RPD procedure syringe provided a 37.2% greater reduction in procedural pain ($p = 0.005$), a 53.8 percent reduction in significant procedural pain (VAS ≥ 5 cm) ($p = 0.016$), and a 109.7% increase in aspirated fluid volume. At the 2 week outcome, relative the conventional syringe, the RPD group demonstrated 43.1% less joint pain (RPD VAS: 1.40±2 cm.11, Syringe VAS: 2.46±2.48, $p = 0.04$), a 25.6% greater reduction in VAS score from baseline (RPD: 80.0±30.4%, Syringe VAS: 63.7±38.2%, $p = 0.025$), 76.4% more asymptomatic individuals (VAS ≤ 1 cm) (RPD: 65.1% (41/63); Syringe: 36.9% (24/65), $p = 0.005$), 26.7% fewer non-responders (VAS ≥ 2 cm) (RPD: 34.9% (22/63); Syringe: 47.6% (31/65), $p = 0.005$), and a longer duration of therapeutic effect (RPD: 4.43±2.00 months, Syringe: 3.16±2.18 months, $p = 0.006$). As expected pain scores at the 6 month outcome were not significantly different between the two syringe treatment groups ($p = 0.11$).

Conclusion: The present study demonstrates that intraarticular injection technologies that permit more accurate placement of the procedure needle significantly improve the outcomes of intraarticular injections for osteoarthritis of the knee**.**

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PN400 Significantly Reduces the Incidence of Gastric Ulcers Compared with Enteric-Coated Naproxen in Patients Requiring Chronic NSAID Therapy Regardless of Low-Dose Aspirin Use: Results From Two Prospective, Randomized Controlled Trials. Jay L. Goldstein[1], Marc C. Hochberg[2], John G. Fort[3], Ying Zhang[3], Mark Sostek[4] and Lynsey Stevenson[5], [1]University of Illinois at Chicago, Chicago, IL, [2]University of Maryland School of Medicine, Baltimore, MD, [3]POZEN Inc., Chapel Hill, NC, [4]AstraZeneca, Wilmington, DE, [5]Complete Medical Communications Ltd, Glasgow, United Kingdom

Purpose: Co-therapy with proton pump inhibitors reduces the risk of NSAID-associated ulcers but, in practice, adherence is often sub-optimal, leading to poor long-term clinical outcomes (Van Soest et al. *Aliment Pharmacol Ther* 2007;26:265-275). Two Phase 3 studies evaluated the upper gastrointestinal (UGI) efficacy and safety of PN400, a fixed-dose combination tablet designed to provide sequential delivery of immediate-release (IR) esomeprazole (20 mg) and enteric-coated (EC) naproxen (500 mg), compared with EC naproxen (500 mg) alone in at-risk patients.

Method: Two randomized, double-blind, controlled, multicenter studies enrolled *H. pylori*-negative patients with OA, RA, or any other condition requiring chronic NSAID therapy at risk of ulcers (age ≥50 yrs or 18-49 yrs with a history of gastric ulcer [GU] or duodenal ulcer [DU] within the past 5 yrs). Patients were randomized to PN400 BID or EC naproxen 500 mg BID for 6 months. The primary endpoint was the cumulative incidence of GUs (≥3 mm diameter with depth) observed by endoscopy at 1, 3, and 6 months. A planned pooled analysis to assess the effect of low-dose aspirin use (LDA ≤325 mg) on GU incidence, and an analysis of pre-specified NSAID-associated UGI AEs (including DU) were also conducted.

Results: Study A: 438 patients were randomized, 434 were treated; Study B: 423 patients were randomized, 420 were treated. Baseline demographics were similar between groups in both studies. Approximately 82% of patients had OA and 6% had RA. In both studies, the incidence of GUs over 6 months was significantly lower in the PN400 groups vs the EC naproxen groups (Table). The pooled incidence of GUs was significantly lower in the PN400 group vs the EC naproxen group in LDA users (n=201) (3.0% vs 28.4%, p<0.001) and non-users (n=653) (6.4% vs 22.2%, p<0.001). The previously described pre-specified secondary endpoint was significantly lower in the PN400 groups (Table).

Conclusion: PN400 significantly reduces the incidence of GUs, regardless of concomitant LDA use, and DUs in at-risk patients. PN400, a fixed-dose combination of EC naproxen 500 mg and IR esomeprazole 20 mg, provides built-in gastroprotection and offers a treatment option for decreasing NSAID-ulcer occurrence in an appropriate target patient population.

		Study A			Study B	
	PN400 (n=218)	EC naproxen (n=216)	p	PN400 (n=210)	EC naproxen (n=210)	p
GU, n (%)	9 (4.1)	50 (23.1)	<0.001	15 (7.1)	51 (24.3)	<0.001
DU, n (%)	1 (0.5)	11 (5.1)	0.003	2 (1.0)	12 (5.7)	0.007
UGI AE/DU, n (%)	114 (52.3)	149 (69.0)	<0.001	114 (54.3)	151 (71.9)	<0.001

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Analgesic Effects of Intra-Articular Botulinum Toxin Type B (BoNT B) in a Murine Model of Chronic Degenerative Knee Arthritis Pain. Stephanie R. Anderson[1], Pari McGarraugh[2], Sandra Frizelle[2], Hollis E. Krug[2] and Maren L. Mahowald[1], [1]U of MN, Mpls, MN, [2]VAMC, Mpls, MN

Purpose: Studies have shown joint inflammation may cause peripheral and central sensitization of neurons leading to spontaneous joint pain at rest and hyperalgesia with stimulation. Inflammatory mediators induced by neuropeptide release activate peripheral nerve receptors. Given this peripheral sensitization we hypothesize arthritis pain may be treated by intra-articular (IA) neurotoxins. Efficacy of IA botulinum toxin (BoNT) Type A for refractory arthritis pain has recently been reported, prompting interest in screening other botulinum toxins that may prove more effective for arthritis pain. BoNT B may produce greater pain relief and may be effective in different types of pain than BoNT A. We hypothesized that BoNT B would reduce chronic arthritic knee pain and tested this hypothesis in a murine model of chronic degenerative arthritis.

Method: Chronic arthritis was produced in 12 C57Bl6 mice by IA injection of 10 IU Collagenase. BoNT B (MYOBLOC) 0.02 was given IA in the left knee 3 days before testing. Normal right knee served as internal control. Mice were studied before, after induction of arthritis and after IA BoNT B. Video gait analysis was performed using Treadscan™ hardware and software.Evoked pain behavior was measured by tallying fights + vocalizations/1 min in response to repeated firm palpation of the knee. Gait and strength were observed visually and graded. Strength was measured as ability to grasp and cling. Student's t-test was used for statistical comparisons.

Results:

	BASELINE Mn (SEM)	**ARTHRITIC** Mn (SEM)	*P* c/w Baseline	**TREATED** Mn (SEM)	*P* c/w Arthritic
Gait	3.50 (.17)	2.08 (.14)	**0.0001**	3.33 (.15)	**<0.0001**
Evoked Pain Response	1.83 (.81)	5.50 (1.14)	**0.0009**	3.58 (.87)	0.21
Variability in Stance/Stride	.102 (.007)	.126 (.009)	**0.003**	.099 (.006)	**0.02**
Variability in Lt Rear Propel time	62.8 (4.36)	75.0 (2.49)	**0.02**	63.7 (3.36)	**0.02**
Variability in Rear Tract Width	2.76 (.26)	3.37 (.28)	**0.03**	2.55 (.19)	**0.02**
Grasp	3.83 (.07)	2.54 (.38)	**0.007**	3.12 (.16)	0.11
Cling	3.66 (.13)	2.7 (.37)	**0.04**	3.04 (.27)	0.53

Conclusion: Chronic degenerative arthritis pain can be quantitated in a murine model using visual and computerized gait analysis, and evoked pain scores. Visual and computerized gait analysis both showed a significant impairment in gait in arthritic mice, improving after IA BoNT B suggesting a substantial analgesic effect. Evoked pain responses increased overall with arthritis, decreasing with IA BoNT B, but not reaching statistical significance in this small sample.

These results support the hypothesis that chronic arthritis pain is amplified by neuropeptide release in the periphery due to efferent neurogenic signals. Interruption of neuropeptide release by IA BoNT B appeared to decrease pain behaviors and improve gait abnormalities. No limb weakness was noted. These results support further investigation of this novel approach to treatment of arthritis pain with IA neurotoxin.

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Intra-Articular Injection (Tribosupplementation) with Native and Recombinant Lubricin (PRG4) Prevents Cartilage Degeneration in the Rat ACL Injury Model. Gregory D. Jay[1], Raphael Nir[2], Bryn Watkins[3], Karen McHugh[3], Scott Anderson[3], Braden C. Fleming[4], Ling X. Zhang[1], Erin Teeple[5], Kimberly Waller[6] and Khaled A. Elsaid[1], [1]Rhode Island Hospital Department of Emergency Medicine, Providence, RI, [2]SBH Sciences, Natick, MA, [3]Biomodels, Inc., Watertown, MA, [4]Division of Orthopaedics, The Warren Alpert School of Medicine at Brown University, Providence, RI, [5]Division of Orthopaedics The Warren Alpert School of Medicine at Brown University, Providence, RI, [6]Brown University-Department of Engineering, Providence, RI

Purpose: To determine if cartilage degeneration is prevented or minimized in a rat ACL transection (ACLT) model following intra-articular injection of human synovial fluid lubricin (HSFL), recombinant human lubricin (rhLub) or human synoviocyte lubricin (SynL).

Method: Surgical transection of the ACL of the right knee was performed on 19 eight week old Lewis rats. The rats were sacrificed on post-operative day 32. Intra-articular injections of HSFL from patients undergoing knee reconstructive surgery, rhLub expressed in Chinese hamster ovary cells or SynL from human synoviocyte culture began on post-operative day 7. Injection of lubricin was at a concentration of 200µg/ml in a 40µl volume and was repeated twice weekly for a total of 7 injections. Histology was scored using OARSI modified Mankin criteria by investigators blinded to treatment group. Collagen type II degradation epitope (CTX-II) was assayed in lavaged synovial fluid by ELISA (Cartilaps, Nordic BioSciences).

Results: ACLT joints receiving SynL demonstrated significantly lower OARSI histology scores 2.7 ± 2.3 than both the untreated ACLT joints 5.4 ± 1.9 (p =0.03) and placebo (PBS) treated ACLT joints 5.5 ± 1.8 (p=0.05). Both rLub and HSFL also demonstrated lower OARSI scores 3.8 ± 2.2 and 2.8 ± 1.9 but were not statistically significant. Joints which were chondroprotected by any lubricin showed more Safranin O staining in the superficial and intermediate zone and smoother articular surfaces. Immunostaining for lubricin showed preservation of lubricin expressing superficial zone chondrocytes across the three lubricins. SF lavage CTX-II concentration in PBS treated joints was 608±303 pg/ml compared with 226 ± 152 in SynL, 347 ± 213 in HSFL, 260 ± 72 in rhLub and 1100 ± 154 in untreated joints. CTX-II levels in SynL-treated joints were significantly lower (p=0.045) than CTX-II levels in PBS-treated joints, while HSFL and rhLub treatments did not result in significant differences in CTX-II levels compared to PBS. Only joints receiving any lubricin showed reactivity with mAb 3B3(-) in peri-cellular areas of chondrocytes, indicating the presence of non-sulphated isoforms of chondroitin-6-sulphate which is consistent with repair activity.

Conclusion: Intra-articular injection of lubricin prevents cartilage degeneration in the rat ACLT model and may promote repair activity. The practice of tribosupplementation with lubricin may be translatable to humans.

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The Effect of Glucosamine On Glucose Metabolism in Humans: A Systematic Review of the Literature. Nathaniel Dostrovsky[1], Tanveer E. Towheed[2], Robert W. Hudson[2] and Tassos P. Anastassiades[3], [1]Queen's University, Internal Medicine Training Program, Kingston, ON, [2]Queens Univ, Kingston, [3]Etherington Hall Rm 2050, Kingston, ON

Purpose: Glucosamine (GlcN) is a commonly used nutraceutical for the treatment of osteoarthritis. There is concern from animal experiments that GlcN may alter glucose metabolism through the hexosamine biosynthetic pathway.

Method: An English-language literature search of MEDLINE, EMBASE and EBM Reviews (1950 – December 2008) was conducted for studies that evaluated the effect of exogenous GlcN on glucose metabolism in humans. The bibliographies of selected papers were manually searched for additional references. All types of study designs published in English language, peer-reviewed journals were included. Unpublished data as well as animal studies were excluded. Two reviewers independently analyzed studies for quality and content using a standardized data extraction form.

Results: 11 studies were found which met our inclusion and exclusion criteria. Six studies were randomized controlled trials and the remaining 5 were prospective studies with or without controls. Six of the studies used GlcN sulphate, two used GlcN hydrochloride and three did not report the type of GlcN used. Two studies included diabetic subjects and seven included obese subjects. Overall, 4 out of the 11 studies demonstrated decreased insulin sensitivity or increased fasting glucose in subjects taking GlcN. More studies using glucose

tolerance tests and composites of fasting insulin and glucose detected an effect on glucose metabolism than those using fasting insulin, fasting glucose or hemoglobin A1c (see table 1).

Conclusion: Four out of 11 studies detected decreased insulin resistance or increased fasting glucose in humans taking GlcN while seven studies did not. Differences in subject characteristics, type of GlcN and study design do not explain this discrepancy. Thus, research to date suggests GlcN may have a clinically relevant effect on glucose metabolism in humans. Additional studies are needed which include subjects with diabetes or risk factors for diabetes and that use sensitive methods to measure glucose metabolism before a firm conclusion can be made.

Table #1: Tests of glucose metabolism and study outcome

	# Studies	# Positive[1]
Fasting glucose	10	0
Fasting insulin	9	1 (11%)
Hemoglobin A1c	4	0
Oral glucose tolerance test	2	1 (50%)
Intravenous glucose tolerance test	2	1 (50%)
Composites of fasting glucose and fasting insulin[2]	3	2 (66%)
Hyperinsulinemic- Isoglycemic Glucose Clamp	3	0

[1] Demonstrated an effect of glucose metabolism

[2] Fasting Insulin Resistance Index (FIRI), Quantitative Insulin Sensitivity Check Index (QUICKI) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

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Effectiveness of Pulsed Electrical Stimulation in the Treatment of Osteoarthritis of the Knee: a Randomized Controlled Trial. RE Fary[1], Graeme Carroll[2], TG Briffa[3] and NK Briffa[4], [1]School of Physiotherapy, CHIRI, Curtin University of Technology, Bentley, Australia, [2]Arthrocare, Mt Lawley, Australia, [3]University of Western Australia, Nedlands, Australia, [4]Curtin Health Innovation Research Institute, Curtin University of Technology, Bentley, Australia

Purpose: Evidence suggests that short term, sub-sensory, pulsed electrical stimulation (PES) is effective in reducing OA knee pain. The purpose of this study was to examine its effectiveness over a longer duration.

Method: A double-blind, randomized, placebo-controlled, repeated measures trial was conducted to examine the effectiveness over 26 weeks of sub-sensory PES in people with OA of the knee. The trial was registered (ANZCTR: ACTRN12607000492459) and conformed to CONSORT guidelines for clinical trials. Seventy people (mean age 70 years, 53% male) with clinician diagnosed (100%) and radiologically confirmed (91%) OA knee were randomized to either active treatment or placebo, stratified for age, gender and baseline pain levels. PES electrodes were worn inside a neoprene brace. Participants were directed to wear the device for $\geq$ 7 hours/day, usually overnight, for 26 weeks. The primary outcome measure was change in pain (100mm VAS) from baseline to 26 weeks. Secondary outcome measures included pain (WOMAC 3.1), function (WOMAC 3.1), stiffness (WOMAC 3.1), total WOMAC score, patient global assessment - PGA (100mm VAS) and quality of life (SF-36). These outcomes were measured at baseline, 4, 16 and 26 weeks. Physical activity (Human Activity Profile and accelerometer) were measured at baseline and 16 weeks. A patient global perceived effect scale (11-point Likert) was completed at 16 and 26 weeks.

Results: Both groups achieved statistically significant improvement in pain VAS ($p \leq 0.001$) but there was no difference between the groups ($p = 0.89$). Similarly no difference was noted between the groups in WOMAC pain ($p = 0.23$), stiffness ($p = 0.45$), function ($p = 0.62$), WOMAC total score ($p = 0.74$), PGA ($p = 0.62$), SF-36 physical and mental component scores ($p = 0.29$, $p=0.55$, respectively), from

baseline to 26 weeks. Similarly there was no difference between groups at baseline and 16 weeks in any activity measure ($p > 0.16$). More participants in the treatment group achieved the minimal clinically important improvement (MCII) in pain VAS of 19.9 (treatment 56%: placebo 44%) but the difference between the two groups was not significant ($p = 0.47$). Similarly there was no difference in the proportions of those achieving the MCII in WOMAC function of 9.1 ($p = 1.00$) and PGA of 18.3 ($p = 0.78$). Results were unaffected after adjustment for age, gender, BMI and radiological disease severity.

Conclusion: Sub-sensory PES over 26 weeks did not improve symptoms of OA knee. However, given that baseline mean scores for pain and function were of only moderate severity and that more than 90% of participants achieved recommended activity levels, our findings do not preclude the possibility of PES providing clinically meaningful improvements in samples with other characteristics.

Disclosure: R. Fary, None; **G. Carroll**, None; **T. Briffa**, None; **N. Briffa**, None.

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Evaluation of the Structure-Modifying Effect of Avocado-Soybean Unsaponifiables (ASU) in Hip Osteoarthritis (OA): Results of the ERADIAS Study, a 3-Year, Prospective, Randomized, Double-Blind, Placebo Controlled Trial. E. Maheu[1], C. Cadet[2], M. Marty[3], D. Moyse[4], I. Kerloch[5], P. Coste[5], M. Dougados[6], B. Mazières[7], TD. Spector[8], E. Vignon[9], Jm. Grouin[10] and M. Lequesne[11], [1]Saint Antoine Hospital - AP-HP, Paris, France, [2]Cabinet médical, Paris, France, [3]Henri-Mondor Hospital, Creteil, France, [4]DM Consultant, Tours, France, [5]Expanscience Labs, Courbevoie, France, [6]Hospital Cochin, Descartes Univ, Paris, France, [7]CHU Larrey, Toulouse, France, [8]St Thomas Hospital, London, United Kingdom, [9]Claude Bernard University, Lyon, France, [10]Rouen University, Rouen, France, [11]Rheumatology, Paris

Purpose: To assess the long-term ability of ASU to slow radiographic progression in symptomatic Hip OA.

Method: This was a prospective, randomized, double-blind, placebo-controlled 3-year trial. Symptomatic patients (pain ≥ 1 year, Lequesne index ≥ 3), aged ≥ 45 years, with primary hip OA fulfilling the ACR criteria, and a minimum joint space width (JSW) of the target hip between 1 and 4 mm on a pelvic radiograph were randomized into 2 strata (baseline JSW: < 2.5 or ≥ 2.5 mm) and assigned to receive either ASU 300 mg or placebo once daily. 3 standing radiographs were taken annually: pelvis, target hip anteroposterior (AP), and oblique views. JSW was measured at the narrowest point on pelvic or target hip AP view by manual measurement using a 0.1 mm-graduated magnifying glass. This method was deemed the most sensitive to change in a pilot study and the best of 2 readers was selected prior to unblinding. The primary outcome was based on the change in the narrowest JSW over 3 years. *Statistics:* All patients having at least 2 radiographs of the same view were included in the Full Analysis Set (FAS). An Analysis of Covariance Mixed Model for Repeated Measurements (MMRM) was performed and Missing At Random used to handle missing data. The minimum JSW change was compared between groups by both a continuous approach: 3-year JS narrowing mean in millimeters and a comparison of the percentage of "progressors" defined by a JSW loss ≥ 0.5 mm (based on the smallest detectable change of the reader).

Results: 499 patients were selected, 399 randomized, 345 in the FAS (166 ASU and 179 placebo). Baseline demographic and hip OA characteristics were similar in the 2 groups. Patients were aged 62 (8) years, 54% women, mean BMI 27 (4), 0-100 normalised Lequesne index 30 (9), VAS global pain 37 (23) mm. Mean baseline JSW was 2.8 (0.9) mm in both groups. 166 patients discontinued the study (41%), 55% of these for lack of efficacy.

Mean JSW change and % of progressors at year 3 are below.

	% progre	**ssors**		**Mean JSW**	**change (sem)**	
Group	ASU	Placebo	*P*	ASU	Placebo	*P*
Total	40%	50%	0.039 *	- 0.64 (0.07)	- 0.67 (0.06)	0.72 #

sem: standard error of the adjusted mean in the MMRM Model ; *: Cochran-Mantel-Haenszel Test p-value ; #: t-test p-value in the MMRM

Although no significant intergroup difference was observed on JSW change, the number of progressors was 20% lower in the ASU group ($p = 0.039$). ASU had no evident effect on the symptoms in this study.

Conclusion: This study shows that 3-year treatment by ASU appears to reduce the percentage of JSW deteriorating patients compared to placebo, indicating a potential structure-modifying effect of ASU in progressive hip OA. The clinical relevance of these encouraging radiographic results requires further assessment.

Disclosure: E. Maheu, Ibsa - Genevrier, 5, Rottapharm Labs, 5, Pierre Fabre Labs, 2, Expanscience Labs, 5, Genzyme Corporation, 5, Servier, 2 ; **C. Cadet**, Expanscience Labs, 5, Servier, 2 ; **M. Marty**, Expanscience Labs, 5 ; **D. Moyse**, Expanscience Labs, 5 ; **I. Kerloch**, Expanscience Labs, 3 ; **P. Coste**, Expanscience Labs, 3 ; **M. Dougados**, Expanscience Labs, 5 ; **B. Mazières**, Expanscience Labs, 5 ; **T. Spector**, expanscience Labs, 5, Merck Pharmaceuticals, 2, Pfizer Inc, 2 ; **E. Vignon**, Expanscience Labs, 5 ; **J. Grouin**, Expanciences, 5 ; **M. Lequesne**, Expanscience Labs, 5 .

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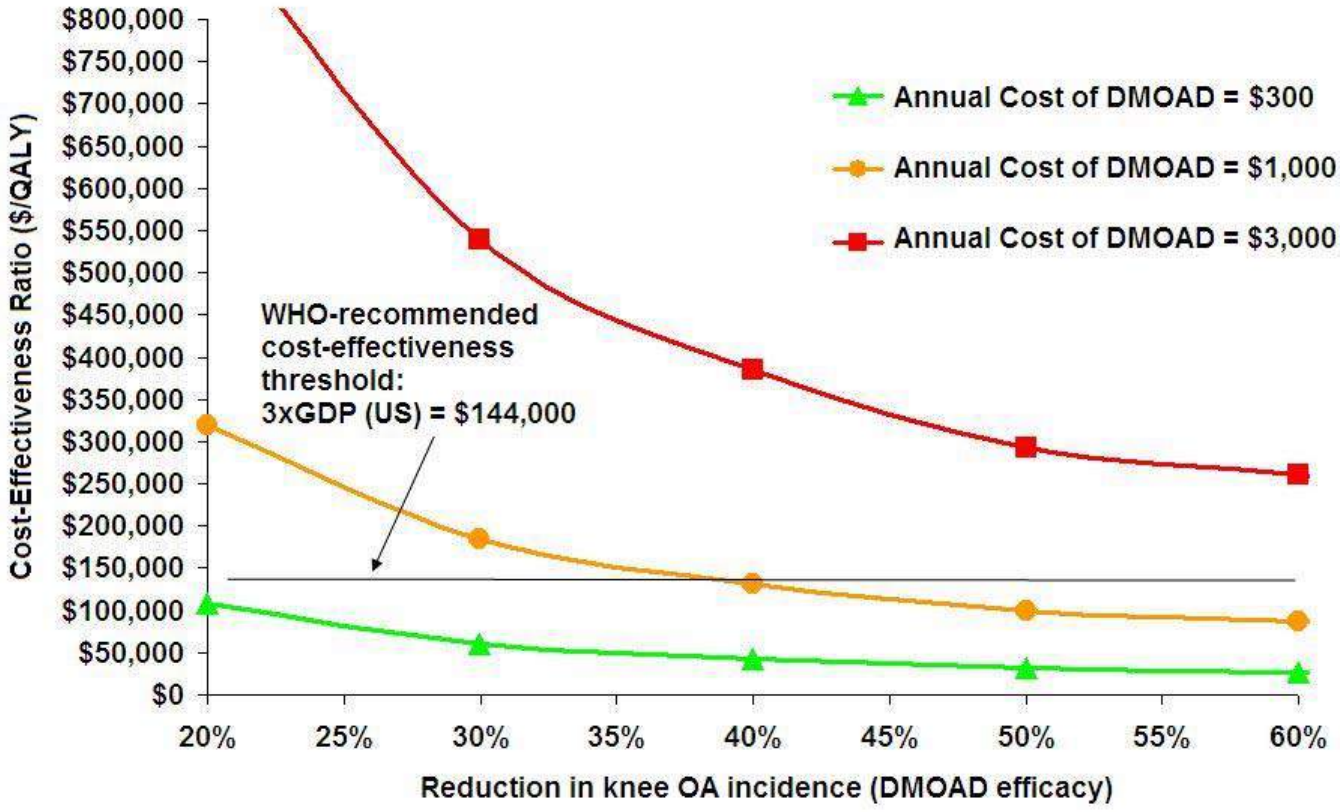
Disease Modifying Drugs to Prevent Knee OA: Can They Be Cost-Effective? E. Losina[1], H. Gerlovin[2], H.L. Holt[2], L.G. Suter[3], D.J. Hunter[4], N.N. Niu[5], D.H. Solomon[2], R.P. Walensky[6], A.D. Paltiel[7] and J.N. Katz[5], [1]Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Yale University and VA Healthcare System, New Haven, CT, [4]New England Baptist Hospital, Boston, MA, [5]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [6]Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA, [7]Yale University, New Haven, CT

Purpose: In theory, disease modifying osteoarthritis drugs (DMOADs) will slow structural change and thus may be used to prevent or delay incident knee osteoarthritis (OA). We sought to determine the efficacy and cost thresholds under which DMOADs would be cost-effective as knee OA prophylaxis.

Method: We used a validated computer simulation model of knee OA to examine costs and effectiveness of DMOADs as knee OA prevention. We considered three cohorts: 1) General population, 2) High-Risk (1 risk factor, e.g. obesity, relative rate [RR] for knee OA 2.8), 3) Highest Risk (2 risk factors, e.g. obesity and history of knee injury, RR 7.4). We introduced prophylactic DMOADs at the time of entry to the model (mean age 58 ± 8 years, knee OA free). We examined DMOAD characteristics along two domains: efficacy (defined as reduction in knee OA incidence) and cost. We varied DMOAD efficacy across a wide range from 20 -- 60% and considered costs from $300 -- $3,000/year. We assumed DMOAD toxicity similar to NSAID toxicity. Cost-effectiveness (C-E) was estimated as the ratio of incremental costs to incremental effectiveness (difference in quality-adjusted life years, QALYs). Both costs and QALYs were discounted at 3% per

Figure. Cost-effectiveness of DMOAD prophylaxis for the Highest Risk Cohort



Results: In the General population, 10-year cumulative incidence of knee OA decreased from 16.7% (no prophylaxis) to 14.3 -- 10.3% for DMOAD efficacies ranging from 20 -- 60%. DMOAD prophylaxis in this population increased costs and either decreased QALYs (efficacy <40%) or led to negligible improvement in QALYs (efficacy ≥40%), resulting in incremental cost-effectiveness ratios (ICER) >$500,000/QALY, under all cost scenarios. In the High-Risk cohort, 10-year cumulative incidence decreased from 39.0% (no prophylaxis) to 34.5 -- 25.5%. In this population, ICERs <3xGDP were obtained only when DMOAD efficacy was ≥40% and cost was $300/year or when DMOAD efficacy was >50% and cost was $500/year. For the Highest Risk cohort, 10-year cumulative incidence changed from 76.3% (no prophylaxis) to 69.9 -- 49.4%. ICERs for DMOAD-based prophylaxis in the Highest Risk group are presented in the Figure, showing that DMOADs costing >$3,000/year have ICERs >$200,000/QALY regardless of efficacy.

Conclusion: Using DMOADs for preventing or delaying knee OA may improve quality adjusted life expectancy at cost-effectiveness levels comparable to other accepted therapies in persons at high risk of developing knee OA. DMOADs priced at $2,000/year or higher are unlikely to be cost-effective by current US standards, even for Highest Risk groups.

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Variations of Responders Rates According to Response Criteria Used in a Randomized Controlled Trial (RCT) in Knee Osteoarthritis (OA). E. Maheu[1], Mohammed Zaïm[2], François Aubin[3] and Francis Berenbaum[4], [1]Saint Antoine Hospital - AP-HP, Paris, France, [2]Pierre Fabre Laboratories, Ramonville, France, [3]Cardinal System, Paris, France, [4]Faculty of Medicine P&M Curie, Paris, France

Purpose: The results of clinical trials in OA are usually reported as group comparisons of the mean (+/- standard deviation, sd) in score of the selected outcome. It might be more clinically relevant to show the results at a patient level, using a response criterion. Several response criteria are available: OARSI/OMERACT modified set of responder criteria (1), the Patient Acceptable Symptom State (PASS) (2) and the Minimum Clinically Important Improvement (MCII) (3).

Objectives: To assess differences in responder rates using various response criteria in a RCT in knee OA.

Method: Data were extracted from a prospective, multicentre, double-blind RCT comparing two hyaluronans over 24 weeks (F60027-Structovial and Hylan G-F 20-Synvisc) according to a non inferiority design. The main outcome was the Lequesne index score (LFI). The secondary outcome was global pain on a Visual Analog Scale (VAS). 236 patients were available in the main analysis (per protocol analysis, PP). Demographic and knee OA characteristics were identical to those usually reported in knee OA trials. Since no value of the PASS is validated for the LFI yet, the results on pain VAS were used to classify patients as responders or not using OMERACT/OARSI modified criteria, PASS and MCII (using absolute value or % of improvement). **Results:** are reported as mean (sd) and number (%).

Results: Table 1 shows the response rates according to the different criteria. Rates of responders varied considerably: from 60 to 80% in each group and from 63% to 78% in the overall population (both treatment groups can be merged since non-inferiority was proven). The most liberal definition seems to be MCII (absolute), while the strictest appears to be PASS.

Responder rates according to various definitions of response in a RCT in knee OA

PP dataset	F60027 group	Hylan G F-20 group	Global population
Baseline pain score (0-100, mm) (sd)	68.6 (13.2)	67.5 (11.6)	68.1 (12.5)
Mean change from baseline at week 24 (mm) (sd)	-38.8 (24.7)	-37.1 (25.4)	-38.0 (25.0)
N (%) of patients at PASS for pain at week 24 </= 32.3 mm	71 (59.7%)	78 (66.7%)	149 (63.1%)

N (%) of patients achieving MCII(absolute) on pain at week 24 >/= 19.9 mm	96 (80.7%)	88 (75.2%)	184 (78%)
N (%) of patients achieving MCII (%) on pain at week 24 >/= 40.8% improvement	83 (69.7%)	83 (70.9%)	166 (70.3%)
OMERACT/OARSI response criteria	77 (64.7%)	79 (67.5%)	156 (66%)
Baseline LFI score	13.6 (3.2)	13.2 (2.9)	13.4 (3.1)
Mean LFI score change from baseline at week 24	-5.7 (3.8)	-5.6 (4.0)	-5.7 (3.9)

Conclusion: Reporting clinical trial results at a patient level using response rates might be meaningful in knee OA. However this study clearly demonstrate that results significantly vary according to the response criterion used which is likely to lead to "positive" or "negative" results accordingly. More work is needed to help assessing the most clinically relevant response definition in knee OA.

References:
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Disclosure: E. Maheu, Pierre Fabre, 2, Servier, 2, Genzyme Corporation, 5, Expanscience, 5, Rottapharm, , 5, Genevrier-Ibsa ; **M. Zaïm**, Pierre Fabre Laboratories, 3 ; **F. Aubin**, Pierre Fabre Labs, 2 ; **F. Berenbaum**, Pierre Fabre Labs, 2, Expanscience, 2, Combinatorx, 5, Negma Lerads, 5, NiCox, S.A., 5, Rottapharm, 5 .

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Effects of Tapentadol Extended Release On the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Pain Intensity in Patients with Chronic Osteoarthritis Pain: Results of a Randomized, Phase 3, Active- and Placebo-Controlled Study. Kathleen Kelly[1], Alison Greene[1], Brigitte Kuperwasser[2], Bettyanne McCann[2], Bernd Lange[3], Achim Steup[3], Akiko Okamoto[1], Mila Etropolski[2] and Christine Rauschkolb[1], [1]Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Raritan, NJ, [2]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, [3]Grünenthal GmbH, Aachen, Germany

Purpose: Tapentadol is a new, centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition.

Method: This study evaluated the efficacy and safety of controlled, adjustable, oral bid doses of tapentadol extended release (ER; 100-250 mg), oxycodone HCl controlled release (CR; 20-50 mg), or placebo over a 12-week maintenance period preceded by a 3-week titration period in patients with moderate to severe chronic osteoarthritis pain. Efficacy endpoints included the change from baseline to Week 12 of the maintenance period in average pain intensity scores (using an 11-point numerical rating scale and last observation carried forward to impute missing values) and the change from baseline to Week 12 in the WOMAC (24 items scored from 0 = least disability to 4 = greatest disability). WOMAC results were analyzed using mixed effects models.

Results: Efficacy and safety were evaluated for patients (n = 1,023) who received ≥1 dose of study drug. Compared with placebo, tapentadol ER and oxycodone CR both significantly reduced average pain intensity from baseline to Week 12 of maintenance (least squares

mean difference vs placebo: tapentadol ER, –0.7 [P <0.001]; oxycodone CR, –0.3 [P = 0.049]). Mean global WOMAC scores improved significantly from baseline to Week 12 of maintenance compared with placebo for tapentadol ER (P = 0.005) and oxycodone CR (P = 0.038); numerical improvements were seen in all 3 WOMAC subscales and improvements were statistically significant on the pain (P <0.001) and physical function (P = 0.006) subscales for tapentadol ER and on the physical function (P = 0.019) subscale for oxycodone CR (**Table**). Treatment-emergent adverse events (TEAEs) were reported by 61.1%, 75.9%, and 87.4%, of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively; the most common TEAEs in the active treatment groups were nausea, constipation, vomiting, dizziness, and headache.

Conclusion: Tapentadol ER was effective for the management of moderate to severe chronic osteoarthritis pain over 15 weeks of treatment. Compared with placebo, improvements in pain intensity, physical function, and global WOMAC scores were significant for tapentadol ER (100-250 mg bid).

Table. Mean Change in WOMAC Scores From Baseline to Week 12 of Maintenance (Patients in the Intent-to-treat Population With WOMAC Assessments at Week 12)

	Placebo (n = 158)	Tapentadol ER (n = 149)	Oxycodone CR (n = 92)
Pain subscale			
LS mean change (SE)	-0.9 (0.05)	-1.2 (0.05)	-1.0 (0.07)
LS mean difference vs placebo (95% CI)		-0.3 (-0.42, -0.13)	-0.2 (-0.34, 0.00)
P value		<0.001	0.051
Physical function subscale			
LS mean change (SE)	-0.8 (0.06)	-1.0 (0.06)	-1.0 (0.07)
LS mean difference vs placebo (95% CI)		-0.2 (-0.36, -0.06)	-0.2 (-0.37, -0.03)
P value		0.006	0.019
Stiffness subscale			
LS mean change (SE)	-1.0 (0.06)	-1.2 (0.06)	-1.1 (0.08)
LS mean difference vs placebo (95% CI)		-0.2 (-0.34, 0.00)	-0.1 (-0.29, 0.10)
P value		0.053	0.321
Global WOMAC score			
LS mean change (SE)	-0.9 (0.05)	-1.1 (0.05)	-1.1 (0.07)
LS mean difference vs placebo (95% CI)		-0.2 (-0.36, -0.06)	-0.2 (-0.34, -0.01)
P value		0.005	0.038

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ER, extended release; CR, controlled release; LS, least squares; SE, standard error; CI, confidence interval.

Disclosure: K. Kelly, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **A. Greene**, Johnson & Johnson, 3 ; **B. Kuperwasser**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **B. McCann**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **B. Lange**, Grunenthal GmbH, 3 ; **A. Steup**, Grunenthal GmbH, 3 ; **A. Okamoto**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **M. Etropolski**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **C. Rauschkolb**, Johnson & Johnson, 1, Johnson & Johnson, 3 .

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26-Week Efficacy and Safety Evaluation of Naproxcinod, A First-in-Class Cyclooxygenase Inhibiting Nitric Oxide Donator (CINOD), in Patients with Osteoarthritis of the Knee. CE Marrero[1], C. Tuten[2], T. Shamin[3], V. Awasty[4], J. Agaiby[5], D. Hassman[6], J. Sutphen[7], A. Pivodic[8], B. Duquesroix[8] and Thomas J. Schnitzer[9], [1]Deep South Clinical Research, Nederland, TX, [2]Clinical Center of Asheville, Asheville, NC, [3]Heartland Clinical Reserach, Omaha, NE, [4]Internal Medicine R&R Research, Marion, OH, [5]Clinical Investigation Specialist Inc., Gurnee, IL, [6]Comprehensive Clinical Research, Berlin, MD, [7]NicOx inc., NJ, [8]NicOx SA, Sophia Antipolis, France, [9]Northwestern University, Chicago, IL

Purpose: Naproxcinod is a first-in-class Cyclooxygenase Inhibiting Nitric Oxide Donator (CINOD) under development for the relief of signs and symptoms of osteoarthritis (OA). Naproxcinod has shown anti-inflammatory and analgesic properties similar to traditional NSAIDs and COX-2 inhibitors, as well as a good safety profile in previous trials in knee OA.

Method: 1011 patients with primary knee OA with a pain flare after analgesic washout were randomized at 129 US sites to naproxcinod 375mg or 750mg, naproxen 500mg or placebo (all *bid*). After 13 weeks, patients randomized to placebo received naproxcinod 375mg or 750mg. Naproxcinod efficacy was compared with placebo during the first 13 weeks and with naproxen during the 26-week period, using the co-primary efficacy assessments of WOMAC™ pain and function, and patients' global assessment of disease status. Several other secondary efficacy assessments were evaluated. The co-primary efficacy variables were analyzed using an ANCOVA model with treatment group as factors, and the appropriate baseline value as covariate. Safety was assessed by adverse events (AEs), standardized blood pressure (BP) monitoring and orthostatic tests, ECGs, laboratory assessments, and physical examinations.

Results: 1011 patients were randomized: 71% female, 79% Caucasian, mean age 60 years. At Week 26, 6.1% patients in naproxcinod 750mg group, 10.4% in naproxcinod 375mg group and 8.1% in naproxen 500mg group discontinued due to lack of efficacy/worsening of disease. Naproxcinod 750mg was non-inferior to naproxen 500mg for WOMAC™ pain and function subscale scores at Week 26 in the intent-to-treat population, with the upper limit of the 95% CI less than the 8mm margin for non-inferiority (pain scores: difference in LS means -2.8±2.45mm, 95% CI [-7.6, 2.0]; function scores: difference in LS means -2.3±2.36mm, 95% CI [-6.9, 2.4]). The percentage of patients with ≥1 AE was similar for all groups (ranging from 59.9% to 63.7%). Most AEs were mild or moderate in severity. BP mean changes from baseline for naproxcinod 750mg remained similar to placebo at each time point and, on average, did not increase over 26 weeks.

Conclusion: Naproxcinod 750mg was non-inferior to naproxen 500mg at Week 26 based on WOMAC™ pain and function assessments. Both doses of naproxcinod administered for 26 weeks were well tolerated.

Ref: HCT 3012-X-302 (26 weeks)

Disclosure: C. Marrero, NicOx Inc, 9 ; **C. Tuten**, NicOx Inc, 9 ; **T. Shamin**, NicOx Inc., 9 ; **V. Awasty**, NicOx Inc., 9 ; **J. Agaiby**, NicOx Inc., 9 ; **D. Hassman**, NicOx Inc., 9 ; **J. Sutphen**, NicOx Inc., 3 ; **A. Pivodic**, NicOx S.A, 3 ; **B. Duquesroix**, NicOx, S.A., 3 ; **T. J. Schnitzer**, NicOx S.A., 5 .

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Effect of Blood Loss On Physical Functioning: Pooled Analysis of Patients with Osteoarthritis or Rheumatoid Arthritis. V. Strand[1], X. Luo[2], AG Bushmakin[2], J. Cappelleri[2], AR Assaf[2], B. Cuffel[3] and G. Sands[4], [1]Stanford University, Palo Alto, CA, [2]Pfizer Inc, New London, CT, [3]Pfizer Inc, New York, NY, [4]Pfizer Global Pharmaceuticals, New York, NY

Background: It is well recognized the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with arthritis may cause gastrointestinal (GI) blood loss, but the impact of blood loss on quality of life has not been well established in this patient population.

Purpose: To assess the effect of clinically significant blood loss on physical functioning and other aspects of health-related quality of life in patients with osteoarthritis (OA) or rheumatoid arthritis (RA).

Method: Data from 14 pooled clinical trials ranging in length from 2 to 52 weeks assessing celecoxib vs placebo or active comparators were analyzed. Only trials that included data on both Hemoglobin (Hb) and Short Form Health Survey SF-36 were included in these analyses.

Clinically significant blood loss was defined as a decrease from baseline in Hb ≥2g/dL. The effect of blood loss was evaluated by mixed-effects modeling of the change in SF-36 domain scores from baseline as a function of change in Hb, baseline Hb, gender, and Hb change-by-gender interaction.

Result: The median number of subjects with data across SF-36 domains was 9,850. On average, most domain scores improved from baseline. Improvements in Physical Functioning domain scores were lower in patients with Hb decreases ≥2g/dL compared with those with lesser changes in Hb (from -1 to 1 g/dL). Differences between the two groups were statistically significant and clinically meaningful, defined by changes ≥5 points in domain scores in both female (p=0.02; 6.3) and male (p=0.01; 6.8) subjects. In the subgroup of females with baseline Hb ≤14g/dL, this effect was even more pronounced (p=0.001; 12.1); and in males with baseline Hb ≤15g/dL (p=0.001, 12.6). Statistically significant and clinically meaningful group differences in improvements from baseline were also observed in Role-Physical domain scores among male subjects (p=0.01; 13.7). Differences between improvements in the other domain scores with respect to blood loss were neither statistically significant nor clinically meaningful.

Mean change from baseline	Decrease in Hb ≥2g/dL (p-value)	Change in Hb -1 to 1g/dL (p-value)	Difference (p-value)
Physical Function (n=9864)			
Female	4.6 (0.21)	10.9 (<0.01)	-6.3 (0.02)
Male	2.3 (0.54)	9.0 (<0.01)	-6.8 (0.01)
Role-Physical (n=9826)			
Female	25.2 (<0.01)	26.5 (<0.01)	-1.3 (0.81)
Male	8.4 (0.26)	22.2 (<0.01)	-13.7 (0.01)

Conclusion: Subjects with blood loss characterized by decreases in Hb ≥2g/dL did not report clinically meaningful or statistically significant improvements in physical functioning, whereas those lesser Hb changes of -1 to 1g/dL reported statistically significant and clinically meaningful improvements during treatment. This impact appears to be dependent upon baseline Hb levels.

Disclosure: V. Strand, Abbott Immunology Pharmaceuticals, 9 ; **X. Luo**, Pfizer Inc, 1 ; **A. Bushmakin**, Pfizer Inc, 1 ; **J. Cappelleri**, Pfizer Inc, 1 ; **A. Assaf**, Pfizer Inc, 1, Pfizer, Inc., 3 ; **B. Cuffel**, Pfizer Inc, 1 ; **G. Sands**, Pfizer Inc, 1 .

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May An Intervention On Clinical Inertia Influence the Perception of Pain, Functionality and Quality of Life in Patients with Knee and/or Hip Osteoarthritis? Agustín Gómez de la Cámara[1], Alejandro Tejedor Varillas[2] and Fernando León Vázquez[2], [1]Research Unit, Hospital Universitario Doce de Octubre, CIBERESP, Madrid, Spain, [2]Sociedad Española de Medicina de Familia y Comunitaria (semFYC), Madrid, Spain

Purpose: Despite the availability of evidence-based guidelines for the management of asymptomatic chronic diseases such as osteoarthritis, physicians often do not initiate, intensify or optimize therapy when indicated, so that patients are not treated effectively. This phenomenon is known as clinical inertia. The main objective of this study was to evaluate whether an intervention on primary care physicians to avoid clinical inertia, could improve the perception of pain, functionality and quality of life in patients with hip and/or knee osteoarthritis (OA).

Method: In this prospective, randomized, multicenter, parallel-group study, clusters of primary care physicians working at the same healthcare center, for a period of time longer than six months, were randomly assigned to one of two study groups (i.e. Group 1 or proactive intervention and Group 2 or control). Each physician included three patients with knee and/or hip OA who fulfill eligibility criteria. Physicians in the proactive intervention group (Group 1) received a 45-60 minute training session on the latest European League Against Rheumatism recommendations on OA management, therapeutic goals, and motivational techniques. Both groups were trained on the use of the Visual Analog Scale (VAS), Western Ontario and McMaster Universities (WOMAC) and Short Form-12 (SF-12) questionnaires. All

patients were scheduled for two visits (Visit 1 and Visit 2), six-months apart. During the visits, a complete medical evaluation was carried out, and the VAS, WOMAC and SF-12 questionnaires were filled-out.

Results: A total of 1,361 (Group 1 n=403; Group 2 n=958) physicians were selected to participate in the study. A total of 4,076 patients (Group 1: n=1,208; Group 2: n=2,868) with hip and/or knee OA were included. No significant differences were observed between Group 1 and Group 2 when we compared the results of VAS, WOMAC and SF-12 questionnaires obtained in Visit 1 and Visit 2. On the contrary, after grouping the results of Group 1 and Group 2, a significant improvement was observed in Visit 2, compared to Visit 1, in the VAS ($p<0.001$), WOMAC ($p<0.001$) and SF-12 ($p<0.001$) questionnaires.

Conclusion: Patients did not seem to obtain any benefit from the proactive intervention addressed to reduce physicians' clinical inertia. Yet, small variations in the usual clinical practice generated an important improvement in the patients' pain, functionality and quality of life. Other potentially modifiable factors contributing to clinical inertia, besides physician-related factors, should be further investigated in patients with OA.

Disclosure: A. Gómez de la Cámara, None; **A. Tejedor Varillas**, None; **F. León Vázquez**, None.

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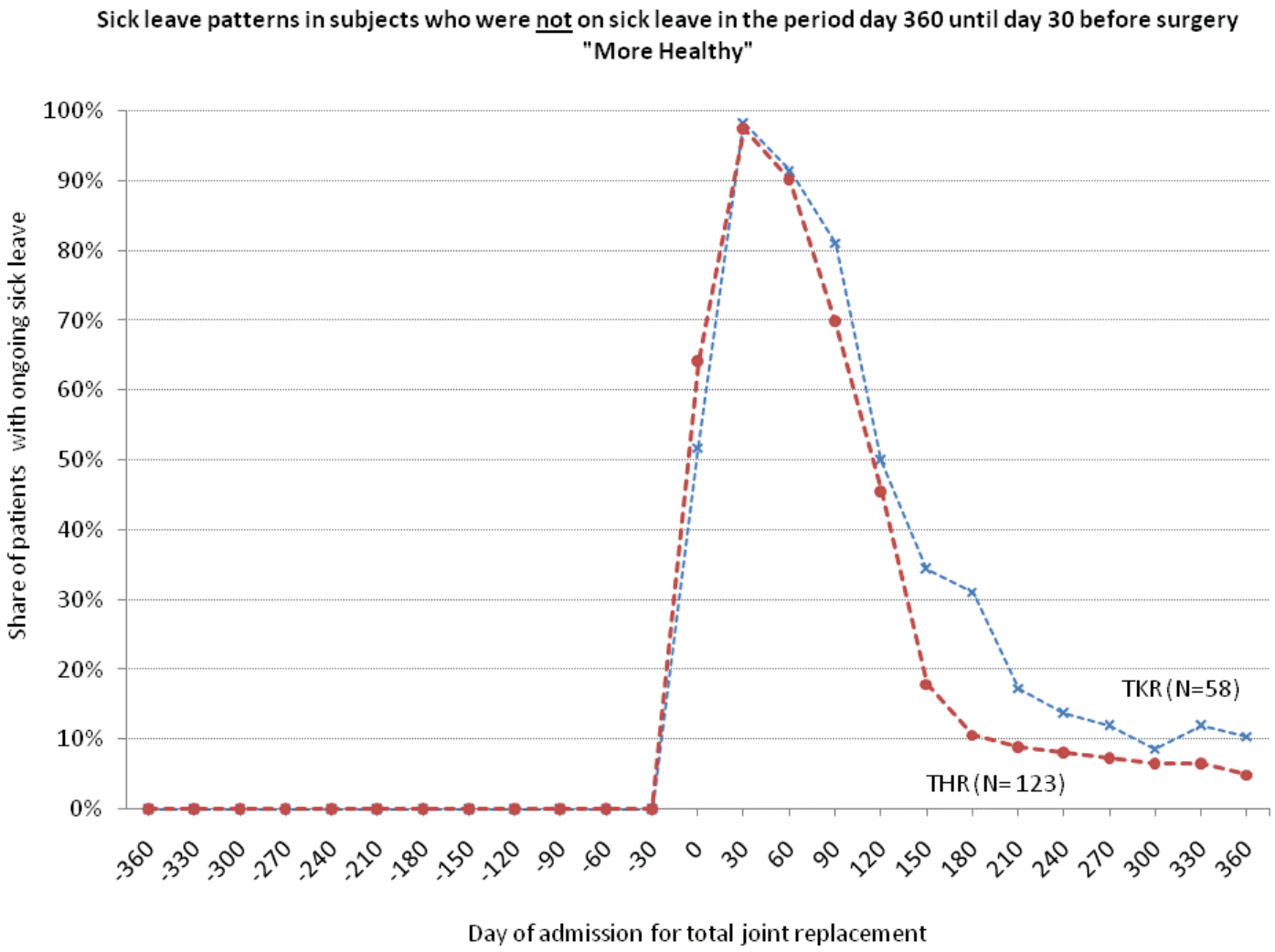
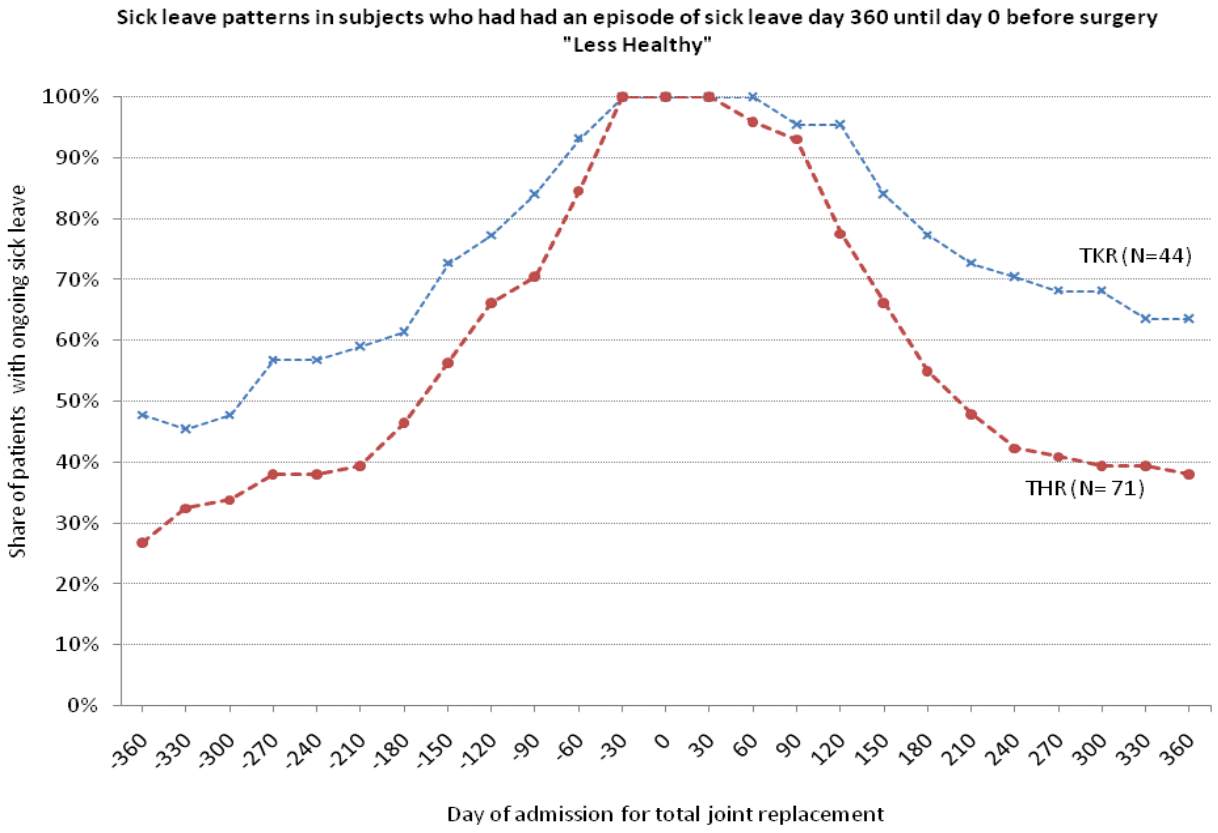
Total Hip and Knee Joint Replacement for OA and Sick Leave Patterns. Martin Englund[1], Leif Dahlberg[2] and Ingemar F. Petersson[3], [1]Lund University, Lund, Sweden, [2]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, [3]Section of Orthopedics and Section of Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden

Purpose: Total knee and hip joint replacement (TKR/THR) are well established treatments for painful OA when other treatments are unsatisfactory. However, in younger patients the effect on sick leave has been insufficiently studied. Our objective was to assess the patterns of sick leave before and after total joint replacement in OA patients.

Method: We identified all hip and knee OA patients in southern Sweden aged 58 years or younger who have had a TKR or THR between Jan 2003 and Oct 2006 using the Skåne Health Care Register. Subjects who died, started on disability pension, or had had more than one TKR/THR during the study period were excluded. The sample included n=276 with THR (46% women) and n=199 with TKR (56% women). Data were cross-referenced individually with data for sick leave from the National Insurance Agency. We calculated the proportion of patients with ongoing sick leave in 30-days intervals from 360 days before until 360 days after the TKR/THR. We compared the 6 month preop. period (day -210 to -30) vs. the 6 month postop. period (day 180 to 360) for the total sample using paired statistics. We also created two subgroups for graphical presentation; those without sick leave in the period 360 to 30 days before surgery, but were then sick listed at time of surgery =“more healthy” and those subjects who had had a sick leave episode in the 360 day period before surgery =“less healthy”.

Results: The proportion of subjects with sick leave pre- and postop. was higher among patients with TKR compared to patients with THR. The percentage of patients on sick leave returned towards the preoperative level by the end of the study period but almost 20 to 30% were still sick-listed, the higher share being in persons with TKR. Hip OA patients tended to have more sick days before than after the THR (mean [SD] 98 [74] vs. 83 [82], p=0.08), while there was no such trend for TKR patients (96 [79] vs. 104 [79], p=0.3). The sick leave patterns (proportion of patients on sick leave) for subjects “more healthy” and “less healthy”, respectively, are illustrated (Figure).


Sick leave patterns in subjects who were not on sick leave in the period day 360 until day 30 before surgery
"More Healthy"
Share of patients with ongoing sick leave
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
TKR (N=58)
THR (N= 123)
-360
-330
-300
-270
-240
-210
-180
-150
-120
-90
-60
-30
0
30
60
90
120
150
180
210
240
270
300
330
360
Day of admission for total joint replacement



Conclusion: The return to work is quicker after THR than TKR. About 5% to 10% of patients who were not sick listed preoperatively are sick-listed 1 year after surgery, the higher share being in patients after TKR. The contributing effect of comorbidities associated with prolonged sick leave needs to be further studied.

Disclosure: M. Englund, None; **L. Dahlberg**, None; **I. F. Petersson**, None.

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Psychosocial and Educational Barriers to Surgical Success After Knee Arthroplasty. Maria Lopez-Olivo[1], Michael Kallen[2], Chong Pak[1], Sherwin J. Siff[3], Glenn C. Landon[4], David Edelstein[4], Kausha C. Robinson[2], Hong Zhang Zhang[2] and Maria E. Suarez-Almazor[2], [1]MD Anderson Ctr Univ of TX, Houston, TX, [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [3]St. Luke's Episcopal Hospital, Houston, TX, [4]Kelsey Seybold, Houston, TX

Purpose: The objective of this study was to identify psychosocial and educational barriers to surgical success after total knee arthroplasty (TKA).

Method: We assessed 252 patients with knee osteoarthritis (OA) at baseline and 24 weeks post TKA. The assessments included 4 questionnaires and a physical evaluation of the affected joint. An objective outcome was obtained by measuring knee range of motion, using the ROM - Knee Society Rating System. Patient's subjective outcomes included pain, stiffness, and activity limitation and were measured using the WOMAC (Western Ontario MacMaster) scale. The WOMAC is a well-known and validated instrument designed specifically for the assessment of lower extremity pain and function in osteoarthritis (OA) of the knee or hip.

Results: In our sample, 65% of patients were female; mean age was 65 (8.9) yrs. Sixty-five percent lived with a significant other, 70% were White and 25% African American, and 73% were seen in a Kelsey Seybold clinic. Multiple regression models were estimated to evaluate the association of patient demographics (e.g., age, gender, socioeconomic status, education, hospital where surgery was performed) and

psychological factors (i.e., depression, anxiety, and stress as measured using the DASS scale) with absolute change of surgical success (i.e., 6 months outcome score minus baseline score). Other independent variable included: number of co-morbidities, post-operative complications, and affective factors (as measured using the Medical Outcome Study Social Support Scale). Regression analysis indicated that gender (female), psychological factor-anxiety, and number of co-morbidities were associated with changes in ROM (p=.020, .007, .050, and .007, respectively). Higher education (i.e., more than high school), low depression scores, and more tangible social support (i.e., provision of material aid or behavioral assistance) were associated with better WOMAC scores (p=.005, .010, and .070, respectively).

Conclusion: Patients' level of depression, education, tangible social support, number of co-morbidities, and gender are associated with outcomes in total knee arthroplasty. Further analyses are needed to determine if these findings are mediated through the effect of patient expectancies of improvement, high self-efficacy, goals, and compliance with rehabilitation recommendations.

Disclosure: M. Lopez-Olivo, None; **M. Kallen**, None; **C. Pak**, None; **S. J. Siff**, None; **G. C. Landon**, None; **D. Edelstein**, None; **K. C. Robinson**, None; **H. Z. Zhang**, None; **M. E. Suarez-Almazor**, None.

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Preliminary Results of a Phase II Placebo Controlled Trial with Adalimumab in Erosive Hand Osteoarthritis: Predictors of Erosive Evolution and the Potential Effect of Adalimumab in Specific Subgroups. Gust Verbruggen, Ruth Wittoek, Bert Vander Cruyssen and Dirk Elewaut, University Hospital Ghent, UGent, Ghent, Belgium

Purpose: Investigate a therapeutic role of TNFα-blocking agents, adalimumab, in erosive osteoarthritis (OA) of the Interphalangeal (IP) finger joints.

Methods: A total of 60 patients were allocated to adalimumab 40 mg sc every other week, or placebo. To be eligible, the patient had to present with at least one IP finger joint with the appearance of an erosive ('E') phase joint on XRays as defined by the anatomical phase scoring system [1]. Posteroanterior XRays of both hands were taken at 3 time points (baseline, after 6 and 12 months). The anatomical phase of all IP joints was characterized on the XRays. Potential changes in phase were recorded. Joints presenting in the 'E' phase at baseline or presenting new erosions over the year were scored by a novel quantitative radiographic scoring system, the Ghent University Scoring System, GUSS™ [2], with better ability to detect progression over a shorter period of time in erosive OA. Erosive progression and signs of repair or remodelling in this particular scoring system were scored by indicating the proportion of normal subchondral bone, subchondral plate and joint space on 10 point incremental Likert scales. A difference between baseline scores and scores after 12 months of more than 40 units is considered to be more erosive or showing more repair, depending on the direction of the difference.

A two-step method was used to evaluate subgroups of patients that might benefit from the anti-TNF therapy. First, predictors of erosive progression were evaluated. This was done by the calculation of odds ratios. Variables that showed a 50% difference in odds between erosive and non-erosive joints where retained as potential predictors. Second, interaction terms between the potential predictors and therapy (placebo or adalimumab) were evaluated by regression analysis (GEE, Generalized Estimated Equations, modeling with a logit link function).

The study was registered at Clinical trial.gov (EudraCT number: 2006-000925-71).

Results: Preliminary analysis of the data retained the following potential predictors for erosive evolution: age, proximal IP involvement, a tender joint at baseline and palpable synovial effusion at baseline.

Of those variables, only palpable synovial effusion at baseline showed a significant interaction effect with adalimumab therapy ($p<0.005$, figure 1).

Conclusion: The preliminary results of this phase II-study show that adalimumab can reduce the occurrence of erosive progression in joints showing palpable synovial effusion at baseline. This is the first report of an obvious disease modifying effect by a therapeutic agent in this severe form of hand OA.

References

[1] Verbruggen G, Veys EM. Arthritis Rheum 1996; 39: 308-320.
[2] Submitted to ACR 2009: The Ghent University Scoring System (GUSS™), an Optimised Scoring System to Monitor Disease Progression in Erosive Osteoarthritis of the Interphalangeal Finger Joints.

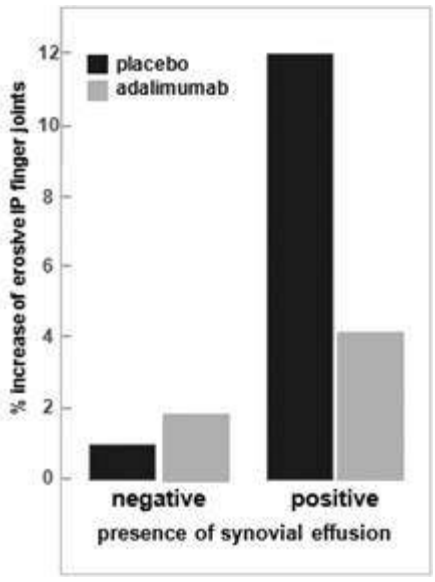

Figure 1: percentage increase in erosive IP finger joints with and without synovial effusion

Disclosure: G. Verbruggen, None; **R. Wittoek**, None; **B. Vander Cruyssen**, None; **D. Elewaut**, None.

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Disability and Knee and Hip Osteoarthritis (OA): Associations with Individual and Community Socioeconomic Status (SES). Joshua B. Knight, Leigh F. Callahan, Jack Shreffler, Jordan B. Renner and Joanne M. Jordan, The University of North Carolina, Chapel Hill, NC

Purpose: Individual level SES measures have been shown to associate with disability and restricted function in OA and limited studies have also demonstrated associations with community level SES measures independent of one's individual SES. To date this has not been evaluated in knee and hip OA. This study examined associations between education, occupation, and community poverty with disability in persons with knee or hip radiographic OA (rOA) in the Johnston County OA Project.

Method: A cross-sectional analysis was conducted on 1037 individuals (63% White, 37% African American [AA]) with knee rOA and 824 individuals (67% white, 33% AA) with hip rOA, rOA defined as Kellgren-Lawrence ≥ 2. Education (^{3}HS) and occupation (physically demanding or not) were the individual SES measures. Census block group poverty rate (<12%, 12-25%, >25%) was the community SES measure. Disability was measured by the Health Assessment Questionnaire (HAQ). Covariates were age, gender, race, and BMI. Race was not an effect modifier and was included as a covariate. Bivariate analyses with and without covariates were used to find associations of disability with each of the SES effects separately. Multivariable analyses were conducted with all SES variables, adjusting for covariates and allowing for random intercepts based on block group. Separate models were run for people with knee or hip rOA.

Results: In persons with knee rOA, education (β=0.101, C.I.= [0.024, 0.178]) and occupation (0.115, [0.034, 0.197]) were significantly associated with disability in unadjusted bivariate models. Adjusting for covariates, education and occupation were no longer significant. In persons with hip rOA, unadjusted and adjusted bivariate models both revealed associations between disability and education (adjusted 0.111, [0.025, 0.196]), occupation (0.127, [0.039, 0.215]) and residing in a block group with >25% poverty (0.173, [0.048, 0.298]). In multivariable models, no SES variables correlated with disability in persons with knee rOA, but occupation and >25% poverty per block group were both significant in those with hip rOA (Table 1).

Table 1. Regression analyses of HAQ on all SES variables and covariates (not shown) in those with knee or hip rOA

	Knee rOA		**Hip rOA**	
	β	95% C.I.	β	95% C.I.
Education,	0.057	[-0.030, 0.144]	0.056	[-0.039, 0.151]

Occupation, LI	0.057	[-0.030, 0.144]	**0.101**	**[0.007, 0.196]**
Poverty (<12% ref.)				
12-25%	-0.037	[-0.141, 0.066]	0.086	[-0.023, 0.195]
>25%	0.029	[-0.091, 0.149]	**0.181**	**[0.053, 0.310]**

Conclusion: In persons with knee rOA, neither individual nor community SES variables are associated with disability when adjusting for key risk factors like age and BMI. However, in those with hip rOA, both occupation and residing in a high poverty area are independently associated with disability. These data underscore the importance of SES variables with outcomes in OA and indicate that in some cases community may have impact as well.

Disclosure: J. B. Knight, None; **L. F. Callahan**, None; **J. Shreffler**, None; **J. B. Renner**, None; **J. M. Jordan**, None.

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Primary Health Care Use in Osteoarthritis: Link with Depressed Mood. Yehoshua Gleicher[1], Ruth Croxford[2] and Gillian A. Hawker[3], [1]University of Toronto, Toronto, ON, [2]Institute for Clinical Evaluative Sciences, Toronto, ON, [3]Women's College Hospital, Toronto, ON

Purpose: Depressed mood has been associated with chronic painful osteoarthritis (OA). In other chronic conditions, concomitant depression has been linked to higher health care use. We examined the contribution of depressed mood to primary health care use in older individuals with OA.

Methods: A population cohort with hip/knee OA were interviewed annually to assess socio-demographics, health status (SF-36), comorbid conditions, including prior/current treatment for depression/other mental illness, and arthritis severity (WOMAC). Survey data were linked to administrative health databases using anonymized patient identifiers. Primary health care use was evaluated as the number of primary care visits over a 2 year period overall and for a mental health diagnosis (defined using a validated algorithm). Using the SF36 Mental Component score (MC score) to define depressed mood, the relationship between depressed mood and the log-transformed number of overall and mental health-specific physician visits was assessed using ordinary least squares regression and zero-inflated Poisson regression, respectively, adjusting for confounders. Interactions between MC score and other covariates were included.

Results: 2,204 individuals with OA participated (mean age 71 years; 72% female, 62% ≤ high school education). WOMAC scores indicated moderate OA severity. The mean MH score was 68.2/100 (lower scores indicate worse mental health); scores were significantly lower for those with a prior history of depression/other mental illness, greater arthritis severity, worse general health status, and less education ($p<0.0001$ for all). Participants experienced 37,363 primary care visits over the two-year period. Adjusting for age, comorbidity, education, sex, living arrangements and general health status, MC score was independently predictive of the number of primary care visits (adjusted parameter estimate 1.04 per 10 point decrease in MC score, 95% CI 1.03-1.05). Interactions were observed between MC score and each of education and region of residence; the relationship between MC and number of physician visits was stronger for those with post-secondary education and those residing in a rural versus urban region. Over the two-year period, 589 (26.7%) cohort members experienced 1,979 mental health-related primary care visits. Among those with no history of depression/mental illness, 23% experienced at least one mental health visit compared with 45% of those with a prior history. For every 10 point decrease in MC score, there was a 20% increase in the odds of having one or more mental health visits (unadjusted OR 1.20, 95% CI 1.17-1.22).

Conclusion: Among older individuals with symptomatic hip/knee OA, concomitant depressed mood is associated with greater primary care use both overall, and for mental health diagnoses. Even among individuals without a self-report past diagnosis of depression or other mental illness, over one quarter experienced at least one mental health-related primary care visit over the following two-year period.

Disclosure: Y. Gleicher, None; **R. Croxford**, None; **G. A. Hawker**, None.

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Predictors of Assistive Walking Device Use and Association with Changes in Knee Osteoarthritis and Falls: Findings From the Health ABC Study. Laura Carbone[1], Suzanne Satterfield[2], Grant W. Somes[3], Elizabeth A. Tolley[3], C. Kent Kwoh[4], Hepei Chen[5] and Michael C. Nevitt[6], [1]Univ of Tenn at Memphis, Memphis, TN, [2]University of Tennessee, Memphis, TN, [3]The University of Tennessee Health Science Center, Memphis, TN, [4]University of Pittsburgh, Pittsburgh, PA, [5]NIH, Rockville, MD, [6]University of California, San Francisco, San Francisco, CA

Purpose: Few studies have examined the effect of factors that predict, and are concurrently associated with, new use of assistive walking devices in people with osteoarthritis (OA) of the knee. The purpose of this study was to determine factors that predicted incident use of an AWD and to determine the relationship of use of these devices by those with knee pain to WOMAC pain scores, x-ray changes of osteoarthritis and falls in elderly men and women.

Methods: We examined clinical predictors of incident use of an assistive walking device in all 3075 Health Aging and Body Composition (Health ABC) participants (n=258 AWD users and n=2769 nonusers of assistive walking devices (NAWD)) and predictors of incident use of an AWD in Health ABC participants with prevalent knee pain who had knee x-rays (n=823) (n=91 AWD users and n=732 NAWD) that preceded use of an AWD. Among these participants with prevalent knee pain, we also examined the association of incident use of an AWD with changes in knee pain (WOMAC pain score); medial and lateral x-ray joint space narrowing and falls, over an average of 3 years of follow-up.

Results: After multivariable adjustment, the common predictors of use of an AWD in the entire Health ABC cohort and in the subset with prevalent knee pain were older age (≥ 73 (OR 1.75 (95% CI 1.23-2.49) and (OR 1.42 (95% CI 1.21-2.84), black race (OR 1.27 (95%CI 1.59-3.23) and (OR 5.04 (95% CI 2.39-10.62) and a history of visual impairment (OR (1.53 (95% CI 1.10-2.14) and (OR 1.95 (95% CI 1.01, 3.79) respectively. In those with knee pain, the presence of at least one knee with x-ray evidence of whole knee osteoarthritis was also a significant predictor of AWD use (p=0.047; univariate analysis); but not in multivariate analysis. Longitudinally, after adjustment for age, race, sex and BMI, incident use of an AWD was not significantly associated with concurrent changes in WOMAC pain scores or medial or lateral tibiofemoral joint space narrowing on x-ray. An increase in the number of falls was significantly associated with AWD use (p=0.005).

Conclusion: Among elderly men and women, including those with and without knee pain, those who are older, Black and who have impaired vision are most likely to initiate use of an AWD. Among those with knee pain, the presence of knee OA on x-rays was also a predictor of initiation of use of an AWD. Use of an AWD was not significantly associated with progression of knee pain. Prevention of falls may be particularly important to consider in AWD users.

Disclosure: L. Carbone, None; **S. Satterfield**, None; **G. W. Somes**, None; **E. A. Tolley**, None; **C. K. Kwoh**, None; **H. Chen**, None; **M. C. Nevitt**, None.

ACR/ARHP Poster Session B

Osteporosis and Metabolic Bone Disease; Clinical Aspects and Pathogenesis

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Association Between Medication Adherence and Risk of Fracture Among Women Initiating Osteoporosis Therapy. Rachel Halpern[1], Laura K. Becker[1], Sheikh Usman Iqbal[2], Enkhe Badamgarav[2] and David Macarios[2], [1]i3 Innovus, Eden Prairie, MN, [2]Amgen, Thousand Oaks, CA

Purpose: Adherence to osteoporosis medication is frequently low and may result in increased risk of non-traumatic fracture. This study examined the relationship between adherence to osteoporosis medication and risk of fracture among women initiating osteoporosis therapy.

Methods: This retrospective analysis used medical and pharmacy claims from a large US health plan. Subjects were female commercial health plan enrollees ≥45 years old who initiated treatment on alendronate, risedronate, teriparatide, ibandronate, or raloxifene from 6/30/2002 to 12/31/2006. The date of the first medication claim was the index date. Subjects were continuously enrolled for 1 year pre-index (baseline) and ≥180 days post-index. Non-traumatic fractures were identified with diagnosis codes and ICD-9 or CPT procedure codes. "Outcome" fractures were those that occurred ≥90 days after index date. Early fractures occurred within 90 days after index date. Prevalent

factures occurred during baseline. Adherence was measured with medication possession ratio (MPR), the number of days with osteoporosis medication divided by number of days observed; adherence categories were “high” (MPR≥0.8), “medium” (0.5≤MPR<0.8), and “low” (MPR<0.5). Control variables included: age; prevalent fracture; early fracture; baseline steroid use; Charlson comorbidity index score; fracture risk-related comorbidities, and geographic region. Time to fracture ≤720 days after index date was modeled with Cox regression with time-dependent adherence.

Results: The study sample included 88,122 women with mean age of 58.6 (±8.3) years; 5,404 (6.13%) subjects had outcome fractures ≤720 days after the index date. Bivariate comparison adjusted for time-dependent adherence showed that low adherence was associated with an 11.2% higher risk of fracture compared with high adherence (p=0.0006). When covariates were included, patients with low adherence had 8.3% higher risk of fracture relative to patients with high adherence (p=0.0110), as shown in Table 1. Other covariates associated with fracture included early fracture (hazard ratio (HR) =5.939, 95% confidence interval (CI) =5.453-6.467), prevalent fracture (HR=2.020 CI=1.865-2.188), and baseline steroid use (HR=1.088, CI=1.017-1.163).

Conclusion: The results indicate that low adherence to osteoporosis therapy is associated with increased risk of fracture. Research to examine factors related to medication non-adherence could inform treatment interventions and may subsequently impact rates of fracture.

Table 1. Role of Adherence in Fracture Risk: Regression Results

Regression (Reference: High Adherence)	Hazard Ratio	95% Confidence Interval	p-value
Bivariate comparison			
Low adherence (MPR<0.5)	1.112	(1.047-1.182)	0.0006
Medium adherence (0.5 <0.8)	1.073	(0.999-1.153)	0.0544
Adjusted for all covariates			
Low adherence (MPR<0.5)	1.083	(1.019-1.152)	0.0110
Medium adherence (0.5 <0.8)	1.052	(0.979-1.131)	0.1651

Disclosure: R. Halpern, None; **L. K. Becker**, None; **S. U. Iqbal**, Amgen, Inc., 1, Amgen, Inc., 3 ; **E. Badamgarav**, Amgen, 1, Amgen, 3 ; **D. Macarios**, Amgen, 1, Amgen, 3 .

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Switching the Dose Regimen of Oral Bisphosphonates, Adherence and Fractures. Becky Briesacher[1], Susan Andrade[2], Leslie R. Harrold[1], Hassan Fouayzi[2] and Robert A. Yood[3], [1]Univ of Massachusetts Med Schl, Worcester, MA, [2]Meyers Primary Care Institute, Worcester, MA, [3]Fallon Clinic, Worcester, MA

Purpose: To assess adherence and fracture risk in patients who switch dose regimens of oral bisphosphonates.

Method: This is a population-based interrupted times-series analysis using a nationwide administrative health data from 2003-2006. We identified 1835 switchers of once-weekly to once-monthly oral bisphosphonates and matched them to two comparators using propensity-score methodology: switchers of different once-weekly oral bisphosphonates, and nonswitchers assigned a random switch. We measured adequate adherence as a monthly medication possession ratio >/=0.80 and calculated monthly incidence rate ratios [IRR] of osteoporotic fractures. We tested for pre- and post-switch differences in adherence and fractures rates.

Results: All study groups experienced considerable attrition in adherence: 1 year post-switch, the proportion of adequate adherers was 41% regimen switchers, 47% drug only switchers, and 37% nonswitchers. The regimen switch was associated with decelerated nonadherence (absolute change in monthly attrition rate, -4% pre-switch vs. -1% post-switch, p<.000). There were no significant changes in nonadherence for nonswitchers (absolute change in monthly attrition rate, -4% pre-switch vs. -2% post-switch, p=.578) or drug only switchers (-1% pre-switch vs. -1% post-switch, p=.745). The regimen switch was not associated with reduced fracture risk: 1 year post-switch, the incidence risk ratios for regimen switchers relative to drug only switchers were 0.85, 95% CI 0.52-1.36, and 0.92, 95% CI 0.56-1.58, relative to nonswitchers).

Conclusion: Reducing the dosing demands of oral bisphosphonates from once-weekly to once-monthly decelerated but did not halt adherence failure. The regimen change did not translate to reduced fracture risk.

Disclosure: B. Briesacher, Novartis Pharmaceutical Corporation, 5 ; **S. Andrade**, None; **L. R. Harrold**, None; **H. Fouayzi**, None; **R. A. Yood**, None.

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Associated Factors for Falls and Fear of Falls in Japanese Patients with Rheumatoid Arthritis. Takefumi Furuya, Kiyotaka Yamagiwa, Tetsuo Ikai, Eisuke Inoue, Atsuo Taniguchi, Shigeki Momohara and Hisashi Yamanaka, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Patients with rheumatoid arthritis (RA) have an increased risk of fractures and falls compared to healthy controls. Utilizing data from our observational study of RA in Japan (IORRA, Institute of Rheumatology Rheumatoid Arthritis), we have previously reported that the incidence of fractures in Japanese women (J Rheumatol 2007;34:303-10) and men (J Bone Miner Metab 2008;26:499-505) with RA was mainly caused by falls. Limited data exist in the literature concerning the risk factors for falls in RA patients. We attempted to determine factors associated with falls in Japanese patients with RA.

Method: Among the Japanese patients who participated our IORRA observational study, 4996 (male 765, female 4231, median age 60 yrs) responded to questions related to falls during the previous 6 months in April or May 2008. Logistic regression was used to determine the association between variables and falls.

Results: Five hundred and five (10.1%), 110 (2.2%), and 958 patients (19.2%) reported at least one fall, multiple falls, and fear of falling, respectively. Those who fell tended to report incident fractures during the same 6 months compared to those who did not (14.7% versus 1.1%, $P < 0.001$). In multivariate models, Japanese health assessment questionnaire (J-HAQ) scores (odds ratios [OR] 1.52, 2.49, and 3.88), tender joint counts (OR 1.39, 1.72, and 1.36), patient-reported visual analog scale (VAS) for general health (OR 1.08, 1.16, and 1.20) and body mass index (BMI) (OR 1.05, 1.08, and 1.04) were associated ($P < 0.05$) with at least one fall, multiple falls, and fear of falling, respectively (Table). Other clinical variables and medications were also associated with falls and fear of falling (Table).

Conclusion: HAQ disability score, tender joint counts, and impaired general health appear to be associated with falls in Japanese patients with RA as previously reported in other ethnicities. BMI appears to be related to falls and fear of falling in Japanese patients with RA. Since our cross-sectional study design may not have been adequate to evaluate the efficacy of medications, further randomized controlled or prospective observational studies are needed to conclude the associations.

Table. Adjusted odds ratios (OR) and associated 95% confidence intervals (CI) for at least one or two falls, and the fear of falling in Japanese patients with rheumatoid arthritis: logistic-regression models with step-wise selection

Variables	At least one fall	At least two falls	Fear of falling
Age, years	1.01 (1.00, 1.01)	not selected	1.03 (1.02, 1.04)
BMI, kg/m^2	1.05 (1.02, 1.08)	1.08 (1.02, 1.15)	1.04 (1.01, 1.07)
J-HAQ score, 0-3	1.52 (1.31, 1.77)	2.49 (1.82, 3.42)	3.88 (3.33, 4.55)
VAS-general health, 0-10cm	1.08 (1.03, 1.13)	1.16 (1.00, 1.34)	1.20 (1.14, 1.26)
Tender joint counts	1.39 (1.14, 1.70)	1.72 (1.26, 2.32)	1.36 (1.05, 1.76)
Swollen joint counts	0.64 (0.43, 0.92)	0.48 (0.19, 1.05)	0.85 (0.60, 1.21)

Prednisolone dose, mg/day	1.02 (0.99, 1.05)	not selected	1.04 (1.01, 1.08)
Methotrexate use	0.85 (0.69, 1.05)	0.53 (0.35, 0.80)	not selected
Active vitamin D_3 use	1.43 (1.10, 1.84)	1.69 (1.02, 2.72)	not selected

Disclosure: T. Furuya, Japanese Osteoporosis Foundation, 2 ; **K. Yamagiwa**, None; **T. Ikai**, None; **E. Inoue**, None; **A. Taniguchi**, Takeda Pharmaceutical Company Limited, 9, Mitsubishi Tanabe Pharma Corporatio, 9, Eisai Co., Ltd., 9, Abbott Japan Co., Ltd., 9 ; **S. Momohara**, Astellas Pharma Inc., 9, Chugai Pharmaceutical Co., Ltd., 9, Dainippon Sumitomo Pharma Co., Ltd., 9, Kaken Pharmaceutical Co., Ltd., 9, Takeda Pharmaceutical Company Limited, 9, Mitsubishi Tanabe Pharma Corporation, 9, Sanofi-aventis K.K, 9, Santen Pharmaceutical Co., Ltd., 9, Wyeth K.K., 9 ; **H. Yamanaka**, Eisai Co., Ltd., 9, F. Hoffmann–La Roche, Ltd., 9, Mitsubishi Tanabe Pharma Corporation, 9, Wyeth K.K., 9, Chugai Pharmaceutical Co., Ltd., 9, Abbott Japan Co., Ltd., 9, Takeda Pharmaceutical Company Limited, 9, 36 pharmaceutical companies , 2 .

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Serum Hydroxyvitamin D, Parathyroid Hormone, and the Risk of Falls: The Osteoporotic Fractures in Men (MrOS) Study. Jeffrey R. Curtis[1], Annette Adams[2], J. Cauley[3], Peggy Cawthon[4], Steven Cummings[5], Kristine Ensrud[6], Andrew Hoffman[7], Suzanne Judd[1], Cora E. Lewis[1], Pongthorn Narongroeknawin[1] and James M. Shikany[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Oregon Health and Science University, Portland, OR, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]California Pacific Medical Center, San Francisco, CA, [5]SFCC, CPMC Research Institute & UCSF, San Francisco, CA, [6]University of Minnesota Medical School, Minneapolis, MN, [7]Stanford University, Stanford, CA

Purpose: Vitamin D deficiency has been associated with falls in frail older persons, but this relationship and the relationship between parathyroid hormone and falls in community-dwelling older men has not been well established. We tested the hypothesis that lower 25(OH)D and increased intact parathyroid hormone (iPTH) is associated with the risk of subsequent falls.

Method: A total of 1592 community-dwelling men age > 65 years participating in MrOS with baseline 25(OH)D(mass spec, Mayo) and iPTH (radio-immunoassay, Columbia) were eligible for analysis after excluding 14 individuals with Parkinson's disease. Poisson regression with generalized estimating equations (GEE) was used to evaluate the relationship between at least 1 self-reported fall (collected via postcard every 4 months), 25(OH)D quintile and intact parathyroid hormone (iPTH) quintile in the subsequent 1 and 5 years of follow-up. We also evaluated the relationship between 25(OH)D and ≥ 2 falls vs. 0-1 falls in the first year of follow-up. Potential confounders were selected based upon a-priori interest and associations with exposure and outcome (univariate $p < 0.10$).

Results: At baseline, 20.4% of men reported a baseline history of falls. In the first one and five years of follow-up, 26.4% and 38.0% men reported falling at least once, respectively. There were no significant differences in the risk for falls among men in the lowest quintile of 25(OH)D (range 3 – 18 ng/ml) compared to the highest quintile (31 – 58ng/ml) in either crude or adjusted results (relative risk = 1.25, 95% CI 0.87 – 1.79, adjusted for age, site, and season). The relationship between 25(OH)D and ≥ 2 falls was only slightly stronger (adjusted relative risk = 1.39, 95% CI 0.91 – 2.11). iPTH also was unrelated to risk for ≥ 2 falls (RR for highest quintile referent to lowest = 0.93, 95% CI 0.63-1.38), and we found no evidence that the relationship between 25(OH)D and falls differed by iPTH levels (interaction p-value= 0.59).

Conclusion: Among participants in MrOS with 25-OH(D) and iPTH measured, there was no significant relationship between 25(OH)D or iPTH and falls. The previously-reported relationship between vitamin D insufficiency and fall risk may not be generalizable to community-dwelling older men.

Disclosure: J. R. Curtis, Novartis, 2, Amgen, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8 ; **A. Adams**, None; **J. Cauley**, Novartis Pharmaceutical Corporation, 5, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2 ; **P. Cawthon**, None; **S. Cummings**, None; **K. Ensrud**, None; **A. Hoffman**, None; **S. Judd**, None; **C. E. Lewis**, None; **P. Narongroeknawin**, None; **J. M. Shikany**, None.

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The Longitudinal Relationship Between Intact Parathyroid Hormone Levels and BMD Loss: The Osteoporotic Fractures in Men (MrOS) Study. Jeffrey R. Curtis[1], Susan Ewing[2], Douglas C. Bauer[3], Peggy Cawthon[4], Suzanne Judd[5], Elizabeth Haney[6] and Areef Ishani[7], [1]University of Alabama at Birmingham, Birmingham, AL, [2]San Francisco Coordinating Center, San Francisco, CA, [3]University of California at San Francisco, San Francisco, CA, [4]California Pacific Medical Center, San Francisco, CA, [5]UAB, Birmingham, AL, [6]Oregon Health and Science University, Portland, OR, [7]University of Minnesota, Minneapolis, MN

Purpose: The longitudinal effect of intact parathyroid hormone (iPTH) levels on hip bone mineral density (BMD) loss in older men has been minimally studied. We evaluated the relationship with a particular interest in conditions associated with increased iPTH including low total serum 25(OH)D and decreased renal function.

Method: We selected a random sample of 1477 community-dwelling men age ≥ 65 yrs participating in MrOS with baseline iPTH data for analysis. Of these, 1144 had at least 2 BMD measurements at the femoral neck (FN) and total hip (TH) over mean follow-up of 4.5 years. Men taking osteoporosis medications were excluded (n = 86). Annualized BMD change associated with iPTH quartile was estimated using mixed effects regression models. We measured 25(OH)D using mass spec (Mayo); iPTH using radio-immunoassay (Columbia) and estimated glomerular filtration rate (eGFR) by the MDRD equation. Effect modification was assessed for race, serum 25(OH)D and eGFR. Multivariable models were adjusted for age, study site, weight change over the study period, history of cardiovascular disease, use of loop diuretics, season of blood draw, serum 25(OH)D and eGFR.

Results: Among the 1058 men eligible for analysis, 33 (3.1%) had iPTH > 65pg/ml and 3 also had serum calcium > 10.2mg/dL. There was a significant relationship between iPTH and BMD loss in Caucasians (Table) but a non-significant relationship in non-Caucasians, although an interaction term for race was not significant (p=0.25). Among Caucasians in the highest quartile of iPTH, the rate of BMD loss was approximately two-fold greater than in the lowest quartile. Results were similar for FN BMD (not shown). There was some evidence for effect modification by eGFR (interaction p-value=0.08). In stratified analysis (Table), men in the highest quartile of iPTH with reduced eGFR (< 60cc/min) had a 1.4 times higher rate of BMD loss compared to the corresponding men with normal eGFR. No effect modification by 25(OH)D was observed (interaction p value=0.95).

Conclusion: Older Caucasian men with higher baseline levels of iPTH had greater subsequent BMD loss; many had iPTH values within the accepted laboratory "normal" range. Concomitant reduced renal function further increased the rate of BMD loss. Based upon our results, iPTH < 38pg/ml is more optimal for maintaining BMD.

Table. Association between iPTH and Total Hip BMD Loss in Caucasian Men

Adjusted* Change in Total Hip BMD, %/yr	Quartiles of Intact PTH Q1 (< 23pg/ml)	Q2 (23-29 pg/ml)	Q3 (29-38 pg/ml)	Q4 (≥ 38 pg/ml)	Adjusted p for trend
Overall	-0.25	-0.25	-0.34	-0.52	0.0003
Stratified Results by eGFR					
eGFR<60 cc/min	-0.26	-0.27	-0.28	-0.71	0.06
eGFR≥60 cc/min	-0.24	-0.24	-0.35	-0.49	0.002

* adjusted for factors described in text

Disclosure: J. R. Curtis, Novartis, 2, Amgen, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8 ; **S. Ewing**, None; **D. C. Bauer**, None; **P. Cawthon**, None; **S. Judd**, None; **E. Haney**, None; **A. Ishani**, None.

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Bisphosphonates and Risk of Atrial Fibrillation: a Meta-Analysis. Seo Young Kim[1] and Daniel H. Solomon[2], [1]University of Pennsylvania, Philadelphia, PA, [2]Brigham & Womens Hospital, Boston, MA

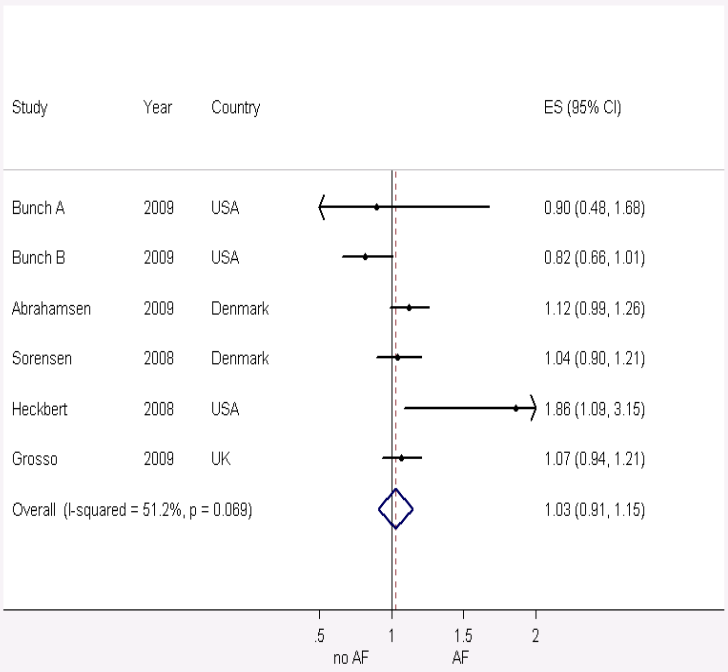
Purpose: Bisphosphonates are the most commonly used drugs for the prevention and treatment of osteoporosis. There have been discordant reports with regard to the risk of atrial fibrillation (AF) in patients on bisphosphonates. A recent meta-analysis of four clinical trials reported that bisphosphonates exposure was significantly associated with risk of AF serious adverse events [odds ratio (OR): 1.47; 95 % confidence interval (CI): 1.01-2.14], but not with all AF events [OR: 1.14; 95% CI: 0.96-1.36].

Methods: We aimed to conduct a meta-analysis of observational (cohort or case-control) studies, using a random-effects model, to evaluate risk of atrial fibrillation associated with bisphosphonates use. Studies were identified by searching MEDLINE using a combination of the Medical Subject Headings and keywords. Our search was limited to English language articles.

Results: Five eligible studies of 180,055 patients were identified. 2 were cohort and 3 were case-control studies (Figure 1). Only one of the studies found a statistically significant elevation in risk. Bisphosphonate exposure was not associated with an increased risk of AF [pooled OR: 1.03; 95% CI: 0.91-1.15]. Moderate heterogeneity was noted (I^2= 51.2%). Stratified analyses by study design yielded similar results. Egger's and Begg's test did not show an evidence of publication bias (p=0.23, 0.45 respectively).

Conclusion: Our study was unable to find an association between bisphosphonate exposure and atrial fibrillation. This agrees with the FDA's findings.

Figure 1. Risk of Atrial Fibrillation



Disclosure: S. Y. Kim, None; **D. H. Solomon**, None.

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Effect of Once-Monthly Oral Ibandronate On Hip Cortical and Sub-Cortical Quantitative Computed Tomography (QCT) Parameters in Postmenopausal Osteoporosis. Harry K. Genant[1], Thomas Fuerst[2], Klaus Engelke[3], Richard Y. Davies[4] and Gorana Dasic[5], [1]University of California, San Francisco, CA, [2]Synarc, Inc, San Francisco, CA, [3]Synarc, Inc., Hamburg, Germany, [4]Glaxo Smith Kline, Collegeville, PA, [5]GlaxoSmithKline, King of Prussia, PA

Purpose: Once-monthly oral ibandronate for 12 months was previously found to increase hip integral and trabecular bone mineral density (BMD) assessed by QCT. Finite element analysis (FEA) showed significantly increased peripheral (outer 3 mm of bone), trabecular, and total femur strength. We examined cortical, sub-cortical, and extended-cortical QCT parameters for potential contributions to the FEA peripheral strength gains.

Method: Postmenopausal women with osteoporosis (N=93) received 150 mg once-monthly ibandronate or placebo for 12 months. QCT BMD, BMC, and cortical volume were measured at baseline (BL) and month 12. Treatment differences in mean percent changes from BL were determined by analysis of variance. This study was not powered for statistical testing; all *P*-values were post hoc, exploratory, and uncorrected for multiple comparisons.

Results: Ibandronate numerically improved cortical BMC and volume versus placebo, and to a lesser extent cortical BMD (Table). Total hip sub-cortical (endosteal surface and underlying trabecular bone to 1.5 mm depth) and extended-cortical BMD (cortical + sub-cortical) significantly improved with ibandronate versus placebo. Within-group ibandronate responses were significant for total hip cortical BMC and volume, femoral neck cortical volume, and trochanter extended-cortical BMD. Placebo within-group changes were significant only for total hip cortical volume.

Conclusion: Significant gains in sub-cortical total hip and extended-cortical total hip and trochanter BMD appear to contribute to the ibandronate-induced FEA peripheral strength improvements, within the limitations of sample size and measurement variability.

	Within-group % change from BL to 12 months (LS mean and 95% CI)		**Treatment difference in % change from BL to 12 months (ibandronate – placebo), LS mean and 95% CI**	***P* value**
	Ibandronate	**Placebo**		
Cortical BMC				
Total hip	2.4 (0.3, 4.4)	0.7 (–1.3 ± 2.7)	1.7 (–1.0, 4.3)	0.21
Femoral neck	3.8 (–0.6, 8.1)	1.7 (–2.5, 5.9)	2.0 (–3.5, 7.5)	0.46
Trochanter	3.1 (–0.1, 6.2)	0.9 (–2.1, 4.0)	2.2 (–1.9, 6.3)	0.28
Cortical Volume				
Total hip	3.1 (1.3, 4.9)	1.9 (0.2, 3.6)	1.2 (–1.0, 3.5)	0.28
Femoral neck	5.7 (1.2, 10.2)	3.6 (–0.6, 7.8)	2.1 (–3.5, 7.7)	0.46
Trochanter	2.0 (–0.6, 4.6)	1.3 (–1.2, 3.7)	0.8 (–2.5, 4.0)	0.64
Cortical BMD				
Total hip	–0.4 (–1.8, 1.0)	–0.9 (–2.2, 0.4)	0.5 (–1.2, 2.2)	0.57
Femoral neck	–1.1 (–2.6, 0.5)	–1.4 (–2.8, 0.05)	0.3 (–1.5, 2.2)	0.72
Trochanter	0.9 (–0.7, 2.5)	–0.4 (–1.9, 1.2)	1.3 (–0.7, 3.3)	0.20
Sub-cortical BMD				
Total hip	2.0 (–0.1, 4.2)	–1.6 (–3.7, 0.4)	3.7 (1.0, 6.4)	0.01
Extended-cortical BMD				

Total hip	0.7 (–0.5, 1.9)	–0.8 (–2.0, 0.3)	1.5 (0.02, 3.0)	0.05
Femoral neck	–0.3 (–1.6, 1.0)	–1.4 (–2.7, 0.2)	1.1 (–0.5, 2,8)	0.20
Trochanter	1.9 (0.4, 3.4)	–0.6 (–2.0, 0.9)	2.4 (0.5, 4.3)	0.01

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Relationships Between Presence, Severity, and Location of Prevalent Vertebral Fractures and Health Related Quality of Life (HRQoL). S. Silverman[1], H. Viswanathan[2], Y. Yang[2], S.R. Eis[3], P. Fardellone[4], N. Gilchrist[5], P. Lips[6], M. Nevitt[7], S. Palacios[8], K. Pavelka[9], D. Revicki[10], J. Simon[11], D. Macarios[2] and E. Siris[12], [1]Cedars Sinai/UCLA, Beverly Hills, CA, [2]Amgen Inc., Thousand Oaks, CA, [3]CEDOES Diagnóstico e Pesquisa, Vitória, Brazil, [4]Hôpital Nord, Amiens, France, [5]Princess Margaret Hospital, Christchurch, New Zealand, [6]VU University Medical Center, Amsterdam, Netherlands, [7]University of California San Francisco, San Francisco, CA, [8]Palacios Institute of Women's Health, Madrid, Spain, [9]Charles University, Prague, Czech Republic, [10]United Biosource Corporation, Bethesda, MD, [11]Women's Health Research Center, Laurel, MD, [12]Columbia University Medical Center, New York, NY

Purpose: The objectives were to examine 1) the relationship between presence of prevalent vertebral fractures and HRQoL in the FREEDOM trial, and 2) the relationships between number, location, and severity of prevalent vertebral fractures and HRQoL in women with at least 1 prevalent vertebral fracture.

Methods: Baseline data from 7,808 women (60-90 years, lumbar spine and/or total hip T-score < –2.5 and not <–4.0) included in the phase 3, denosumab FREEDOM trial were used. Prevalent vertebral fractures were assessed by radiography. The 34-item Osteoporosis Assessment Questionnaire-Short Version (OPAQ-SV) was used to measure physical function, emotional status, and back pain with higher scores representing better HRQoL (subscale scores range from 0 to 100). Multiple regression was used to examine relationships between prevalent vertebral fractures and OPAQ-SV scores in all women, and relationships between number, location, fracture severity, and OPAQ-SV scores in women with at least 1 prevalent vertebral fracture, adjusting for age, race, region, and body mass index.

Results: Presence of one vertebral fracture vs no fracture was significantly associated with worse physical function (coefficient [coeff] = –1.3, SE=0.5), emotional status (coeff = –2.0, SE=0.6), and back pain (coeff = –3.0, SE=0.8), adjusting for covariates. Presence of ≥2 vs no fracture was significantly associated with worse emotional status (p<0.05) and back pain (p<0.05) but not physical function. In women with at least 1 prevalent vertebral fracture (N=1,844), no differences were found in OPAQ-SV dimensions for those with ≥2 (mean [SD], 2.5 [1.1]) vs 1 fracture (Table). Moderate or severe fractures were associated with lower scores in all OPAQ-SV dimensions (p<0.05) compared to mild fractures (Table). Prevalent lumbar (L2 to L4) fractures were associated with significantly lower scores in all OPAQ-SV dimensions (p<0.05) compared to thoracic (T4 to T9) fractures (Table). Thoracolumbar fractures (T10-L1) were associated with worse physical function (p<0.05) compared to thoracic fractures (Table).

Conclusion: Consistent with published literature, presence of prevalent vertebral fractures was significantly associated with worse physical function, emotional status, and back pain. Moderate or severe prevalent vertebral fractures and those in the lumbar compared to thoracic location showed significantly lower scores in all OPAQ-SV dimensions.

Table: Relationships between the number, severity, or location of prevalent vertebral fractures and baseline QPAQ-SV scores in women with at least one prevalent vertebral fracture

	Physical Function n = 1,826 β (SE)	Emotional Status n = 1,826 β (SE)	Back Pain n = 1,461 β (SE)
Models examining number of prevalent vertebral fractures [a]			
Intercept	146.4 (6.5)*	128.3 (7.3)*	93.6 (9.6)*
≥2 vs 1	0.4 (0.9)	-0.6 (1.0)	-1.2 (1.3)
Models examining severity of prevalent vertebral fractures [a]			
Intercept	147.0 (6.6)*	128.9 (7.3)*	94.6 (9.6)*
Moderate or Severe vs Mild	-2.0 (0.8)*	-2.2 (0.9)*	-2.6 (1.2)*
Models examining location of prevalent vertebral fractures [a,b]			
Intercept	148.0 (7.1)*	128.9 (8.1)*	96.0 (10.7)*
Lumbar (L2-L4) vs Thoracic (T4-T9)	-4.9 (1.4)*	-3.4 (1.6)*	-6.8 (2.0)*
Thoracolumbar (T10-L1) vs Thoracic (T4-T9)	-2.2 (1.0)*	-1.5 (1.1)	-2.8 (1.5)

n = Number of subjects with observed data included in the ANCOVA model.
[a] All regression models also included age, race, region, and BMI as covariates.
[b] Women with prevalent vertebral fractures at multiple locations (thoracic, thoracolumbar, or lumbar) were excluded.
*p<0.05

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Systematic Review of the Risk of Fracture with Medication Non-Adherence in Post Menopausal Osteoporotic (PMO) Women. E. Samuels[1], Ethel Siris[2], Sheikh Usman Iqbal[3], K. Gairy[1], S. Ross[4] and E. Badamgarav[5], [1]Heron Evidence Development, Luton, United Kingdom, [2]Columbia University Medical Center, New York, NY, [3]Amgen, Thousand Oaks, CA, [4]SD Ross Consulting, Cohasset, MA, [5]Amgen, California, CA

Purpose: In the US, as many as 8 million women and 2 million men have osteoporosis. In 2005, osteoporosis was responsible for more than 2 million fractures, costing an estimated $19 billion in direct medical care costs. Osteoporosis drug treatments have shown to increase bone mass and significantly reduce the risk of fracture in clinical trials. However, real world adherence (compliance and persistence) to currently available therapies is suboptimal and may reduce the effectiveness of these interventions. This systematic review assessed the risk of fracture in women who were non-adherent to medication for PMO.

Method: Three databases were searched (Medline, Embase, CINAHL) for English-language publications from 1998 to 2009. Recent symposia were also searched. Key study selection criteria were: observational studies of PMO patients ≥ 45 years, receiving bisphosphonates, parathyroid hormone, and/or SERMs, and reporting fracture risk in relation to adherence, as defined by the individual authors. The medication possession ratio [MPR] was the primary measure of interest. Two independent reviewers evaluated all identified studies, with disagreements reconciled by a third reviewer.

Results: The database search yielded 487 citations, of which 18 studies were eligible. The vast majority of patients were prescribed bisphosphonates. The MPR at an 80% threshold was most commonly used to assess adherence, and, in the 7 studies using this metric, the proportion of study subjects who were adherent ranged from 43% to 48%, for follow-up times ranging from 40 to 140 weeks (see Table). The hazard ratio of fracture in non-compliant versus compliant patients in these MPR studies ranged from 1.17* to 1.41.

Conclusion: Poor medication adherence (as measured by MPR) is a common occurrence in women treated for PMO. Poor adherence to osteoporosis medication is associated with significantly increased risk of osteoporotic fracture in women, and thus enhancing adherence may lead to a greater reduction in fracture. Table: Studies reporting data for <80% (non-compliance; NC) vs. MPR ≥80% (compliance; C)

	N	**Results**
Blouin 2008	21 105	RR of non-vertebral fracture for NC (N = 8650) vs. C (N = 12455): 1.22 (1.08-1.39) RR of hip fracture for NC (N = 2748) vs. C (N = 3954): 1.27 (1.02-1.59)
Caro 2004	11 249	HR for fractures in C vs. NC: 0.84, p = 0.006 NC vs. C: 1.19 (1.05-1.34)*
De Lusignan 2006	1286	Total fracture rate for C vs. NC: 123/584 vs. 171/702, p = 0.16 OR for NC vs. C: 1.21 (0.93-1.57)*
Huybrechts 2006	38 120	HR for fractures in NC vs. C: 1.17, p < 0.0001 HR for hospitalisation in NC vs. C: 1.37 (1.32-1.43), p < 0.0001 Direct medical costs (mean US$) in NC vs. C: $600 vs. $340, p < 0.0001
Penning-van Beest 2008	8822	HR for fractures in NC vs. C: 1.41 (1.04-1.91)
Rabenda 2008	54 807	OR for hip fractures in C vs. NC:

		0.996 (0.994-0.998), p < 0.001 NC vs. C: 1.004 (1.002-1.006)*
Siris 2006	35 537	OR for fractures in C vs. NC: 0.789, p < 0.001 NC vs. C: 1.29 (1.20-1.38)*

***Data derived**

RR: risk ratio

OR: odds ratio

HR: hazard ratio

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Denosumab and Risk of Fractures in Subgroups of Women with Osteoporosis. Michael McClung[1], Henry G. Bone[2], Jonathan D. Adachi[3], Steven Boonen[4], Claus Christiansen[5], Richard Eastell[6], Jordi Farrerons[7], Nathalie Franchimont[8], Kurt Lippuner[9], Zulema Man[10], Salvatore Minisola[11], Ian Reid[12], Rene Rizzoli[13], Javier San Martin[14], Ethel Siris[15], Ove Torring[16], Andrea Wang[14] and Steven Cummings[17], [1]Oregon Osteoporosis Center, Portland, OR, [2]Michigan Bone and Mineral Clinic, Detroit, MI, [3]McMaster University, Hamilton, ON, [4]University of Leuven, Leuven, Belgium, [5]CCBR, Ballerup, Denmark, [6]University of Sheffield, Sheffield, United Kingdom, [7]Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, [8]Amgen Inc., Zug, Switzerland, [9]Inselspital Bern, Bern, Switzerland, [10]Centro T.I.E.M.P.O., Buenos Aires, Argentina, [11]Universita' Di Roma “Sapienza”, Rome, Italy, [12]University of Auckland, Auckland, New Zealand, [13]University Hospital, Geneva, Switzerland, [14]Amgen Inc., Thousand Oaks, CA, [15]Columbia University Medical Center, New York, NY, [16]Karolinska Institutet Sodersjukhuset, Stockholm, Sweden, [17]SFCC, CPMC Research Institute & UCSF, San Francisco, CA

Purpose: Denosumab reduces the risk of new vertebral fracture and nonvertebral fracture. Previous trials suggest that the efficacy of antiresorptives on nonvertebral fractures might differ by patients' bone density, age, presence of vertebral fracture or other characteristics.

Methods: In FREEDOM 7,868 women aged 60-90 years with osteoporosis were randomly assigned to denosumab 60 mg every 6 months or placebo; all received daily calcium (≥ 1g) and vitamin D (≥ 400 IU). Nonvertebral and new vertebral fractures were radiologically confirmed. We prospectively planned 9 subgroup analyses of the effect of denosumab on new vertebral and nonvertebral fractures. Statistical significance was based on tests for quantitative interactions.

Results: Denosumab reduced all nonvertebral fractures by 20% (95% CI, 5 to 33%) over 3 years. The effect was significantly greater in women with low BMI, femoral neck BMD T-score ≤-2.5, and those without prevalent vertebral fracture (Table) but did not differ by age (< 75 vs. ≥ 75 years; p = 0.64) or prior nonvertebral fracture (p = 0.61). Compared with placebo, denosumab decreased the risk of new vertebral fracture by 68% (95% CI, 59 to 74%) over 3 years. This effect did not significantly differ by age, prevalent vertebral fracture, prior nonvertebral fracture and BMI (P>0.29 for all potential interactions).

Conclusion: Denosumab 60 mg for 3 years in women with osteoporosis reduced the risk of new vertebral fractures to a similar degree in all subgroups tested. However, as observed in several other trials, treatment reduced the risk of nonvertebral fractures significantly more in women with femoral neck BMD T-score ≤-2.5 (RRR: 35%) than in those with higher BMD. It was also more effective in thin than heavier women and those without existing vertebral fractures.

Reduction in Risk (Hazard Ratio) for Nonvertebral Fractures in Subgroups

Subgroup		Hazard ratio (95% CI)	Interaction P-value
Femoral neck BMD T-score	< -2.5	0.65 (0.51, 0.83)	
	> -2.5	0.97 (0.76, 1.23)	0.02
BMI (kg/m2)	<25	0.62 (0.48, 0.80)	
	25 to <30	0.98 (0.75, 1.30)	
	>30	1.13 (0.71, 1.78)	0.01
Baseline vertebral fracture	Yes	1.06 (0.78, 1.44)	
	No	0.71 (0.58, 0.88)	0.04

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Relationship Between the Effect of Denosumab On Bone Turnover Markers and Change in Bone Mineral Density in Postmenopausal Osteoporosis. M. McClung[1], C. Christiansen[2], A. Grauer[3], S. Kutilek[4], C. Libanati[3], H. Resch[5], I. Reid[6], E. Siris[7], D. Uebelhart[8], A. Wang[3], G. Weryha[9], S. Cummings[10] and R. Eastell[11], [1]Oregon Osteoporosis Center, Portland, OR, [2]CCBR, Ballerup, Denmark, [3]Amgen Inc., Thousand Oaks, CA, [4]CCBR, Pardubice, Czech Republic, [5]St. Vincent Hospital Vienna, University of Vienna, Vienna, Austria, [6]University of Auckland, Auckland, New Zealand, [7]Columbia University Medical Center, New York, NY, [8]University Hospital of Zurich, Zurich, Switzerland, [9]CHU de Nancy, Vandoeuvre, France, [10]SFCC, CPMC Research Institute & UCSF, San Francisco, CA, [11]University of Sheffield, Sheffield, United Kingdom

Purpose: Denosumab (DMAb), an investigational human monoclonal antibody to RANKL, reduced the risk of vertebral, nonvertebral and hip fractures in the FREEDOM trial. With DMAb treatment, levels of bone resorption markers (BRM) were reduced below the premenopausal reference range in all women tested. In a subset of women, the level of BRM reduction attenuated at the end of the 6-month dosing interval, while other women had sustained BRM reduction throughout the study. We evaluated the relationship between change in bone turnover markers (BTM) and change in BMD and if there were similar BMD increases in women with sustained BTM reduction vs those with a transient attenuation of BTM.

Methods: FREEDOM was a phase 3 trial in women ages 60-90 years with postmenopausal osteoporosis randomized to sc DMAb 60mg or placebo (Pbo) every 6 months for 36 months with daily calcium (1000mg) and vitamin D supplements (400-800 IU). Osteoporosis was defined as a T-score <-2.5 at the spine or hip but not <-4 at either site. We measured BTM (serum CTX [ELISA, Osteometer] and PINP [RIA, Orion]) in 944 women (505 DMAb, 439 Pbo) at baseline, 1, 6, 12, 24 and 36 months, and BMD of the proximal femur annually and lumbar spine at baseline and 36 months.

Results: DMAb decreased CTX and PINP at 6 months and increased BMD at the lumbar spine and total hip at 36 months (Table). Overall, BTM changes in DMAb and Pbo groups at 6 months were negatively correlated with BMD changes at 36 months (Table). Mean (SD) BMD changes with DMAb at 36 months were identical (+0.08 [0.04] g/cm^2 at the lumbar spine, and +0.04 [0.02] g/cm^2 at the total hip) in women treated with DMAb who had sustained reduction in BTM (n=146 CTX, n=103 PINP) vs those who had transient attenuation of BTM levels before repeat dosing (n=359 CTX, n=402 PINP).

Conclusion: There were weak to modest correlations between changes in BTM and changes in BMD. Additionally, there were similar increases in BMD whether or not BTM remained below the premenopausal reference range throughout the study or showed attenuation of BTM before the next dose.

	Placebo	DMAb
CTX Absolute Change (ng/mL) at 6 mo, median (interquartile range)	-0.07 (-0.20 to +0.04)	-0.40 (-0.59 to -0.26)†††
PINP Absolute Change (ng/mL) at 6 mo, median (interquartile range)	-14 (-26 to -5)	-39 (-54 to -25)†††
Lumbar Spine BMD Change (g/cm^2) at 36 mo, mean (SD)	0.00 (0.04)	+0.08 (0.04)†††
Total Hip BMD Change (g/cm^2) at 36 mo, mean (SD)	-0.01 (0.03)	+0.04 (0.02)†††
Correlation Between CTX at 6 mo and Lumbar Spine BMD Change at 36 mo	-0.09	-0.20***
Correlation Between PINP at 6 mo and Lumbar Spine BMD Change at 36 mo	-0.07	-0.31***
Correlation Between CTX at 6 mo and Total Hip BMD Change at 36 mo	-0.16**	-0.34***
Correlation Between PINP at 6 mo and Total Hip BMD Change at 36 mo	-0.09	-0.39***

†††p<0.001 indicates the difference in BTM/BMD changes between treatment groups is different from zero.
**p<0.01 and ***p<0.001 indicate the correlation between BTM change at 6 months and BMD change at 36 months is different from zero.

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Relationship of Baseline Bone Turnover Marker Levels and Month 12 Bone Mineral Density Change in Postmenopausal Women Transitioned From Alendronate to Denosumab. M.A. Bolognese[1], C. Roux[2], G. Bianchi[3], J. Supronik[4], I. Valter[5], M.C. de Vernejoul[6], D.L. Kendler[7], H.G. Bone[8], S. Ortolani[9], S. Siddhanti[10], H.S. Man[10], J. San Martin[10] and M.L. Brandi[11], [1]Bethesda Health Research Center, Bethesda, MD, [2]Paris Descartes University Hôpital Cochin, Paris, France, [3]Azienda Sanitaria Genovese, Genova, Italy, [4]Niepubliczny Zaklad Opieki Zdrowotnej Centrum Medyczne, Bialystok, Poland, [5]Center for Clinical and Basic Research, Tallinn, Estonia, [6]Hôpital Lariboisiere, Paris, France, [7]Clinical Research Centre, Vancouver, BC, [8]Michigan Bone and Mineral Clinic, Detroit, MI, [9]Istituto Auxologico Italiano, Milan, Italy, [10]Amgen Inc., Thousand Oaks, CA, [11]Azienda Ospedaliera Careggi, Firenze, Italy

Purpose: Denosumab is an investigational fully-human monoclonal antibody that reduces bone resorption by inhibiting RANKL, an essential mediator of osteoclast formation, function, and survival. In previous studies in postmenopausal women, denosumab increased bone mineral density (BMD) and reduced the risk of fracture.

Methods: Subjects were eligible for this randomized, double-blind, double-dummy study if they were postmenopausal women ≥55 with a lumbar spine or total hip T-score ≤–2.0 and ≥–4.0 and were receiving generic or branded alendronate for ≥6 months. After a 1-month alendronate run-in phase, subjects were randomized to treatment with continued alendronate (70 mg weekly) or denosumab (60 mg every 6 months subcutaneously) and the effects on BMD were compared. The relationship between baseline bone turnover marker levels and month 12 percent changes in BMD at the total hip or lumbar spine was also evaluated.

Results: The 504 enrolled women (251 alendronate, 253 denosumab) had a baseline mean age of 68, a mean lumbar spine BMD T-score of –2.63, and a median sCTX-I level of 0.20 ng/mL (range, 0.05-0.89 ng/mL). As previously reported, transition to denosumab resulted in greater increases in total hip, lumbar spine, femoral neck, and 1/3 radius BMD compared with continued alendronate (P□0.012). For subjects receiving alendronate, month 12 BMD gains were generally similar across quartiles of baseline bone turnover marker levels. For subjects transitioned to denosumab, month 12 BMD gains at the total hip and lumbar spine were largest and significantly differed from the alendronate group among subjects in the 2 highest quartiles of baseline sCTX-I or PINP levels (Table – total hip vs. sCTX-I).

Conclusion: In postmenopausal women with low bone mass who were previously receiving alendronate, transition to denosumab 60 mg every 6 months increased BMD. The greatest BMD increases as compared with continued alendronate occurred among women with the two highest quartiles of baseline levels of bone turnover markers.

Table: Percent Change in Month 12 Total Hip BMD by Baseline sCTX-I

Baseline sCTX-I (ng/mL)		Alendronate	Denosumab
<0.128	N	56	62
	BMD % Change	1.24	1.58
	95% CI	0.66, 1.82	1.03, 2.12
0.128 – <0.202	N	57	62
	BMD % Change	1.24	1.38
	95% CI	0.61, 1.87	0.78, 1.97
0.202 – <0.308	N	58	63
	BMD % Change	1.15	2.16*
	95% CI	0.56, 1.74	1.57, 2.74
≥0.308	N	62	54
	BMD % Change	0.68	2.65**
	95% CI	0.12, 1.23	2.05, 3.24

*P=0.015 vs. alendronate, **P<0.0001 vs. alendronate

Disclosure: M. A. Bolognese, Roche, Lilly, 9, Roche, Lilly, Novartis, Glaxo Smith Kline, 8, Roche, Lilly, Procter and Gamble, Novartis, Amgen, Glaxo Smith Kline, 2 ; **C. Roux**, Alliance, Amgen, Lilly, MSD, Novartis, Roche, Servier, 5, Alliance, Amgen, Lilly, MSD, Novartis, Roche, Servier, 9, Alliance, Amgen, Lilly, MSD, Novartis, Roche, Servier, 2 ; **G. Bianchi**, Schering Plough, Pfizer, 5, Roche, Abbott, Novartis, Servier, 8, MSD, Roche, Servier, Amgen, 9 ; **J. Supronik**, Amgen Inc., 9 ; **I. Valter**, Amgen Inc., 9 ; **M. C. de Vernejoul**, Amgen Inc., 9 ; **D. L. Kendler**, Lilly, Amgen, Novartis, Wyeth, GSK, Roche, 2, Lilly, Amgen, Novartis, 8, Lilly, Amgen, Novartis, Wyeth, Nycomed, 9, Lilly, Amgen, Novartis, Wyeth, Nycomed, 5 ; **H. G. Bone**, Amgen, Merck, Lilly, Zelos, 2, Amgen, Merck, 9, Amgen, Merck, GSK, Zelos, Novartis, 5, Novartis , 8 ; **S. Ortolani**, Amgen Inc., 9, Institut International de Recherche Servier, 5, GSK, 8, Institut International de Recherche Servier, Nycomed, 2 ; **S. Siddhanti**, Amgen Inc., 1, Amgen Inc., 3 ; **H. S. Man**, Amgen Inc., 1, Amgen Inc., 3 ; **J. San Martin**, Amgen Inc., 1, Amgen Inc., 3 ; **M. L. Brandi**, MSD, Lilly, Wyeth, Amgen, Nycomed, Servier, 2, MSD, Lilly, Wyeth, Amgen, Nycomed, Servier, 5 .

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Development of Natural Calcium and Phosphate-Donating Molecules and a New Iontophoretic Device for the Topical Treatment of Osteoporosis. Lajos Pap[1], Izabella Gomez[2], Lajos Pap Jr.[3], Andrea Szabó[4] and Zoltan Szekanecz[2], [1]University of Debrecen, Debrecen, Hungary, [2]University of Debrecen medical and Health Sciences Center, Debrecen, Hungary, [3]Digitaltechnik, Vienna, Austria, [4]University of Szeged, Szeged, Hungary

Purpose: Apart from systemic treatment of osteoporosis, topical treatment may be useful to treat local bone defects, fractures and other bone disorders. We have developed a novel iontoforesis device and a topical treatment protocol. Two natural-based, chemically modified molecules including bentonites and montmorillonites have been developed. In addition, a novel 3-electrode electrophoretic device has been constructed.

Method: This device 'knocks out' Ca2+ and PO43- ions from the molecules with its impulse-like positive and negative charges transmitted through its electrodes placed on the skin. The current and the voltage of the electrodes can be adjusted separately in both leads. Subsequently, these 'knocked out' ions are channelled into the porotic bones with the help of the thirs - reference – electrode. In our preliminary in vitro studies, we used porcine tissues to test their calcium and phosphate content after iontophoresis; with or without using nanomolecules. In addition, we performed preliminary in vivo experiments in ovariectomized rats.

Results: Our major results are the development of two molecules that are able to donate calcium and phosphorous into the bone. Also, a new 3 electrode iontophoresis apparatus has been developed. In vitro studies revealed that both calcium and phosphate ions became incorporated into the porcine bone. When only iontophoresis was applied without using molecules, the calcium content of the muscle tissue on the anode side decreased after iontophoresis (235.7 ± 66.7 μg/g) compared to controls (278.2 ± 33.2 μg/g) ($p<0.05$). When molecules were also applied in addition to iontophoresis, calcium content of the skin and bone significantly increased in treated tissues (793.0 ± 108.6 μg/g and 207628 ± 16198 μg/g, respectively) in comparison to controls (319.7 ± 38.9 μg/g and 124560 ± 15551 μg/g, respectively) ($p<0.05$). Similar results were found regarding the phosphate content. In the rat in vivo studies, quantitative ultrasound indicated significant bone loss in the tibia in ovariectomized rats compared to sham-operated animals. Five courses of iontophoresis resulted in increased bone density as indicated by significantly higher AD-SoS values in both ovariectomized and sham-operated animals in comparison to untreated rats ($p<0.05$). This favourable effect of iontophoresis was sustained even 150 days after treatment ($p<0.05$).

Conclusion: A three-electrode new iontophoretic apparatus, as well as calcium- and phosphate-donating molecules have been developed. Preliminary in vitro experiments using pig tissues suggest that calcium and phosphate ions indeed penetrate into the bone during iontophoresis. In vivo studies in rats suggest that iontophoresis may increase local bone density. Further in vivo biomechanical and fracture studies in rats have also been performed and will soon be demonstrated.

Disclosure: L. Pap, None; **I. Gomez**, None; **L. Pap**, None; **A. Szabó**, None; **Z. Szekanecz**, None.

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To What Degree Does the FRAX Case Finding Algorithm Underestimates Fracture Risk in Patients with a Recent Fall? Piet P.M.M. Geusens, Maastricht University Medical Center and Hasselt University, Biomedical Research Institute, Diepenbeek, Belgium

Purpose: Identifying patients at highest risk for fracture starts with clinical case finding, based on the presence of well-documented bone and fall-related clinical risk factors for fractures. The FRAX algorithm does not include risk factors for falls. The Fracture Prediction Tool in Glucocorticosteriod users (FIGS) includes a history of recent falls and the Garvan algorithm the number of recent falls.

Method: We compared FRAX with FIGS and Garvan to calculate the 10-year risk of major fractures (FRAX: clinical spine, hip, forearm an humerus; FIGS: also rib, femur and pelvis fractures; Garvan: all low-trauma fractures).

Results: In 60 yr old subjects with a body weight of 70 kg without clinical fracture risks, calculated fracture risk was 6.0% with FRAX, 6.9% with FIGS and 9.4% with Garvan. After a recent fall, the fracture risk increased with FIGS (14.3%) and Garvan (11.4% after one fall up to 16.7% after 3 falls). After a history of fracture, the fracture risk increased with all algorithms compared to patients without a recent fall (FRAX: 12.0%, FIGS: 12.0%, Garvan:16.1%), but further increased substantially if they had a recent fall (FIGS: 24.0%. Garvan: 19.3% after one fall up to 27.6% after 3 falls). Similar differences in fracture prediction between the algorithms were found in 70 or 80 yr old subjects and in subjects with a low or high body weight.

Conclusion: We conclude that FRAX substantially underestimates fracture risk in subjects who have as only risk factors a history of a recent fall or a recent fall-related fracture.

Disclosure: P. P. M. M. Geusens, None.

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Bisphosphonate Use Increases Risk of Transverse Minimal Trauma Fracture of Femoral Diaphysis. Michael H-Y. Tjeuw, Stephen P. Oakley, Zsolt Balogh and Gabor AC. Major, Newcastle Bone & Joint Institute, Newcastle, Australia

Purpose: While bisphosponates (BP) protect against osteoporotic fracture recent case series have suggested that BP may actually increase the risk of a sub-type of fracture - Simple Transverse Minimal Trauma Fracture (MTF) of Femoral Diaphysis[1-2]. However, a recent register-based case-controlled study found no such association[4]. Our Orthopaedics Department have maintained a database of all femoral fractures presenting between March 2005 – September 2008, providing an opportunity to conduct a retrospective cohort analysis. We used this data to evaluate whether BP increased the risk of Simple Transverse MTF of Femoral Diaphysis.

Method: We identified 112 diaphyseal MTF in patients over 50 years old. MTF was defined as "a fall from standing height". Records were reviewed for information regarding BP use, medications and co-morbidities. X-rays were reviewed by a second investigator blind to BP status and classified according to the AO Classification as: 1. Simple (further grouped as transverse, spiral or oblique) 2. Non-simple (further grouped as wedge or complex) or 3. Peri-prosthetic.

Results: Within the simple fracture group, BP use was associated with a RR of 2.09 (CI: 1.12-3.89) for transverse diaphyseal fractures as opposed to spiral or oblique fractures. When non-simple fractures were included in the analysis, the RR was 1.43 (CI: 1.07-1.90) and with the further addition of peri-prosthetic fractures the RR was 1.89 (CI: 1.01-3.55). Spiral, oblique, non-simple and peri-prosthetic fractures were not associated with BP use.

Conclusion: We found that BP use was associated with double the risk of transverse MTF of the femoral diaphysis. While BP use clearly reduces the overall risk of osteoporotic fracture, our results support the notion that it may change the fracture type. Prospective clinical research is needed to confirm these results, to determine whether there is a dose-effect and to see if this risk is associated with all bisphosphonates.

References: 1. Schneider J. Geriatrics 2006; Jan. 2. Neviaser et al. J Orthop Trauma 2008; 22(5):346-350. 3. Abrahamsen B et al. JBMR. 2008; published online 29/12.

Disclosure: M. H. Y. Tjeuw, None; **S. P. Oakley**, None; **Z. Balogh**, None; **G. A. Major**, None.

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The Clinical and Economic Burden of Non-Adherence with Oral Bisphosphonates in Osteoporotic Patients. Mickaël Hiligsmann, Véronique Rabenda, Olivier Bruyere and Jean Y. Reginster, University of Liège, Liège, Belgium

Purpose: Poor compliance and failure to persist with oral bisphosphonates are common, but the clinical and economic consequences have not been well described. This study aims to estimate the clinical and economic burden of nonadherence with oral bisphosphonates in osteoporotic patients and to examine the scope for adherence-enhancing interventions.

Method: A validated Markov microsimulation model estimated costs and outcomes (i.e. the number of fractures and the quality-adjusted life-year (QALY)) for three adherence scenarios: no treatment, real-world adherence and full adherence over 3 years. Simulated patients matched the populations where osteoporosis medications are reimbursed. The real-world adherence scenario employed adherence data from a published observational studies and adherence was divided into persistence and compliance. The incremental cost per QALY gained was estimated comparing the three adherence scenarios. We also examined the clinical and economic implications of adherence-enhancing interventions assuming that adherence failure would be reduced by 10%, 20% or 30%.

Results: The estimated number of fractures prevented and the lifetime QALY gained in the real-world adherence scenario represents only 42.0% and 41.9% to that obtained under full adherence scenario, respectively. The cost per QALY gained of real-world adherence versus no treatment was estimated at €11,175, and full adherence was found to be cost-saving compared to real-world adherence. An intervention that

decreases adherence failure by 20% was associated with a 28% increase in the number of fractures prevented and the costs per QALY gained compared to real-world adherence were respectively €29,350 and €46,275 if the intervention costs €100 and €150 per year.

Conclusion: This study suggests that more than half of the potential benefits from oral bisphosphonates in patients with osteoporosis are lost due to poor compliance and failure to persist. Depending on its cost, interventions that improve adherence to therapy have the potential to be an attractive use of resources. So, therapies that optimize adherence should remain cost-effective compared to oral bisphosphonates even if they cost up to €150 more, per year, and may therefore represent a promising approach to reduce clinical and economic consequences of osteoporosis.

Key-words : adherence, economic analysis, osteoporosis

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Physiologically Optimal Vitamin D Levels in African Americans Based Upon Intact Parathyroid Hormone Suppression: What Vitamin D Should Be Considered "Normal"? J. R. Curtis[1], L. Chen[1], J. Niu[2], E. Delzell[1], David T. Felson[3], M.K. Javaid[4], C. Katholi[1], M. A. Nevitt[5] and C. E. Lewis for the MOST Group[1], [1]UAB, Birmingham, AL, [2]BUSM, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]University of Oxford, Oxford, United Kingdom, [5]UCSF, San Francisco, CA

Purpose: 'Normal' 25(OH) vitamin D levels are commonly accepted in Caucasians to be approximately 30-35ng/ml based upon physiologic outcomes including maximal suppression of intact parathyroid hormone (iPTH). The optimal 25(OH)D level among non-Caucasians, including African-Americans, is unclear. We evaluated the relationship between serum 25(OH)D and iPTH among older community dwelling adults, hypothesizing that African-Americans would have a lower normal 25(OH)D level than Caucasians based upon maximal iPTH suppression.

Method: The Multicenter Osteoarthritis Study (MOST) is a longitudinal observational study of individuals who have or are at high risk for knee OA. Using data from MOST, we evaluated serum 25(OH)D [Diasorin RIA] and iPTH [Immulite CIA; Diagnostic Products Corp]. Those with self-reported chronic kidney disease were excluded; we also excluded 24 persons with iPTH > 120 pg/ml (~2x the upper limit of lab normal) due to concern that increased iPTH was from other than low 25(OH)D.

We modeled the relationship between 25(OH)D and iPTH in 3 ways. First, we did a segmented regression with grid search by sequentially placing the knot (i.e. joinpoint) at 0.1 unit increments of 25(OH)D from 5-50ng/ml. The comparative fit of the models that varied the knot was evaluated by determining mean squared error (MSE) of each model, looking for local minimums. Secondly, we used Helmert contrasts to identify 25(OH)D thresholds at which iPTH values increased. Our third approach used OLS regression to evaluate the relationship between 25(OH)D and iPTH by race, using 25(OH)D categories. OLS results were adjusted for age, gender, body mass index, education, and season.

Results: Among 1263 Caucasian and 437 African Americans, mean age was 62.8±7.9 and 59.8±8.2 years respectively. After exclusions, the range of 25(OH)D and iPTH values was 4-51ng/ml and 2-120 pg/ml for Caucasians and was 3-32ng/ml and 3-119pg/ml for African Americans. Local minimums of the MSE for Caucasians were observed at 25(OH)D levels of 12, 24, 31, and 40ng/ml, indicating better model fit with joinpoints at these values. In contrast, only one minimum MSE among African Americans was observed, at 9ng/ml. Plots of the race-specific Helmert contrasts were concordant with these results. The relationship between vitamin D and iPTH by race in the Table showed a continual decrease in iPTH as 25(OH)D increased among Caucasians. In contrast for African Americans, there was no further decline in iPTH if 25(OH)D was at least 20ng/ml.

Conclusion: In this sample of community-dwelling older adults, and in contrast to results for Caucasians, we observed minimal incremental benefit in suppression of iPTH for 25(OH) vitamin D levels greater than 20ng/ml in African Americans. The common clinical practice of using 30-35ng/ml to define a 'normal' vitamin D level based upon studies conducted in Caucasians may not be applicable to African Americans.

Caucasian			African American		
Vitamin D (ng/ml)	Mean iPTH (pg/ml)	Adj* p value	Vitamin D (ng/ml)	iPTH (pg/ml)	Adj* p value
<= 12	57.3	< 0.0001	<= 12	59.7	0.0002
12 - 15	52.2	< 0.0001	12 - 15	55.1	0.02
16 - 19	48.7	< 0.0001	16 - 19	52.6	0.07
20 – 23	45.9	0.002	20 – 23	41.5	0.60
24 – 32 (referent)	41.0	-	24 – 32 (referent)	44.3	-
33-51	35.6	0.03			
P for trend		<0.0001	P for trend		<0.0001

* adjusted for age, gender, body mass index, education, season

Disclosure: J. R. Curtis, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Corrona, 5, Novartis Pharmaceutical Corporation, 2, Amgen, 2, Merck Pharmaceuticals, 2, Procter and Gamble, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Corrona, 2, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Eli Lilly and Company, 8, Roche Pharmaceuticals, 8, Merck Pharmaceuticals, 8 ; **L. Chen**, None; **J. Niu**, None; **E. Delzell**, Amgen, Inc, 2 ; **D. T. Felson**, None; **M. K. Javaid**, None; **C. Katholi**, None; **M. A. Nevitt**, None; **C. E. Lewis for the MOST Group**, None.

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Hypophosphatasia: Treatment of Life-Threatening Disease Using Bone-Targeted Human Recombinant Tissue Non-Specific Alkaline Phosphatase. MP Whyte[1], Cheryl R. Greenberg[2], Terence Edgar[3], Bradley J. Van Sickle[4], Mohammad Hamdan[5], Nada J. Salman[5], Michael B. Bober[6], William H. McAlister[7], Deborah Wenkert[1] and Hal Landy[8], [1]Shriners Hospital for Children, St Louis, MO, [2]University of Manitoba, Winnipeg, MB, [3]Prevea Allouez Health Center, Greenbay, WI, [4]Vanderbilt University, Nashville, TN, [5]Tawam Hospital, Al Ain, United Arab Emirates, [6]Nemours, Wilmington, DE, [7]Washington University School of Medicine, St Louis, MO, [8]Enobia Pharma, Montreal, QC

Purpose: Hypophosphatasia (HPP) features low serum alkaline phosphatase (ALP) activity due to deactivating mutation(s) within the gene that encodes the "tissue nonspecific" isoenzyme of ALP (TNSALP). Consequently, inorganic pyrophosphate, a natural substrate for this ectoenzyme, accumulates extracellularly and blocks skeletal mineralization. HPP severity spans stillbirth from profound skeletal hypomineralization to osteomalacia presenting in adult life. There is no established medical treatment. ENB-0040 is a bone-targeted, human recombinant, TNSALP fusion protein that preserved skeletal mineralization and survival and prevented vitamin B6-responsive seizures and dental defects in a tnsalp knockout mouse model of infantile HPP (JBMR 23:777, '08). Patient trials began in the summer '08. In a phase 1, month-long, multi-center, open-label protocol, 6 adults received 1 IV infusion of 3 mg/kg ENB-0040 followed by weekly SC injections of 1 or 2 mg/kg (Endo Soc, abstract, in press).

Method: Here, we report findings from our 6-mo, open-label protocol involving 5 patients with life-threatening HPP (ages 0.5-36 mo at baseline), with up to 6 mo of ENB-0040 treatment. Previously, each had shown worsening skeletal disease and respiratory symptoms predicting a lethal outcome.

Results: At age 7 mo, pt 1 with infantile HPP received a single IV infusion of 2 mg/kg of ENB-0040 followed by 1 and then 3 mg/kg SC 3X/wk. During therapy, there was substantial remineralization of the skeleton, weaning from ventilatory support, and improved growth and motor development. After receiving only 3 wk of treatment, pt 2, also with infantile HPP, showed skeletal remineralization, and then improved ventilation. Both patients 1 & 2 have been released from hospital to continue ENB-0040. Patient 3 with perinatal HPP has also shown substantial radiographic and respiratory improvement, and corrected hypercalcemia soon after treatment began. There have been no drug-related serious adverse events, or development of anti-ENB-0040 antibodies. SC dosing has resulted in ENB-0040 activity in the therapeutic target range.

Conclusion: Substantial skeletal remineralization and improved clinical status has been demonstrated in association with ENB-0040 bone-targeted enzyme replacement therapy in 3 severely affected infants with HPP in this short term study.

Disclosure: M. Whyte, Enobia Pharma, Montreal, Canada, 5, Enobia Pharma, Montreal, CanadaEnobia Pharma, Montreal, Canada, 2 ; **C. R. Greenberg**, Enobia Pharma, Montreal, Canada, 5 ; **T. Edgar**, Enobia Pharma, Montreal, 5 ; **B. J. Van Sickle**, Enobia Pharma, Montreal, 5 ; **M. Hamdan**, Enobia Pharma, Montreal, 5 ; **N. J. Salman**, Enobia Pharma, Montreal, 5 ; **M. B. Bober**, Enobia Pharma, Montreal, 5 ; **W. H. McAlister**, None; **D. Wenkert**, Enobia Pharma, Montreal, Canada, 2 ; **H. Landy**, Enobia Pharma, Montreal, 3 .

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Hypophosphatasia: Natural History of 177 Pediatric Patients. Deborah Wenkert[1], Fan Zhang[1], Marci C. Benigno[1], Janice A. Zerega[1], Karen E. Mack[1], Vivienne T. Lim[1], Stephen P. Coburn[2], Karen Ericson[2], William H. McAlister[3], Steven Mumm[3] and Michael P. Whyte[1], [1]Shriners Hospital for Children, St. Louis, MO, [2]Indiana University - Purdue University, Fort Wayne, IN, [3]Washington University School of Medicine, St. Louis, MO

Purpose: Hypophosphatasia (HPP) is the inborn-error-of-metabolism caused by deactivating mutation(s) within the gene that encodes the tissue nonspecific isoenzyme of alkaline phosphatase (TNSALP). Consequently, inorganic pyrophosphate (PPi) and pyridoxal 5'-phosphate (PLP), natural substrates for this ectoenzyme, accumulate extracellularly. Excess PPi blocks skeletal mineralization causing rickets or osteomalacia. Pediatric HPP spans stillbirth (profound skeletal hypomineralization) to premature loss of primary teeth without skeletal disease. An indepth, longitudinal evaluation of untreated HPP patients was undertaken not only to provide a greater understanding of the role of TNSALP in bone development, but also to serve as a basis for the assessment of future pharmacotherapy.

Method: During the past 26 years, 177 pediatric HPP patients had 1 or more inpatient evaluations when fasting blood and 24-hour urine collections were obtained while we matched ad libitum dietary calcium intakes. Disturbances in endochondral bone formation were followed radiographically using single views of wrists and knees. We evaluated the following pediatric forms of HPP: 65 odonto-HPP (dental disease only), 99 childhood HPP (41 mild), 12 infantile HPP, and 1 perinatal/infantile HPP. To date, 52 of the 177 patients had 4-14 admissions (usually occurring once every few years).

Results: Principal complications identified were premature tooth exfoliation, joint hypermobility, lower extremity malalignment or bowing, skeletal pain, muscle weakness, craniosynostosis, chest deformity, scoliosis, clubfoot, and fractures. Serum total ALP activity, analyzed for ages ≤10 yr, correlated with HPP severity; lower values reflected more severe disease, but also showed 'physiological' decrements after puberty. Elevated plasma PLP levels correlated with skeletal disease severity and the number of teeth lost prematurely, but in contrast to serum ALP, did not change over time according to a 2-stage statistical analysis. This indicates that plasma PLP is a good diagnostic test that correlates with HPP severity even when only measured once. Height z-scores were without gender differences, reflected HPP severity, and showed no significant changes over time; height assessments at >2 yrs of age predicted adult heights. Radiographic features were highly individualized (physeal widening, irregularity of zones of calcification, “tongues of radiolucency”, metaphyseal osteopenia or osteosclerosis, and cortical thinning), but typically changed little during follow-up.

Conclusion: Accordingly, we have defined major clinical, biochemical and radiographic features of HPP which will serve as a basis for assessment of future therapies.

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Chromosomal Localization of Four Autosomal Dominant Skeletal Diseases, Including Osteogenesis Imperfecta Type V and Metachondromatosis. Michael P. Whyte[1], Deborah Wenkert[1], Fan Zhang[1], William H. McAlister[2], Peter Tebben[3], Anne Bowcock[2] and Steven Mumm[2], [1]Shriners Hospital for Children, St Louis, MO, [2]Washington University School of Medicine, St. Louis, MO, [3]Mayo Clinic, Rochester, MN

Purpose: In recent years, the genetic basis of rare bone diseases has revealed novel pathways involved in bone metabolism opening new avenues to potential drug therapy. We chose four highly penetrant autosomal dominant skeletal diseases of unknown etiology to identify additional chromosomal locations critical to bone metabolism. Two 4-generation kindreds had unique disorders featuring either (Kindred A) diffusely dense and painful bones, cranial nerve compromise, and brittle and translucent teeth (JBMR 19:S464, '04), or (Kindred B) short stature, abnormally modeled bones, and dentition with enamel hypoplasia and dwarfed roots (JBMR 21:S430, '06). One 3-generation kindred

and two smaller unrelated families had osteogenesis imperfecta (OI) type V (OMIM % 610967). One 4-generation family had metachondromatosis (OMIM 156250).

Method: Chromosomal mapping was performed by contract with deCODE Genetics using a medium density genome-wide scan at an average of 8 cM density with a standard marker set of 500 validated microsatellites. Peripheral leukocyte DNA from 88 individuals within the 6 families was analyzed using one 96 well plate. The reaction volume was 5 µl, and for each PCR 20 ng of genomic DNA was amplified in the presence of 2 pmol of each primer, 0.25 U AmpliTaq Gold, 0.2 mM dNTPs, and 2.5 mM MgCl2 (buffer was supplied by Applera). Cycling conditions were: 95°C for 10 min, followed by 37 cycles of 94°C for 15 sec, 30 sec at 55°C, and 1 min at 72°C. Alleles were automatically called using the deCODE Allele Caller and the program deCODE GT was used to fractionate called genotypes according to quality, and to edit when necessary.

Subsequently, we performed genome-wide linkage analysis for the deCODE Genetics data using Merlin software for singlepoint linkage analysis (http://www.sph.umich.edu/csg/abecasis/MERLIN/download), and then verified the findings and refined the analyses using Allegro software for multipoint linkage analysis (www.decode.com/software/allegro).

Results: The two dento-osseous disorders localized, using multipoint analysis, to chromosomes 11 (distant from *LRP5*) with peak LOD score of 2.6 (Kindred A) and to chromosome 6 and 8 with peak LOD score of 6.1 and 6.0 (Kindred B). Therefore, they are unique conditions and not variants of Albers-Schonberg osteopetrosis or OI caused by chromosomal defects elsewhere. Multipoint analysis of the data combined from the 3 families with OI type V mapped the disorder to chromosome 4 with a peak LOD score of 2.8. Metachondromatosis mapped to chromosomes 9 and 12 where peak LOD scores were 3.8 and 3.6 respectively.

Conclusion: Accordingly, we have mapped two unique dento-osseous disorders as well as OI type V and metachondromatosis to chromosomes 11, 6 or 8, 4, and 9 or 12, respectively, in order to pursue the underlying gene defects.

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Biochemical Response to Bolus Oral Cholecalciferol Treatment. Helen Linklater and Patrick D.W. Kiely, St George's Hospital, London, United Kingdom

Purpose: Hypovitaminosis D is increasingly recognized in patients attending a rheumatology clinic. There is no consensus concerning the optimum target minimum concentration of serum 25(OH)D3 to be achieved with replacement therapy. Neither is there a validated standard protocol to either replenish or maintain serum 25(OH)D3 in an acceptable ‘normal' range. Vitamin D replacement using daily oral calcium and cholecalciferol tablets is limited by unpalatability and a disappointing biochemical response, possibly related to poor long term adherence. We have studied the serum 25(OH)D3 response to single high dose bolus supplementation of cholecalciferol.

Method: Patients attending the rheumatology department of St George's Hospital, London, UK found to have hypovitaminosis D (< 55nmol/L), despite prescription of conventional oral supplements of vitamin D3 800U, were treated with oral bolus cholecalciferol 300,000U in 100ml sunflower oil (Martindale pharmaceutical, Essex, UK). Serum calcium, phosphate, PTH and 25(OH)D3 (IDS ELISA assay, ImmunoDiagnostics systems Ltd, Tyne and Wear, UK) were measured at regular intervals over the following 32 weeks.

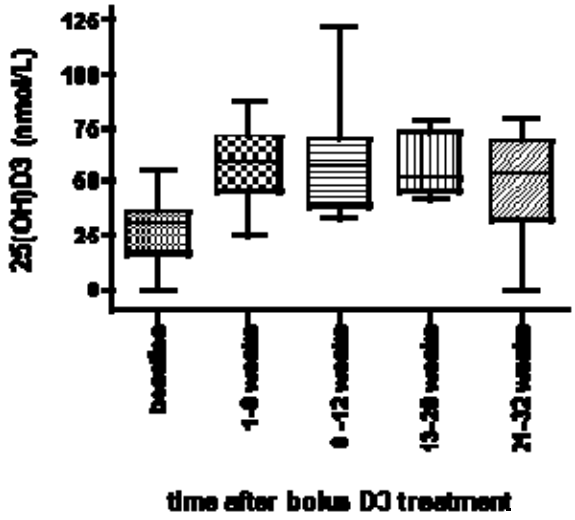
Results: 37 patients were treated, mean age 54 years (range 17–86, 95% CI 48-59), 8 male. 25/37 were of Asian or Black African origin. Mean baseline 25(OH)D3 concentration was 25.5 nmol/L (range 0–55, 95% CI 20 - 30). The bolus cholecalciferol drink was well tolerated, with no subjective or biochemical hypercalcaemic adverse effects. Total serum 25(OH)D3 (nmol/L) and change from normalized baseline values (nmol/L) at successive time intervals following treatment are shown in Table 1.

Table 1

Time	Baseline	1-8 weeks	9-12 weeks	13-20 weeks	21-32 weeks
Number	37	17	12	13	13
Mean D3	25.5	58.3	58.0	58.0	49.5
95% CI	20-30	49-67	42-73	49-66	36-62

Change from baseline		31.6	31.4	32.5	23.7
95% CI		22-41	14-48	21-44	10-37

Figure 1 shows a box and whisker pot of serum 25(OH)D3 at each time interval. Season had no effect on baseline 25(OH)D3 concentration or the response to bolus treatment. PTH was elevated in 10/27 patients, and found to normalize in 5/7 who had repeat PTH measurement within 6 months. Figure 1



Conclusion: In patients with hypovitaminosis D, bolus treatment with 300,000U cholecalciferol in sunflower oil is safe and well tolerated. In the majority of patients this results in a rise in serum 25(OH)D3 to within the normal range (> 55 nmol/L) within 8 weeks. Serum 25(OH)D3 concentrations remain in the normal range for up to 28 weeks but in some patients fall below 55 nmol/L within 12 weeks. Therefore measurement of serum 25(OH)D3 should be performed regularly from at least 12 weeks after bolus replacement to determine the time for repeat treatment in individual cases.

Disclosure: H. Linklater, None; **P. D. W. Kiely**, None.

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Does Use of the FRAX Tool Change Management in Female Patients with Osteopenia? Israa Al-Shakarchi, A. Louise Dolan, Jehan Karim and Lucy Powell, South London NHS Trust, London, United Kingdom

Purpose: Many patients suffering from fractures are osteopenic rather than osteoporotic. Those with fractures are at increased risk of further fractures and fracture risk also increases with age. FRAX is a tool that computes the 10-year probability of a fracture from clinical risk factors. Could this change management? The aim of this study is to assess the 10-year fracture risk in female patients with osteopenia using FRAX.

Method: 1446 women aged 55 – 87 years with osteopenia confirmed on DEXA scans (T score of ≤ -1 to ≤2.4) at the femoral neck were identified on our hospital osteoporosis service database based on referrals from primary and secondary care. The FRAX score was computed using risk factors previously recorded on the database and bone mineral density (BMD) at the hip, using the FRAX website calculator.

Results:

Age range	Number of patients	Previous history of any fracture	Previous hip fracture	FRAX 10-year hip fracture risk ≥ 3%	FRAX 10-year all fracture risk ≥20%
55 – 87 (All patients)	1446	781/1446 (54.0%)	67/781 (8.6%)	581/1446 (40.2%)	250/1446 (17.3%)
55 – 64	529/1446 (36.6%)	260/529 (49.2%)	14/260 (5.38%)	68/529 (12.9%)	57/529 (10.8%)
65 – 74	564/1446 (39.0%)	307/564 (54.4%)	19/307 (6.2%)	232/564 (41.1%)	106/564 (18.8%)
>75	353/1446 (24.4%)	214/353 (60.6%)	34/214 (15.9%)	281/353 (79.6%)	87/353 (24.7%)

Conclusion: Currently treatment decisions on osteoporosis and osteopenia are based largely on BMD measurement via DEXA scanning. DEXA scanning is specific but not sensitive, and as such DEXA BMD measurement alone is insufficient to identify all patients at risk. Our results concur with previous studies that show that fractures are common in those with osteopenia (54%) and increase with age. Hip fractures are more common in those over 75 years of age (15.9%). International guidance based on FRAX recommends treatment for those with a 10-year hip fracture risk of ≥ 3% and all fracture risk of ≥ 20%. Our results identified that 40.2% of patients required treatment based on FRAX score who would not have been treated based on DEXA alone (T score ≥ -2.5). Those over 75 years of age had the highest 10-year hip fracture risk with 79.6% having a score of ≥ 3%. These results suggest that FRAX increases the sensitivity of fracture risk assessment and has the potential to improve treatment intervention strategies.

Disclosure: I. Al-Shakarchi, None; **A. L. Dolan**, None; **J. Karim**, None; **L. Powell**, None.

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Risk of Atypical Subtrochanteric Fractures in Older Veterans at High Risk for Osteoporosis. Monika M. Safford[1], Kelly Richardson[2], Mary Sarrazin[2], Peter Cram[2], Jeffrey R. Curtis[1], Elizabeth Delzell[1], Andrei Barasch[1] and Kenneth G. Saag[1], [1]UAB, Birmingham, AL, [2]Iowa City VAMC, Iowa City, IA

Purpose: Atypical subtrochanteric fractures may be a risk for longer-standing bisphosphonate (BP) users. We examined the risk of these atypical fractures associated with BP therapy among veterans at high risk of osteoporotic fracture.

Method: National administrative VA data from 1999-2008 included inpatient and outpatient utilization files and pharmacy data. We included individuals presumed to have osteoporosis, i.e., admitted for a non-trauma fracture to a VA facility at age ≥45. We excluded individuals with enrollment in the VA system for < 180 days prior to 1st fracture, metastatic cancer, and history of chemotherapy. The primary outcome was a subsequent "atypical" subtrochanteric fracture, defined by ICD-9 code "fracture of subtrochanteric section of femur, closed" [820.22] in the absence of trauma ICD-9 codes or open fractures. Cumulative BP use was the main exposure of interest, and only individuals who initiated BP use at least 365 days after first appearance in VA data were included to better define duration of use. We constructed Cox proportional hazards models to examine associations between BP and risk of subsequent atypical fracture or more typical hip fracture. Available covariates included demographics (age at 1st fracture, sex, and race), baseline comorbid medical conditions, medications associated with osteoporosis, fall risk, and distance to the nearest VA Medical Center. Covariates bivariately associated with p<.20 were included in multivariable models.

Results: Of 80,684 eligible veterans, 95% were men, 3.6% used BPs before their 1st fracture, and another 6.4% had BPs initiated afterward. We detected 45 atypical subtrochanteric and 1,805 typical hip 2nd fractures over a mean follow-up of 4.2 years. BP use duration of individuals with atypical subtrochanteric, typical hip and those with no 2nd fractures are shown in the Table. Compared with nonusers, BP users had the following hazard ratios (HR) for subsequent atypical subtrochanteric fractures: <1 year of BP use, HR 1.4 (95% CI 0.18-10.46); 1-6 years, HR 0.47 (95% CI 0.06-3.57); >6 years, HR 4.5 (95% CI 0.58-34.24). In contrast, compared with nonusers, BP users had the following HR for subsequent typical hip fractures: <1 year of use, HR 1.27 (95% CI 0.98-1.66); 1-6 years, HR 0.80 (95% CI 0.65-.099); >6 years, HR 0.39 (95% CI 0.16-0.95).

Conclusion: While BP use >6 years trended towards an association with increased risk for atypical subtrochanteric fractures, atypical fractures were rare, and long-term BP use was associated with a substantially decreased risk for hip fractures, which were 40 times more common than atypical fractures. These findings should be confirmed to provide information for long-term BP users and their physicians about overall risks and benefits.

		Type of 2nd fracture		
		Atypical subtrochancteric (N=45)	Typical hip (1,805)	No 2nd fracture (70,305)
Total BPs up to time of 2nd fracture or end of observation	None	41 (91%)	1,618 (90%)	64,083 (91%)
	<1 yr	1 (2%)	71 (4%)	1,344 (2%)
	1-6 yrs	1 (2%)	85 (5%)	2,811 (4%)
	>6 yrs	2 (4%)	31 (2%)	2,067 (3%)

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Relationship Between Increases in BMD On Denosumab and Reduction in Fracture Risk. Michael McClung[1], Steven Cummings[2], Yu-Ching Yang[3], Eric Vittinghoff[4], Silvano Adami[5], Gerolamo Bianchi[6], Michael Bolognese[7], Claus Christiansen[8], Andreas Grauer[3], Federico Hawkins[9], David L. Kendler[10], Cesar Libanati[3], Carlos Mautalen[11], Ian Reid[12], Jose Zanchetta[13], Cristiano A. F. Zerbini[14], Richard Eastell[15] and for the FREEDOM Trial, [1]Oregon Osteoporosis Center, Portland, OR, [2]SFCC, CPMC Research Institute & UCSF, San Francisco, CA, [3]Amgen Inc., Thousand Oaks, CA, [4]UCSF, San Francisco, CA, [5]University of Verona, Verona, Italy, [6]Ospedale La Colletta, Genoa, Italy, [7]Bethesda Health Research Center, Bethesda, MD, [8]CCBR, Ballerup, Denmark, [9]Hospital Universitario, Madrid, Spain, [10]Clinical Research Centre, Vancouver, BC, [11]Centro de Osteopatías Médicas, Buenos Aires, Argentina, [12]University of Auckland, Auckland, New Zealand, [13]Instituto de Investigaciones Metabolicas and University of Salvador, Buenos Aires, Argentina, [14]Hospital Heliopolis, Sao Paulo, [15]University of Sheffield, Sheffield, United Kingdom

Purpose: Previous studies suggest changes in BMD in response to osteoporosis treatment with bisphosphonates and raloxifene explain only a small portion of the observed fracture risk reductions.

Methods: The FREEDOM trial randomly assigned 7,868 women aged 60-90 years with spine or total hip BMD T-score <-2.5 and not <-4.0 at either site to placebo or subcutaneous denosumab 60 mg every 6 months. Total hip BMD was measured at baseline and annually. New vertebral fractures were defined as ≥ 1 grade increase in semiquantitative grade of fracture on annual lateral spine films from a baseline grade of 0. Nonvertebral fractures were confirmed by imaging. The proportion of treatment effect on fracture risk explained (PTE) by percent change in total hip BMD was estimated as proposed by Li et al (2001) and by a novel approach of using percent changes in BMD corresponding to scheduled and unscheduled fracture assessments (time-dependent models).

Results: Compared with placebo, denosumab increased total hip BMD by 3.2% at 12, 4.4% at 24, and 5.0% at 36 months. Denosumab decreased the risk of new vertebral fractures by 68% (P<0.0001) and nonvertebral fracture by 20% (P=0.01) over 36 months. Using time-dependent models, change in total hip BMD explained about half of denosumab's effect on risk reduction of new vertebral fractures (table). It seemed to explain most of the reduction in risk of nonvertebral fracture although the confidence limits were wide.

Conclusion: Using time-dependent models, change in total hip BMD with denosumab explained about half of the reduction in new vertebral fracture risk. Change in total hip BMD may explain a substantial portion of the reduction in risk of nonvertebral fracture observed with denosumab treatment.

Percent of treatment effect on fracture risk explained by % change in total hip BMD

	Percent of treatment explained (95% CI)	
Timing of hip BMD	New vertebral fracture	Nonvertebral fracture
12 months	23% (13%, 40%)	35% (9%, *)
24 months	30% (16%, 54%)	89% (37%, *)
36 months	35% (20%, 61%)	87% (35%, *)
At fracture measurement/occurrence	51% (39%, 68%)	72% (24%, *)

*Upper Limit of CI was >100%

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Fracture Incidence in Postmenopausal Women at Higher Risk of Fracture After 3 Years of Denosumab Treatment. Jonathan D. Adachi[1], Michael McClung[2], Salvatore Minisola[3], Kurt Lippuner[4], Ove Torring[5], Rene Rizzoli[6], Zulema Man[7], Henry G. Bone[8], Jordi Farrerons[9], Claus Christiansen[10], Richard Eastell[11], Ian Reid[12], Ethel Siris[13], Steven Cummings[14], Andrea Wang[15], Nathalie Franchimont[16], Javier San Martin[15] and Steven Boonen[17], [1]McMaster University, Hamilton, ON, [2]Oregon Osteoporosis Center, Portland, OR, [3]Universita' Di Roma “Sapienza”, Rome, Italy, [4]Inselspital Bern, Bern, Switzerland, [5]Karolinska Institutet Sodersjukhuset, Stockholm, Sweden, [6]University Hospital, Geneva, Switzerland, [7]Centro T.I.E.M.P.O., Buenos Aires, Argentina, [8]Michigan Bone and Mineral Clinic, Detroit, MI, [9]Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, [10]CCBR, Ballerup, Denmark, [11]University of Sheffield, Sheffield, United Kingdom, [12]University of Auckland, Auckland, New Zealand, [13]Columbia University Medical Center, New York, NY, [14]SFCC, CPMC Research Institute & UCSF, San Francisco, CA, [15]Amgen Inc., Thousand Oaks, CA, [16]Amgen Inc., Zug, Switzerland, [17]University of Leuven, Leuven, Belgium

Purpose: FREEDOM, a randomized double-blind placebo-controlled phase 3 trial, showed denosumab (DMAb) significantly reduced risk of new vertebral, hip, and nonvertebral fractures over 3 years. In this analysis, we studied the fracture rates in FREEDOM subjects identified as having higher fracture risk.

Methods: Postmenopausal women (60-90 years old) with a spine or hip T-score <-2.5 and not <-4.0 were randomized to twice yearly DMAb (60 mg) or placebo injection for 3 years. Established clinical criteria were used to identify subgroups of women at higher fracture risk. Prespecified analyses included women with ≥2 risk factors: age >70; baseline spine, hip, or femoral neck T-score ≤-3.0; and prevalent vertebral fracture. Post hoc analyses used known risk factors for hip (age >75 or baseline femoral neck T-score ≤-2.5) or vertebral (≥2 prevalent vertebral fractures, prevalent vertebral fractures of moderate or severe severity, or both) fractures.

Results: Of 7808 women analyzed, 45% were at higher fracture risk by the prespecified criteria. Greater fracture rates in the higher risk placebo group suggest relevant risk factors were used. DMAb reduced hip, new vertebral, and nonvertebral fracture risk in women at higher risk, although nonvertebral fracture reduction was not statistically significant (Table). The risk factors used in the posthoc analyses also showed that DMAb significantly reduced risk of fractures in women specifically at higher risk for hip (by age or low BMD) or new vertebral fractures (Table).

Conclusion: Twice yearly DMAb for 3 years reduced fracture risk in women with osteoporosis. Reduction in risk of hip fracture in women ≥ age 75 could be of particular clinical relevance.

Table. Fracture Incidence and Risk Reduction With Denosumab Treatment Over 3 Years

	Fracture Incidence				
Fracture	Overall Placebo Group	Higher Risk Placebo Group	Higher Risk Denosumab Group	Risk Reduction With Denosumab % (95% CI)	*P*-value
Prespecified Criteria[a]					
Hip fracture	1.2%	2.1%	1.1%	48% (9%, 71%)	0.0209
New vertebral fracture	7.2%	10.0%	3.8%	62% (53%, 70%)	< 0.0001
Nonvertebral fracture	6.0%	8.3%	6.2%	12% (-11%, 30%)	0.2901
Posthoc Criteria					
Hip fracture - age[b]	1.2%	2.3%	0.9%	62% (23%, 82%)	0.0065
Hip fracture - BMD[c]	1.2%	2.0%	1.4%	47% (6%, 70%)	0.0237
New vertebral fracture[d]	7.2%	10.0%	7.0%	62% (51%, 71%)	0.0002

[a]Women with ≥2 of the prespecified risk factors: age > 70 years, baseline BMD T-score ≤ -3.0 at lumbar spine, total hip, or femoral neck, and/or prevalent vertebral fracture at baseline; number of women in each group: overall placebo = 3906; higher risk placebo = 1762, and higher risk denosumab = 1762. [b]Women ≥75 years old (higher risk placebo = 2870; higher risk denosumab = 2837); [c]Women with baseline femoral neck T-score ≤ -2.5 (higher risk placebo = 1400; higher risk denosumab = 1384); [d]Women with ≥2 prevalent vertebral fractures, moderate or severe vertebral fracture, or both (higher risk placebo = 372; higher risk denosumab = 387)

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Zoledronic Acid After 2-Years of Teriparatide: Bone Density and Bone Turnover Markers in 35 Patients. C. Deal[1], K. Tuthill[1] and A. Kriegman[2], [1]Cleveland Clinic, Cleveland, OH, [2]Novartis Pharmaceuticals, East Hanover, NJ

Purpose: Teriparatide (TPTD) is an anabolic agent approved for patients at high risk for fracture and significantly increases bone density (BMD) over a two year course of treatment. After discontinuation of TPTD, BMD declines if antiresorptive therapy is not initiated. Treatment with alendronate has been shown to prevent bone loss and further increase bone mass after TPTD discontinuation. Zoledronic acid 5mg (ZOL) is an IV bisphosphonate approved as a once-yearly infusion for the treatment of osteoporosis. We tested the ability of ZOL to maintain bone mass after treatment with TPTD.

Methods: We treated 35 postmenopausal women with ZOL immediately after finishing a course of TPTD. The primary endpoint was change in bone density (g/cm^2) in the lumbar spine at 12 months. Secondary endpoints were change in bone density at the total hip (TH), femoral neck (FN), and total body (TB). Markers of bone turnover (BTO), serum c-telopeptide type I collagen (CTX) and procollagen type 1 n-terminal propeptide (P1NP) were measured in all patients at baseline and days 10, 60,180, 270 and 365. We report the bone density results on 35 patients, changes in markers of bone turnover are available for the first 24 patients.

Results: The study cohort had a mean age of 68.8 +/- 11.2, a mean T-score of -2.1 for the LS and TH, -2.3 for FN, and -1.7 for TB. Table 1 summarizes the number of patients exhibiting stable, increased or decreased BMD at the LS, TH, FN and TB (LSC +/-0.03g/cm2). In the 35 patients at 140 skeletal sites, 131 sites (93.6%) had stable or increased bone mass. After treatment with ZOL, levels of CTX were significantly lower at day 10, P1NP at day 60 and all subsequent time points. Changes in BMD at 12 Months: N=35 (LSC +/- 0.03 g/cm2)

BMD Site	LS	TH	FN	TB
Stable/Increased	32	32	33	34
Decreased	3	3	2	1

Change in BTO Markers Day 10 to Day 365: % Decline from Day 0, N=24

Day	10	60	180	270	365
CTX	-90% (sd 10.1)	-77% (sd 20.9)	-63%	-63%	-60%
P1NP	-15% (sd 25.1)	-72% (sd 14.9)	-74%	-56%	-56%

Conclusion: A single infusion of zoledronic acid 5mg preserved or increased bone mass in patients after TPTD treatment in the LS, FN, TH and TB in 91%, 91%, 94%, and 97% respectively.

Disclosure: C. Deal, Novartis Pharmaceutical Corporation, 8 ; **K. Tuthill**, None; **A. Kriegman**, Novartis Pharmaceutical Corporation, 3 .

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The Effect of Proton Pump Inhibition On Urinary N-Telopeptide Levels and Urinary Calcium Levels: A Prospective Randomized Cross-Over Study Comparing Use of Calcium Carbonate and Calcium Citrate. Linda M. Burns, Joseph M. Grisanti, Michael W. Grisanti, Mary Brennan and James Hatem, Buffalo Rheumatology, Orchard Park, NY

Purpose: An increased risk of osteoporotic fractures has been reported in patients on proton pump inhibitor (PPI) therapy. Theories for the explanation of these findings have centered around the decreased bioavailability of calcium while on PPI therapy. The purpose of this study is to evaluate the biochemical evidence of the proton pump inhibitor (PPI) class of antacids effect on bone metabolism. The primary endpoint is to determine if the bioavailability of calcium citrate is superior to calcium carbonate in subjects taking proton pump inhibitors.

Method: To analyze the absorption of calcium, a urinary calcium (Ca) to creatinine (Cr) ratio was measured. An assessment of osteoclastic activity was measured using urinary type I collagen N-telopeptide (NTX) before and after proton pump inhibitor (PPI) administration. A total of 31 healthy postmenopausal women were enrolled after meeting inclusion criteria. Requirements for study entry included a normal 25-OH Vitamin D level, a normal baseline urinary NTX, absence of corticosteroid exposure and anti-resorptive therapy for 8 weeks prior to study entry.

All subjects were randomly assigned to receive calcium citrate or calcium carbonate, 600mg twice daily. After four weeks of calcium supplementation, a baseline urinary NTX, urinary Ca, and urinary Cr were obtained on all subjects. Following these baseline measurements, all subjects were started on PPI therapy in the form of omeprazole 20mg twice daily while continuing calcium supplementation. After four weeks of PPI use, the urinary studies were repeated. The last phase of the trial involved continuing the PPI but switching subjects to the alternative calcium supplement for an additional four weeks and repeating the urinary studies a third time.

Results: Baseline urinary data on calcium alone was compared to urinary data obtained post PPI use. Data analysis was done using a paired t-test with a p-value of <0.05 deemed statistically significant. We found the mean urinary NTX increased from 29 to 40 nmol/mmol Cr ($p=0.0003$) in the calcium citrate group and increased from 29 to 40 nmol/mmol Cr ($p=0.0011$) in the calcium carbonate group. There was no difference in calcium excretion after PPI addition as reflected by the Ca to Cr ratio in either calcium citrate or calcium carbonate users.

Conclusion: This study shows a 37.9% increase in urinary N-telopeptide within 4 weeks of initiation of PPI use in healthy postmenopausal women. Our data does not identify a superior calcium supplement in patients concomitantly using proton pump inhibitors. The dramatic increase in bone turnover seen in this study following PPI administration demonstrates biochemical evidence supporting an association of PPI's to osteoporosis. Considering this study in conjunction with others that have implicated an increased fracture risk with PPI use, we suggest that PPI's be deemed an independent risk factor for osteoporosis.

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A Novel Oral Parathyroid Hormone Formulation, PTH134, Demonstrated a Potential Therapeutically Relevant Pharmacokinetic and Safety Profile Compared with Teriparatide s.c. in Healthy Postmenopausal Women After a Single Dose. Markus R. John, Sibylle Haemmerle, Aino Launonen, Evita Harfst, Moise Azria, Michel Arnold and Linda Mindeholm, Novartis Pharma AG, Basel, Switzerland

Purpose: Parathyroid hormone (PTH), currently the only anabolic treatment for osteoporosis, is available as the full-length hormone, PTH_{1-84}, or as the PTH_{1-34} fragment (teriparatide). Both must be given subcutaneously (s.c.). A new oral formulation of PTH_{1-34} (PTH134) is being developed as a more convenient option for patients. In this single-centre, partially-blinded, incomplete cross-over study, the safety, tolerability, and exposure of oral PTH134 (teriparatide combined with 2 different quantities of the absorption enhancer 5-CNAC) were assessed in 32 healthy postmenopausal women.

Method: 16 subjects were randomized to receive single doses of up to six different treatments: placebo, teriparatide 20µg s.c., or 1, 2.5, 5 or 10mg of oral PTH134 formulated with 200mg 5-CNAC. Subsequently, another 16 subjects were randomized to receive up to six different treatments: placebo, teriparatide 20µg s.c, or 2.5 or 5mg of oral PTH134 formulated with either 100 or 200mg 5-CNAC. Doses were given ≥ 6 days apart.

Results: All doses of PTH134 were rapidly absorbed, and showed robust blood concentrations in a dose-dependent manner. Interestingly, PTH_{1-34} was eliminated faster after oral versus s.c. administration. Specifically, 2.5 and 5 mg PTH134 (containing 200 mg 5-CNAC) demonstrated C_{max} and AUC_{0-last} values closest to those of s.c. teriparatide 20µg. The geometric mean estimate for PTH134 2.5mg/200mg 5-CNAC was 98.7 pg/ml (90% CI 67.3-144.7) for C_{max} and 28.3 hr*pg/ml (90% CI 16.4-49.0) for $AUC_{(0-last)}$, while for PTH134 5mg/200mg 5-CNAC the estimated geometric mean values were 502.7 pg/ml (90% CI 304.5-829.6) for C_{max} and 175.4 hr*pg/ml (90% CI 86.0-358.0) for $AUC_{(0-last)}$. The corresponding estimates for teriparatide 20 µg s.c. were 143.6 pg/ml (90% CI 123.7-166.7) for C_{max} and 229.9 hr*pg/ml (90% CI 198.9-263.7) for $AUC_{(0-last)}$.

Ionized calcium remained within normal limits in all treatment groups. Nine subjects withdrew due to treatment-related AEs. Of those, seven were taking PTH134 2.5 or 5mg: three withdrew for symptomatic hypotension (two of whom were in the 200mg 5-CNAC group), three because of delayed vomiting (two from the 200mg 5-CNAC group), one withdrew for symptomatic, but unconfirmed, hypercalcemia

(receiving 2.5mg/100mg 5-CNAC). One subject receiving teriparatide and one receiving placebo withdrew for symptomatic hypotension. No serious AEs were reported.

Conclusion: The study demonstrated potential therapeutically relevant PTH_{1-34} systemic exposure levels after oral administration of PTH_{1-34} formulated with the absorption enhancer 5-CNAC. Doses of 2.5 and 5mg of oral PTH134 achieved exposure levels closest to those of teriparatide 20µg s.c., with a comparable incidence of AEs in healthy postmenopausal women. PTH134 warrants further investigation

Disclosure: M. R. John, Novartis Pharmaceutical Corporation, 3 ; **S. Haemmerle**, Novartis Pharmaceutical Corporation, 3 ; **A. Launonen**, Novartis Pharmaceutical Corporation, 3 ; **E. Harfst**, Novartis Pharmaceutical Corporation, 3 ; **M. Azria**, Novartis Pharmaceutical Corporation, 3 ; **M. Arnold**, Novartis Pharmaceutical Corporation, 3 ; **L. Mindeholm**, Novartis Pharmaceutical Corporation, 3 .

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Is the FRAX Tool Useful in Assessing Fracture Risk in Female Rheumatoid Arthritis Patients? Israa Al-Shakarchi, A. Louise Dolan, Lucy Powell and Jehan Karim, South London NHS Trust, London, United Kingdom

Purpose: Rheumatoid arthritis (RA) is a known risk factor for osteoporosis and fractures are common in those with RA. FRAX is a new tool developed by the WHO to compute the 10-year probability of a fracture from clinical risk factors (CRFs) with or without the measurement of BMD at the femoral neck. This project aims to use FRAX to assess the 10 year fracture risk in female patients with RA.

Method: 349 women aged 40 – 85 years with RA referred for DEXA scans were identified on our hospital osteoporosis service database based on referrals from primary and secondary care. The FRAX score was computed using risk factors previously recorded on the database and bone mineral density (BMD) at the hip.

Results:

Age Range	Number of Patients	Previous history of any fracture	Previous hip fracture	FRAX 10-year hip fracture risk >3	FRAX 10-year all fracture risk >20	% Osteoporotic (T score ≥ 2.5)	% Osteopenic (T score -1.0 – ≤2.4)
40 – 84 (All patients)	349	144/349 (41.3%)	18/349 (5.2%)	125/349 (35.8%)	93/349 (26.7%)	48/349 (13.8%)	140/349 (40.1%)
40 - 54	67/349 (19.2%)	21/67 (31.3%)	3/67 (4.5%)	4/67 (6.0%)	3/67 (4.5%)	1/67 (1.5%)	21/67 (31.3%)
55– 64	110/349 (31.5%)	41/110 (37.3%)	1/110 (0.9%)	17/110 (15.5%)	13/110 (11.8%)	7/110 (6.4%)	41/110 (37.3%)
65– 74	113/349 (32.4%)	47/113 (41.6%)	6/113 (5.3%)	60/113 (53.1%)	43/113 (38.1%)	20/113 (17.7%)	56/113 (49.6%)
> 75	59/349 (16.9%)	35/59 (59.3%)	8/59 (13.6%)	44/59 (74.6%)	35/59 (59.3%)	20/59 (33.9%)	22/59 (37.3%)

Conclusion: Our results concur with previous studies that show that fractures are common in RA (41.3%) and increase with age. A number of non-BMD factors have been identified as contributing to an increased risk of fracture. These include advancing age, a family history of hip fracture, a personal history of fragility fracture, glucocorticoid therapy and current smoking. These CRFs are incorporated within the FRAX tool. Current U.S guidance based on FRAX recommends treatment for those with a 10-year hip fracture risk of ≥ 3 or a 10-year all fracture risk of ≥ 20. Our study identified a greater number of patients requiring treatment based on a FRAX 10-year hip fracture score, than would be suggested by DEXA alone (T score ≥-2.5) (35.8% vs 13.8%). These results suggest that FRAX increases the sensitivity of fracture

risk assessment and has the potential to improve treatment intervention strategies. We recommend that FRAX becomes a routine part of assessment in patients with rheumatoid patients.

Disclosure: I. Al-Shakarchi, None; **A. L. Dolan**, None; **L. Powell**, None; **J. Karim**, None.

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Once Monthly Oral Ibandronate Provides Significant Improvement in Lumbar Spine Bone Mineral Density in Postmenopausal Women Treated with Glucocorticoids for Inflammatory Rheumatic Diseases. Leena Paimela[1], Markku Hakala[2], Tuija Hienonen-Kempas[3] and ONCE study group, [1]ORTON hospital, Invalid Foundation, Helsinki, Finland, [2]Rheumatism Foundation Hospital, Heinola, Finland, [3]Roche Finland, Espoo, Finland

Purpose: To assess the efficacy of once monthly oral ibandronate 150mg in the prevention of glucocorticoid-induced osteoporosis in postmenopausal women with any inflammatory rheumatic disease, including polymyalgia rheumatica.

Method: The ONCE (Osteoporosis preventioN in glucoCorticoid-treated womEn) study was a randomized, double-blind, placebo-controlled, parallel-group study in postmenopausal women in Finland. Women aged 50–85 years, ≥1 year since menopause, with a mean lumbar spine (L1–L4) bone mineral density (BMD) T-score ≥–2.0, receiving treatment with 5-15mg/day of prednisone equivalent were randomized 1:1 to receive either monthly oral ibandronate 150mg or monthly placebo for 12 months. In addition, all patients received vitamin D (800IU/day) and calcium (1000mg/day) supplements. The primary endpoint, the relative change (%) from baseline at 12 months in mean lumbar spine (L1-L4) BMD, was analyzed using ANCOVA. The primary model included treatment, center, duration of glucocorticoid treatment, diagnosis of rheumatic disease and baseline BMD as covariates. Treatment difference was assessed using least square means with a 95% confidence interval (CI).

Results: In total, 140 postmenopausal women were randomized, and 124 completed the study. Mean age was 64 (range 50–83) years and mean BMI was 29 (range 19–45) kg/m^2. At baseline, mean lumbar spine BMD was 1.14 (range 0.90-1.61) g/cm^2. Primary diagnoses were rheumatoid arthritis (48%), polymyalgia rheumatica (36%), or other inflammatory rheumatic disease (16%). The intent-to-treat (ITT) analyses showed a significant mean change from baseline in mean lumbar spine BMD with ibandronate (2.6% and 3.3%) compared with placebo (0.3% and -0.2%) at 6 and 12 months, respectively. Estimated treatment difference versus placebo at 12 months was 3.25 (95% CI: 2.09 to 4.41], $p<0.001$. Results were similar in the per protocol population (estimated treatment difference at 12 months versus placebo 3.66 [95% CI: 2.37 to 4.95], $p<0.001$).

Conclusion: Once monthly oral ibandronate provides a significant increase in lumbar spine BMD after 6 months of treatment in postmenopausal women treated with glucocorticoids for inflammatory rheumatic diseases.

Disclosure: L. Paimela, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Abbott Laboratories, 5, schering plough, 5 ; **M. Hakala**, MSD, 5, Meda , 5, Ratiopharm, 5 ; **T. Hienonen-Kempas**, Roche Pharmaceuticals, 3 .

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Change in Serum 25(OH)D Levels Over 2.6 Years in Older Adults: Predictive Effects of Body Fat, Physical Activity, Leptin, Interleukin-6 and Total Cholesterol/HDL Ratio. Changhai Ding[1], Flavia Cicuttini[2] and Graeme Jones[1], [1]University of Tasmania, Hobart, Australia, [2]Monash University, Melbourne, Australia

Purpose: To determine the associations between body fat, physical activity and change in serum 25(OH)D levels over 2.6 years, and if these associations are mediated by serum measures including leptin, interleukin 6 (IL-6) and cholesterol in older adults.

Methods: In a total of 859 randomly selected subjects (mean 62 years, range 51-80, 49% female), serum 25-hydroxyvitamin D [25-(OH)D] were assessed by radioimmunoassay at baseline and 2.6 years later. Baseline serum levels of leptin and IL-6 (assessed by radioimmunoassay in the first 183 subjects), and total cholesterol and high-density lipoprotein (HDL) were determined. Fat mass was measured by dual energy x-ray absorptiometry (DXA). Body mass index (BMI) was calculated, and physical activity measures including steps per day and lower limb muscle strength were measured.

Results: At baseline, the prevalence of vitamin D deficiency [defined as 25-(OH)D of < 50 nmol/L] was 45%. Over 2.6 years, incidence of vitamin D deficiency was 23% and rate of recovery from vitamin D deficiency was 40%. Seasonal variation between baseline and follow-up was associated with change in 25-(OH)D levels (ρ=0.59, P<0.001) so all the analyses were adjusted for this and other potential confounders (including age, sex, BMI, smoking, sunlight exposure and/or steps per day). Change in 25-(OH)D levels per annum [(follow-up value – baseline value)/years between 2 measures] was significantly associated with baseline age (β: -0.06 unit/year, 95% CI: -0.12, -0.004), BMI (β: -0.13 unit/ kg/m^2, 95% CI: -0.22, -0.04), total body fat percentage (β: -0.13, 95% CI: -0.22, -0.05), trunk fat percentage (β: -0.11, 95% CI: -0.17, -0.05), winter physical activity (β: 0.68/grade, 95% CI: 0.11, 1.25), summer physical activity (β: 0.60/grade, 95% CI: 0.03, 1.18), steps per day (β: 0.14/1000 steps, 95% CI: 0.03, 0.25) and lower limb muscle strength (β: 0.19/10 kg, 95% CI: 0.06, 0.33). It was also associated with baseline serum measures such as leptin (β: -0.09/unit, 95% CI: -0.17, -0.03), IL-6 (β: -0.68/quartile, 95% CI: -1.35, -0.02), HDL (β: 1.39/unit, 95% CI: 0.21, 2.57) and total cholesterol/HDL ratio (β: -0.51, 95% CI: -0.88, -0.14).The associations between body fat and change in 25-(OH)D levels all became non-significant after adjustment for leptin, partly decreased (10% to 20%) after adjustment for IL-6, but still remained significant after adjustment for total cholesterol/HDL ratio. In contrast, the associations between physical activity measures and change in 25-(OH)D levels were largely independent on serum measures.

Conclusion: Instead of solely being related to sun exposure and diet, vitamin D levels appear to have many determinants including body composition, hormonal factors and inflammation.

Disclosure: C. Ding, None; **F. Cicuttini**, None; **G. Jones**, None.

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Bone Mineral Density Alone Fails to Recognize Seventy Percent of Men Who Are at High Risk of Fracture Compared to a Global Risk Assessment (Bone DESTINY) That Leads to Significant Undertreatment in This Population. Viktoria Pavlova, Karen A. Beattie, George Ioannidis, Juliana Tricta, Maggie J. Larché, William G. Bensen and Jonathan D. Adachi, McMaster University, Hamilton, ON

Purpose: Diagnosis of Osteoporosis is generally perceived as a simple diagnosis and decision to treat mostly driven by the BMD score alone. Fragility fracture is a major risk factor for Osteoporosis and should be a trigger for diagnosis and therapy. In the Ontario Fracture Program only 30% of people with fracture have Osteoporosis on a BMD.

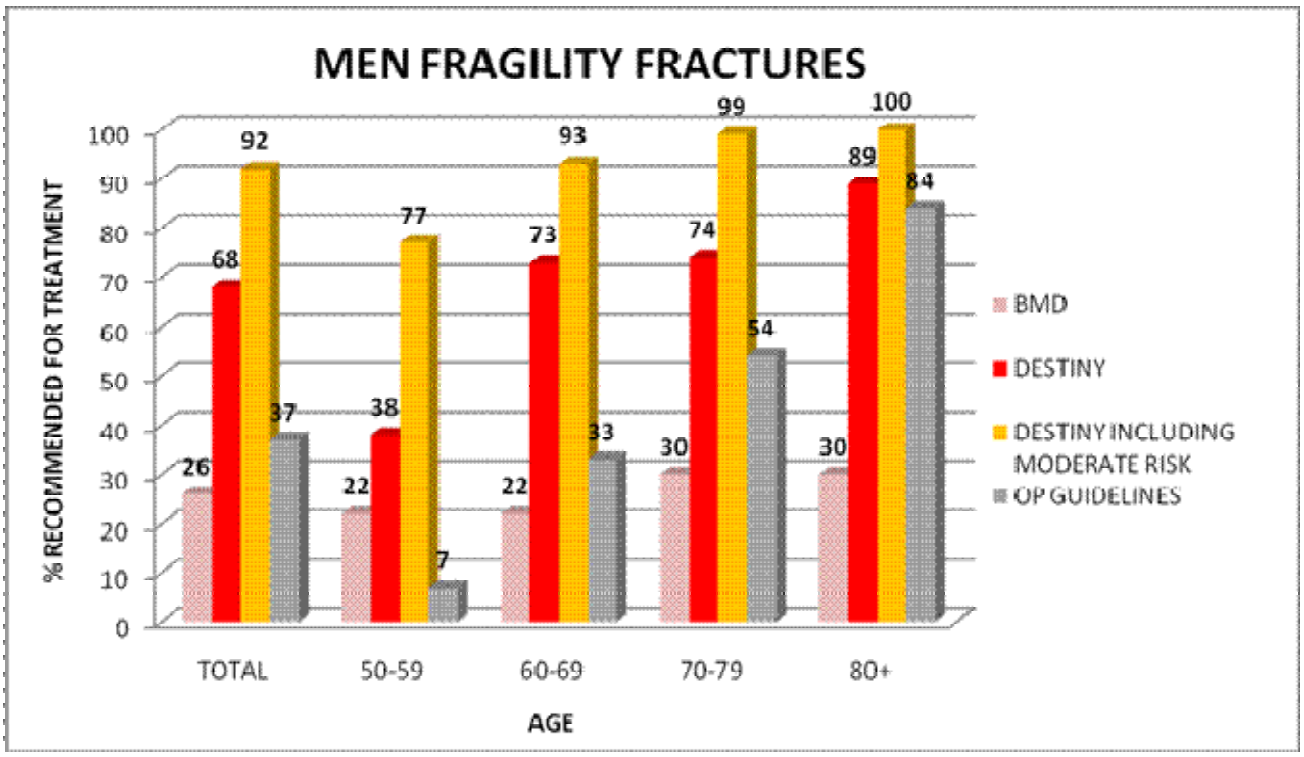
Most studies of Osteoporosis have focused on postmenopausal women, however, older men are also at increased risk of fragility fractures. Undertreatment of osteoporosis in men, even those who have sustained a fracture, remains a significant problem.

Methods: We analyzed our data, one of the largest databases in Canada, of 36,360 patients over 50 years of age who had their BMD done in the greater Hamilton area, Ontario, Canada, from May 2006 and June 2009. We identified 5,519 men total and 777 of whom sustained a fragility fracture.

Primary objective was to determine the proportion of male patients who have already had clinical fracture and would be recommended treatment based on the BMD alone, Bone DESTINY and Osteoporosis Canada guideline (OCG).

According to guidelines, males with BMD less than -2.5, a DESTINY fracture risk and OCG in high risk categories are those who would be recommended for treatment.

Bone DESTINY is a computerized fracture prediction tool that combines BMD, age, steroid use, propensity to fall, previous history of falls and BMI<20kg/m2 while OCG included sex, BMD, age, history of fragility fracture and steroid use.



Results: Of 777 males included in the analysis, 167 were 50-59 years old, 235 were 60-69 years old, 239 were 70-79 and 136 were 80 and older. In the youngest group, 22% would be recommended for treatment according to BMD alone, 38% according to high risk bone DESTINY and 7% according to OCG. In 60-69 year old group, 22%, 73% and 33% would be recommended for treatment according to BMD alone, high risk bone DESTINY and OCG, respectively. In 70-79 year old group, 30%, 74% and 54% respectively. In the eldest group, 30%, 89% and 84% respectively.

To further improve sensitivity of the bone DESTINY fracture risk assessment tool analysis of men in a moderate risk group was performed that resulted in significant fracture prediction improvement above 90% with exception the youngest group of 50-59 years old.

Conclusion: Appropriate recognition of male patients with reduced bone mass who are at high risk for developing fractures and as a result of that, appropriate management of osteoporosis requires a complex assessment. We have showed that BMD alone is only a part of the equation of global fracture risk assessment. Bone DESTINY is a tool that allows to predict risk of fracture to a significantly higher degree compared to BMD alone or OCG. Using a comprehensive tool will help to diagnose osteoporosis in men and reduce a "treatment gap" in this population group.

Disclosure: V. Pavlova, None; **K. A. Beattie**, None; **G. Ioannidis**, None; **J. Tricta**, None; **M. J. Larché**, None; **W. G. Bensen**, Wynne Tech, 4 ; **J. D. Adachi**, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, Procter and Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, Bristol-Myers Squibb, 5, Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter and Gamble, Roche, Sanofi-Aventis, Wyeth, Bristol-Myers Squibb, 8 .

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Zoledronic Acid Substantially Reduces the Risk of Morphometric Vertebral and Clinical Fractures. Ego Seeman[1], Dennis Black[2], Christina Bucci-Rechtweg[3], Richard Eastell[4], Steven Boonen[5] and P. Mesenbrink[6], [1]Austin Health, University of Melbourne, Melbourne, Australia, [2]UCSF, San Francisco, CA, [3]Novartis Pharmaceuticals Corp, East Hanover, NJ, [4]University of Sheffield, Sheffield, United Kingdom, [5]University of Leuven, Leuven, Belgium, [6]Novartis Pharmaceuticals Corp, New Jersey

Purpose: In the HORIZON- Pivotal Fracture Trial (PFT), zoledronic acid (ZOL) was shown to reduce vertebral, hip, and all clinical fractures by 70%, 41%, and 33%, respectively. As the fracture risk is not reduced completely, these fractures can lead to more fractures. Thus we aim to determine if ZOL reduces the increased risk conferred by further fractures. In a pre-planned analysis, we studied the effect of once-yearly ZOL in preventing a second morphometric vertebral fracture over 3 years and the recurrence of clinical fractures

Method: In this double-blind, placebo controlled study, 7765 postmenopausal women (PMW) with osteoporosis were randomly assigned to receive ZOL 5 mg (once-yearly) (n=3889) or placebo (n=3876) for 3 years. Clinical fractures reports from patients were collected every 3 months, and lateral spine x-rays were performed at randomization and yearly in patients not receiving concomitant osteoporosis therapy (stratum 1) and at randomization and end of study in patients receiving concomitant osteoporosis therapy (stratum 2). A multivariate proportional hazards regression model was used to evaluate the recurrence of clinical fractures in all patients stratifying for the usage of concomitant osteoporosis therapy (all intent-to-treat patients). Multiple morphometric vertebral fractures were evaluated using logistic regression adjusting for treatment and number of baseline prevalent fractures (stratum 1 and stratum 2 separately).

Results: In ZOL group, 308 (7.95%) women sustained a clinical fracture of which 36 (11.7%) experienced 2 or more fractures. In the placebo group, 456 (11.81%) women sustained a clinical fracture of which 94 (20.6%) experienced 2 or more fractures. This corresponds to 38% reduction (95% CI: 28%, 46%) in the risk of multiple fractures (p<0.0001). ZOL reduced the risk of two or more morphometric vertebral fractures by 89% (95% CI: 77, 95) in stratum I and by 61% (95% CI: -23, 88) in stratum 2. The most common adverse events were transient post-infusion symptoms.

Conclusion: Once-yearly ZOL substantially reduces the risk of multiple morphometric and clinical fractures suggesting treatment mitigates the worsening fragility accompanying a fragility fracture.

Disclosure: E. Seeman, Aventis, Merck, Sharp & Dome, Eli Lilly, and Novartis, 5 ; **D. Black**, Novartis Pharmaceutical Corporation and Merck, 2 ; **C. Bucci-Rechtweg**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **R. Eastell**, Amgen, Novartis, Procter and Gamble, Servier, Ono, GlaxoSmithKline, Eli Lilly, 5, Medical Research Council, National Institutes of Health Research UK Department of Health, AstraZeneca, Procter and Gamble, Novartis, 2 ; **S. Boonen**, Amgen, Eli Lilly, Novartis, Pfizer, Procter & Gamble, sanofi-aventis, Roche, GlaxoSmithKline, 2, Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, 8, Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, 5 ; **P. Mesenbrink**, Novartis Pharmaceutical Corporation, 3 .

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Sarcopenia: a Relevant Factor for Bone Mineral Density in Elderly Men Community-Dwelling. Camille F. Danilevicius, Jaqueline B. Lopes, Liliam Takayama, Valéria F. Caparbo and Rosa M.R. Pereira, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil

Purpose: The term sarcopenia is used to describe loss of skeletal muscle mass and strength that occurs along with biological aging. The aim of this study was to determine the association between sarcopenia with clinical parameters (including: falls and clinical fractures), lifestyle, bone mineral density (BMD) and body composition in elderly men community-dwelling.

Method: Three hundred and ninety nine men (>65 years-old) were selected in a well established elderly community in the São Paulo city. Body composition and BMD were measured by DXA-HOLOGIC-QDR 4500 (*Discovery A)*. Sarcopenia was defined as a relative skeletal muscle mass index (RSMI: appendicular skeletal muscle mass divided by height) below 7.26 Kg/m² in men (Baumgartner, 2000). Mann-Whitney test, for continuous variables, and Chi-squared test, for categorical variables were used to compare patients with and without sarcopenia and clinical variables and BMD. Logistic regression analysis was performed with the variables that were significant (p<0.05).

Results: The mean of age was 72.71±5.06 years. Fifty four (13.53%) men had sarcopenia. The univariate analysis showed that men with sarcopenia compared with those without this complication had lower weight (55.60±8.07 vs. 72.36±11.61 kg, p<0.001), BMI (21.38±2.50 vs. 27.26±3.66 kg/m^2, p<0.001); physical activity (1.93±0.70 vs. 2.11±0.55 times/week, p=0.035), L1-L4 BMD (0.91±0.2 vs. 1.02±0.2 g/cm^2, p<0.001), femoral neck BMD (0.64±0.1 vs. 0.76±0.1 g/cm^2, p<0.001), total femur BMD (0.78±0.1 vs. 0.95±0.1 g/cm^2, p<0.001), total body lean mass (41,264±4,801.6 vs. 52,523±6,631.9 g, p<0.001), total body fat mass (11,939±4,718.7 vs. 17.617±5,847.5 g, p<0.001), percentage of fat (21.16±5.6 vs. 23.78±4.8 %, p<0.001) and higher frequency of fragility fractures (19 vs. 6%, p=0.002). Logistic regression analysis revealed that sarcopenia was negatively associated with BMD in all sites (lumbar spine: OR=0.04, 95%CI= 0.01-0.25, p=0.001; femoral neck: OR=0.0002, 95%CI= 0.0000-0.0049, p<0.001; total femur: OR=0.0000, 95%CI= 0.0000-0.0007, p<0.001) and percentage of fat (OR=0.91, 95%CI= 0.86-0.97, p=0.004).

Conclusion: In conclusion, our study suggests that an interventional program to prevent sarcopenia will contribute to bone healthy in elderly men community-dwelling.

Disclosure: C. F. Danilevicius, CAPES, 2 ; **J. B. Lopes**, None; **L. Takayama**, None; **V. F. Caparbo**, None; **R. M. R. Pereira**, CNPQ, FAPESP, 2 .

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Vertebral Fracture Assessment by a Fracture Liaison Service in Patients with Incident Non Vertebral Fractures. K. Briot[1], F. Sailhan[2], A. Babinet[2], JP Courpied[2], P. Anract[2] and C. Roux[1], [1]Paris Descartes University; Rheumatology Department, Cochin hospital, Paris, France, [2]Paris Descartes University; Orthopaedics Department, Cochin hospital, Paris, France

Purpose: Despite vertebral fractures, are a significant risk factor for further fractures, they are often unrecognized. Vertebral Fracture Assessment (VFA) technology using current dual-energy X-ray absorptiometry (DXA) scanners is a convenient method to assess vertebral deformities, with lower radiation and lower costs than standard X-rays. This study aimed at evaluating the prevalence of vertebral fractures, using VFA, in patients presenting with non vertebral fractures.

Method: A cohort study undertaken patients aged 50 years or over who presented with non vertebral fractures and who underwent routine post-fracture assessment by a Fracture Liaison Service (FLS) was conducted. Bone mineral density (BMD) was measured by DXA and osteoporosis was defined as T score£ -2.5 at either lumbar spine or hip. The number and severity of vertebral fractures were defined using VFA performed during the same exam from TV4 to LV4.

Results: Among 190 patients hospitalized for low trauma non vertebral fractures from February 2009 to May 2009 in Orthopaedics department, the post fracture assessment was not possible for 70 patients (severe cognitive impairment (n=30), living in a foreign country (n=15), patients missed (n=14), patient's refusal (n=8), deaths before evaluation (n=3)). Data were available for 120 patients (mean age 74.3±11.7 years) presenting with low trauma non-vertebral fracture; 100 were female. 38% of patients reported a previous low trauma fracture. 25% of patients received calcium±vitamin D and 8.3%, an antiosteoporotic treatment. Hip fractures (n=57) and wrist fractures (n=25) were the most frequent fractures. 45.0% of patients were osteoporotic (T-score -2.5 or lower). The overall prevalence of vertebral deformity established by VFA was 53%; 23.5% of patients with vertebral fractures had deformities of more than one vertebra. 40% of patients with an osteopenic T-score or a normal T-score had at least one vertebral fracture.

Conclusion: Half of the patients hospitalized for non vertebral fracture have an undiagnosed vertebral fracture. Our results support the recommendation to perform vertebral fracture assessment in patients who are referred for DXA after a non-vertebral fracture.

Disclosure: K. Briot, None; **F. Sailhan**, None; **A. Babinet**, None; **J. Courpied**, None; **P. Anract**, None; **C. Roux**, None.

ACR/ARHP Poster Session B

Systemic Lupus Erythematosus Assessment /Activity: Antibodies, Biomarkers, Nephritis, and more
Monday, October 19, 2009, 9:00 AM - 6:00 PM

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SLICC Revision of the ACR Classification Criteria for SLE. Michelle Petri and Systemic Lupus International Collaborating Clinic (SLICC), Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: The ACR Classification Criteria for SLE date from 1982 with a 1997 revision that was not validated. Because of new knowledge of autoantibodies, neuropsychiatric lupus, the importance of low complement and the need for lupus nephritis to be a "stand alone" criterion, the SLICC group undertook a revision.

Method: An initial set of relevant variables was determined. Real patient scenarios (n=716) of SLE and non-SLE controls were submitted by SLICC centers. A consensus diagnosis was arrived at for each scenario. The consensus diagnoses were used to identify the variables that were most predictive of SLE. Recursive partitioning was employed to derive a classification rule based on multiple candidates predictor

variables. This preliminary classification rule was discussed at three SLICC meetings, independently validated by a SLICC steering comittee and further refined.

Results: Classify a patient as having SLE if: The patient has biopsy-proven lupus nephritis with ANA or anti-dsDNA OR the patient satisfies four of the criteria, including at least one clinical and one immunologic criterion.

Clinical Criteria
1. Acute or subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral/Nasal ulcers
4. Nonscarring alopecia
5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness
6. Serositis
7. Renal: Urine protein/creatinine (or 24 hr urine protein) representing at least 500 mg of protein/24 hr or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once) OR Lymphopenia (< 1000/mm3 at least once)
11. Thrombocytopenia (<100,000/mm3) at least once

Immunologic Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
3. Anti-Sm
4. Antiphospholipid antibody lupus anticoagulant false-positive test for syphilis anticardiolipin – at least twice normal or medium-high titer anti-b2 glycoprotein 1
5. Low complement low C3 low C4 low CH50
6. Direct Coombs test in absence of hemolytic anemia

When applied to our patient scenarios, this classification rule had better sensitivity than the ACR 11 (94% vs. 86%), and roughly equal specificity (92% vs. 93%), and resulted in significantly fewer misclassifications (p=.0082).

Conclusion: The SLICC SLE classification criteria address the major deficiencies of the ACR. Currently, ongoing validation will determine if they perform better than the ACR criteria.

Disclosure: M. Petri, None.

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SLE Patients with Quiescent Disease Have Comparable but More Stable Type I IFN Scores Than Active Patients. Julie Cherian[1], Emma J. MacDermott[1], Annie Santiago[1], Ziad A. Taimeh[1], Lilliana Barillas-Arias[2], Stephanie Gold[1], Nina Blank[1], Roland Duculan[1], Mary K. Crow[1] and Kyriakos A. Kirou[1], [1]Hospital for Special Surgery, New York, NY, [2]Schneider Childrens Hospital, New Hyde Park, NY

Purpose: We previously reported that SLE patients with Severe and Mild/Moderate SELENA SLEDAI flares had higher IFN scores and greater fluctuations of IFN scores compared to patients with quiescent disease. We also reported that a closely followed group of 15 patients with >7 visits each, showed wide fluctuation of IFN scores that either paralleled (47%), or preceded SLE flares (40%) in the majority of cases. With the expansion and continued follow-up of our cohort of quiescent patients, we now present a comparison of magnitude and fluctuation of IFN scores in SLE patients with active disease (n=15) and those with quiescent disease (n=9).

Method: We defined the quiescent group as those patients with no severe SELENA-SLEDAI scores, either on immunosuppressive medications (n=4) or on no such therapy (n=5). Each SLE patient had a median of 7 visits and was followed from 2/06 until 5/09. The subjects were studied at every rheumatology visit or hospitalization. Research blood was collected at least every 3 months and PBMC were isolated, lysed, and frozen. Relative expression (RE) of three type I IFN inducible genes (IFIT1, IFI44, and PKR) was calculated for each subject and their average value was used as their IFN score. Type I IFN score fluctuation was determined for each patient as the fold increase from the lowest score to the highest score.

Results: All but one of the quiescent patients were female and races included: 77% Caucasian (57% Hispanic) and 22% African American. The mean age was 31 years old, and median disease duration was 7 years. The median IFN score fluctuation in the stable and active groups was 2.02X and 18.1X respectively (p=0.0074). However, median IFN scores were not significantly different in the two groups (18.4 in the active group and 21.1 in the quiescent group). Similarly, there was no difference in the peak IFN scores. The median IFN fluctuations for the quiescent patients did not differ whether they were on or off immunosuppressive medications (3.5 X and 2X respectively). Interestingly, all of our quiescent patients demonstrated a “parallel pattern” between IFN and SLEDAI scores.

Conclusion: Fluctuations in type I IFN scores, assessed by IFN-inducible gene expression in PBMC, were less in SLE patients with quiescent disease compared to patients with active disease and paralleled disease activity. Therefore, fluctuations of IFN scores rather than absolute IFN score values may be more clinically relevant when evaluating SLE patients with severe disease flares.

Disclosure: J. Cherian, None; **E. J. MacDermott**, None; **A. Santiago**, None; **Z. A. Taimeh**, None; **L. Barillas-Arias**, None; **S. Gold**, None; **N. Blank**, None; **R. Duculan**, None; **M. K. Crow**, Biogen Idec, 5, Bristol-Myers Squibb, 5, Idera, 5, MedImmune, 5, Roche Pharmaceuticals, 5, Merck Serono, 5, Novo Nordisk, 5 ; **K. A. Kirou**, None.

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Outcomes in Patients with Systemic Lupus Erythematosus (SLE) with and without a Prolonged Serologically Active Clinically Quiescent (SACQ) Period. Amanda Steiman[1], Dafna Gladman[1], Dominique Ibañez[1] and Murray Urowitz[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: SACQ SLE patients constitute a subset of SLE whose clinical-serologic discordance presents a clinical dilemma. There is debate over whether these patients’ active serology alone warrants treatment. We explore outcomes in patients with and without a prolonged SACQ period by comparing the rate of damage accrual, as measured by the SLICC/ACR Damage Index (SDI), and the incidence of renal damage and of coronary artery disease (CAD).

Method: SLE patients followed between July 1970 and April 2008 with visits ≤18 months apart were identified. SACQ was defined as a ≥2-year sustained period without clinical activity but with persistent serologic activity (increased anti-dsDNA and/or hypocomplementemia), during which antimalarials were permissible, but neither steroids nor immunosuppressives. SACQ patients were then matched for age, sex, disease duration, decade of entry to clinic, and SDI at the beginning of the SACQ period, with non-SACQ SLE controls, in 1:2 ratio. The two groups were compared on the bases of change in SDI over 3-10 years, and incidences of CAD (defined as myocardial infarction, angina, sudden cardiac death) and of renal damage (defined as creatinine doubling or creatinine > 120 at ≥ two consecutive clinic visits and/or proteinuria for ≥ 6 months) at 5 and 10 years from the beginning of the SACQ period. Descriptive statistics were used; comparisons were made using paired t-tests and McNemar tests.

Results: 55 SACQ patients and 110 matched controls were identified. The median SACQ period was 158 weeks. Fewer SACQ patients used antimalarials (60% vs 77.3%) (p=0.004) and, fewer used steroids (18.2% vs 76.4%) or immunosuppressives (5.5% vs 43.6%) (p<0.0001 for both) over the 5 year period following study start.

SLICC damage index scores:

	SACQ (mean ± STD)	**Control (mean ± STD)**	**P-value**
SACQ Start	0.56 ± 1.21	0.56 ± 1.21	n/a
3 years	0.70 ± 1.27	1.13 ± 1.54	< 0.0001
5 years	0.89 ± 1.37	1.36 ± 1.66	< 0.0001
7 years	0.94 ± 1.28	1.71 ± 1.86	0.0001
10 years	1.26 ± 1.68	2.26 ± 2.23	0.001

Incidence of CAD:

	SACQ	**Control**	**P-value**
Start of study	2 (3.6%)	7 (6.4%)	0.32
Incidence @ 5 years	1 (1.8%)	6 (5.5%)	0.16
Incidence @ 10 years	1 (1.8%)	8 (7.3%)	0.06

There was no difference between baseline serum creatinine in the two groups (p=0.90). By definition, baseline proteinuria was not found in any SACQ patient, while it was present in 13 (12.3%) controls (p<0.0001).

Incidence of renal damage:

	SACQ	**Control**	**P-value**
Renal damage @ 5 years	1 (1.8%)	17 (15.5%)	0.0006
Renal damage @ 10 years	2 (3.6%)	26 (23.6%)	<0.0001

Conclusion: SLE patients with a prolonged SACQ period have significantly less damage accrual over 5-10 years compared to matched SLE controls. This supports the practice of active surveillance without treatment (with steroids or immunosuppressives) during the SACQ period.

Disclosure: A. Steiman, None; **D. Gladman**, None; **D. Ibañez**, None; **M. Urowitz**, None.

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SLEDAI-2K 10 Days Versus SLEDAI-2K 30 Days in a Longitudinal Evaluation. Zahi Touma, M.B. Urowitz, Dominique Ibañez and Dafna Gladman, University of Toronto, Toronto Western Hospital, Toronto, ON

Background: The SLEDAI (Systemic Lupus Erythematosus Activity Index) was developed in 1985 through a nominal group process and is based on the presence of 24 features in 9 organ systems over the patient's past 10 days. An updated version SLEDAI-2000 (SLEDAI-2K) was introduced and validated in 2002 again documenting findings in the past 10 days. We showed previously in a cross-sectional study a concordance between SLEDAI-2K scores when descriptors where documented for a 10-day window and for a 30-day window in the same visit.

Purpose: To evaluate SLEDAI-2K 30 days over time and to compare with the original SLEDAI-2K 10 days.

Method: Forty one patients seen at a single centre were followed at monthly intervals for 12 months. A complete history, physical examination and laboratory tests were performed to allow the determination of SLEDAI-2K. The SLEDAI-2K score was completed twice, once for a 10-day window and the second for a 30-day window using the same definitions for the descriptors.

Results: Among the 41 patients 37 were female and 4 were male. 419 patients-visits in 41 patients were recorded for both SLEDAI-2K for a 10-day window and the second for a 30-day window. Patients were 90% female, 56% Caucasian, 17% Black, 7% Chinese, and 20% other. The mean age at SLE diagnosis was 30.5±10.3 years, age at study start 45.4±13.2 and disease duration at study start 14.9±10.3. 268 patient-visits had varying levels of disease activity (3 patients-visits had SLEDAI-2K of 1; 133 had 2, 2 had 3, 68 had 4, 9 had 5, 35 had 6, 11 had 8, 4 had 10, 2 had 12 and 1 had 15) (Table 1 and 2).

In all but 1 patient-visit there was an agreement between the SLEDAI-2K 10 and 30 days. This patient experienced skin rash as a minor lupus flare, however in the last 10 days prior to the visit his rash completely faded.

Table 1. SLEDAI-2K 30 days in all patients-visits

	Inactive	**Active SLEDAI-2K**									
		Distribution by SLEDAI-2K score									
SLEDAI-2K total weight	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**15**
Number of patient-visits	**151**	**3**	**133**	**2**	**68**	**9**	**35**	**11**	**4**	**2**	**1**

Table 2. Clinical and laboratory manifestations

Clinical descriptors	Patients-visits number (%)	Laboratory descriptors	Patients-visits number (%)
Seizure	2 (0.5%)	Hematuria	7 (1.7%)
Headache	2 (0.5%)	Proteinuria	12 (2.9%)
Vasculitis	2 (0.5%)	Pyuria	8 (1.9%)
Arthritis	20 (4.8%)	Low complement	122 (29.2%)
Rash	37 (8.9%)	Increased DNA	179 (42.8%)
Alopecia	10 (2.4%)	Thrombocytopenia	3 (0.7%)
Mucosal Ulcers	11 (2.6%)	Leukopenia	14 (3.4%

Summary: This study confirmed that it is unusual to have a manifestation of active lupus present at 11 to 30 days prior to a visit and have complete resolution in the 10 days prior to the visit.

SLEDAI-2K 30 days scores were concordant with SLEDAI-2K 10 days scores, both in patients in remission and in patients with a spectrum of disease activity levels followed monthly over 1 year.

Conclusion: SLEDAI-2K 30 days was validated against SLEDAI-2K 10 days and may now be used in clinical studies and clinical trials to describe disease activity over the previous 30 days.

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Ibañez**, None; **D. Gladman**, None.

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SLEDAI-2K Responder Index-50 (SRI-50). Zahi Touma[1], Dafna Gladman[1] and Murray Urowitz[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: A number of outcome measures to assess disease activity in SLE patients have been developed. SLEDAI-2K (Systemic Lupus Erythematosus Activity Index-2K) is a reliable valid, simple, one-page activity index recording features of active lupus as present or not present. Thus its utility in clinical trials is limited as it cannot reflect partial improvement in a disease manifestation. The objective of this study is to develop a SLEDAI-2K responder measure which could document a minimum 50% improvement in disease manifestations among lupus patients.

Method: Derivation of SRI-50 (SLEDAI-2K Responder Index-50) from SLEDAI-2K. A new definition for each of the original descriptors of SLEDAI-2K was created to reflect a minimum improvement of 50%. The definitions of descriptors of SRI-50 were constructed based on a literature review for each specific organ system. The new assigned scores for the descriptors of SRI-50 were derived by dividing the score of SLEDAI-2K by 2.

Assessing the content validity of the draft instruments; SRI-50 form was assessed by expert rheumatologists reviewing the instruments and providing critical feedback.

Testing of SRI-50: One hundred patients who had experienced lupus flares or had persistently active disease were assessed initially and then reassessed after treatment was initiated. SLEDAI-2K was determined on the first visit and again at the second visit along with SRI-50.

Results: SRI-50 and the data retrieval form to accurately document the clinical and laboratory findings of each descriptor were developed.

Seventy two patients didn't change their SRI-50 because their manifestations resolved or didn't meet the definition of SRI-50 (table 2). Twenty eight patients with varying levels of disease activity at the first visit (3 had SLEDAI-2K 2, 3 had 4; 6 had 6; 6 had 8; 3 had 10; 2 had 12; 1 had 16, 1 had 18; 2 had 20; 1 had 21) were further studied with SRI-50 (Table 1). SRI-50 was able to demonstrate incomplete (but ≥50%) improvement which would not have been discerned using SLEDAI-2K. Such incomplete improvement was demonstrated in 13 of the 24 SLEDAI-2K descriptors and in 6 of the 9 organ systems that were present in these patients.

Table1. Characteristic of the patients

Sex (F/M)		90%/10%
Race	Caucasian, Black, Chinese, Other	53%, 16%, 10%, 21%
Age at diagnosis		31.6 ± 13.5
Age at 1st visit in study		44.6 ± 15.7
Disease duration at 1st visit in study		13.0 ± 9.7
SLEDAI-2K at 1st visit in study		4.89 ± 4.66
AMS in interval		6.33 ± 4.20
SDI at 1st visit in study		1.69 ± 2.22

Table 2. SLEDAI-2K/SRI-50 on initial and follow up visit with partial improvement

SLEDAI-2K visit 1	2	6	10	4	4	8	6	6	6	2	16	12	8	8	4	6	20	8	8	21	8	20	10	18	10	12	6	2
SLEDAI-2K visit 2	2	6	6	4	4	8	6	6	6	2	16	8	8	4	4	4	10	8	8	3	8	18	10	18	10	12	4	2
SRI-50 visit 2	1	5	4	3	2	6	5	4	4	1	8	4	7	3	2	3	6	4	4	1.5	4	10	9	10	6	6	2	1

Conclusion: SLEDAI-2K Responder Index-50 is a promising instrument that can describe partial improvement in disease activity between visits in lupus patients.

Disclosure: Z. Touma, None; **D. Gladman**, None; **M. Urowitz**, None.

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Characterization of Systemic Lupus Erythematosus Patients with Low or Normal Complement Levels: Longitudinal Evaluation of Disease Flares. Julie Cherian[1], Emma J. MacDermott[1], Annie Santiago[1], Ziad A. Taimeh[1], Lilliana Barillas-Arias[2], Stephanie Gold[1], Rolando Duculan[1], Mary K. Crow[1] and Kyriakos A. Kirou[1], [1]Hospital for Special Surgery, New York, NY, [2]Schneider Childrens Hospital, New Hyde Park, NY

Purpose: SLE is the prototypic systemic autoimmune disease characterized by immune complex (IC) formation and tissue deposition with inflammation. Low C3 and C4 levels are thought to represent active IC formation and complement consumption. Although most SLE patients are presumed to form IC, there are some SLE patients that have active disease without apparent complement activation. We sought to compare typical SLE patients with evidence of IC formation as judged by low complement levels (below the normal level for the testing lab; LC) and others without such evidence (normal complement; NC) in order to identify unique characteristics of the 2 groups.

Method: From our cohort of 77 longitudinally followed SLE patients, all selected to express one or more of anti-Ro/La/Sm/RNP antibodies, we chose 52 patients with data from more than 3 visits available and studied their C3 and C4 levels over a median of 2 years, from 2/06 until 5/09. We also recorded anti-dsDNA titers at least every 3 months. Disease activity was evaluated using the SELENA-SLEDAI and BILAG instruments. Patients were categorized as having low complements at any point of their follow-up (LC; n=28) or normal complement levels at all times of observation (NC; n=15). Nine patients with no severe SELENA-SLEDAI flares and no BILAG A or two concurrent BILAG B flares were excluded from the NC group as the normal complement would simply reflect low disease activity.

Results: There were 4 males in the group and races included: 59% Caucasians (67% Hispanic), 30% African Americans (12.5% Hispanic), 7.6% Asians and 1.9% Other. Demographics were similar between the two groups. Neither the median SLEDAI scores (4.5 and 4) nor the SLICC scores (0.5 and 1) were statistically different in the LC and NC groups, respectively. There were 16 (57%) severe flares in the LC group and 8 (53%) in the NC group. Interestingly, there was perhaps a tendency for more (n= 9; 32%) BILAG A renal flares in the LC group compared to the NC group (n=2; 13%; p=0.3). All renal flares consisted of proliferative disease. With regard to type I IFN expression, median IFN scores were higher in the LC than in the NC group (19.4 vs 7.3; p=0.02).

Conclusion: Patients with SLE may exhibit severe disease without the typical drop in complement levels, a presumptive measure of IC formation. However, SLE patients with low C3 and C4 levels demonstrate higher type I IFN scores and have more renal BILAG A flares. This likely reflects the important role of IC in both of these disease characteristics.

Disclosure: J. Cherian, None; **E. J. MacDermott**, None; **A. Santiago**, None; **Z. A. Taimeh**, None; **L. Barillas-Arias**, None; **S. Gold**, None; **R. Duculan**, None; **M. K. Crow**, Biogen Idec, 5, Bristol-Myers Squibb, 5, Idera, 5, MedImmune, 5, Roche Pharmaceuticals, 5, Merck Serono, 5, Novo Nordisk, 5 ; **K. A. Kirou**, None.

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Type I Interferon Pathway Activation Parallels Therapeutic Response in Patients with SLE. Stephanie Gold, Julie Cherian, Annie Santiago, Nina Blank, Mary K. Crow and Kyriakos A. Kirou, Hospital for Special Surgery, New York, NY

Purpose: Previous cross sectional studies have demonstrated that SLE disease activity is correlated with activation of the type I interferon (IFN) pathway. Our study of a longitudinal lupus cohort indicates that IFN pathway activation fluctuates in many lupus patients. To assess whether clinical response to a defined therapeutic intervention is associated with a decrease in IFN pathway activation, we compared changes in IFN- inducible gene expression and disease activity in lupus patients started on Mycophenolate Mofetil (MMF) or Azathioprine (AZA).

Methods: From our cohort of 77 SLE patients, 15 (8 on AZA and 7 on MMF) were selected for study based on the availability of data prior to the initiation of therapy and a minimum of 4 months follow-up. 3 patients were excluded from the AZA group due to incomplete data. Clinical disease activity (measured by SELENA SLEDAI) and IFN scores were analyzed prior to and following initiation of AZA or MMF. Blood was collected before the drug was started, at the first follow-up (2.9±1.2 months) and at a final follow-up visit on drug (7.3±3.7 months). PBMC lysates were analyzed by real time PCR. Relative expression (RE) of 3 type I IFN inducible genes (IFIT1, IFI44, PKR) was determined, and the mean was used as the IFN score.

Results: 53% of the patients were Caucasian (62.5% Hispanic), 33% African American and 13% Asian. Mean age and disease duration were 32 and 10.1 years respectively, and 93% were female. Baseline SLEDAI scores were similar for MMF and AZA patients (Mean=6.4 and 5.6; p=.28). From the initiation of AZA until the first follow-up, the IFN score and SLEDAI increased 89.4% and 2.6 points respectively. At the last follow up the IFN score increased 161% from drug initiation and the SLEDAI increased 2.6 points. For patients on MMF, the type I IFN score decreased by 21.3% with a corresponding SLEDAI score decrease of 3.14 points from the initiation of drug to the first follow up. At the final follow up the IFN scores had decreased 35.7% from the initial value and the SLEDAI had decreased 1.71 points.

Conclusion: Initiation of lupus therapy with MMF or AZA resulted in changes in disease activity that were reflected in parallel changes in IFN score, based on quantification of IFN inducible gene expression in PBMC. In this cohort, the MMF treated patients showed a superior clinical and IFN response compared with those on AZA. These data support the potential for IFN pathway activation to serve as an informative biomarker of change in lupus disease activity in response to therapy.

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Revision of the SELENA Flare Index. Michelle Petri[1], Jill Buyon[2], K. C Kalunian[3], M.B. Urowitz[4], V. Strand[5], Joan Merrill[6], B H. Hahn[7], J M. Grossman[7], H. Michael Belmont[8], Mary Anne Dooley[9], Joan Marie Von Feldt[10], Mary E. Cronin[11], Lisa R. Sammaritano[12], Graciela S. Alarcon[13] and LM Hanrahan[14], [1]JHU, Baltimore, MD, [2]NYU School of Medicine, New York, NY, [3]UCSD School of Medicine, La Jolla, CA, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]Stanford University, Palo Alto, CA, [6]OK Med Research Foundation, OKklahoma City, OK, [7]UCLA, [8]Hosp for Joint Disease, New York, NY, [9]Univ of NC at Chapel Hill, Chapel Hill, NC, [10]University of Pennsylvania, Philadelphia, PA, [11]Medical College of WI, Milwaukee, WI, [12]Hospital for Special Surgery, New York, NY, [13]University of Alabama at Birmingham, Birmingham, AL, [14]Lupus Fnd of America, Washington, DC

Purpose: The original SELENA Flare Index (SFI) performed well in the SELENA trials to separate severe from mild/moderate flares. However, in current clinical trials it is important to also separate mild from moderate flares.

Method: As part of the Lupus Foundation of America's International Flare Definition and Validation initiative, the SELENA Flare Index (SFI) was revised through a series of consensus conference calls. There was an initial review and discussion of the strengths and weaknesses of the SFI in SELENA and industry trials. Each call reviewed organ specific definitions of mild, moderate and severe flare. Definitions were discussed and re-reviewed until consensus was reached.

Results: The revised SFI is organ-system based, and is not linked to the SLEDAI. For each organ system, suggested clinical manifestations are given for each category, but the intended treatment decision (if it is higher) overrides the clinical description in each category. Specifically, a mild flare is assigned if there is either no treatment, or initiation of hydroxychloroquine, prednisone ≤ 7.5 mg/day or a non-immunosuppressive therapy. Definition of a "Moderate flare" is consistent with use of prednisone > 7.5 mg/day but less than 0.5 mg/kg/day,

or immunosuppressive therapy (other than cyclophosphamide), and "Severe flare" prednisone (or equivalent) ≥ 0.5 mg/kg/day, cyclophosphamide, biologic treatment, or hospitalization. Three "mild" flares are considered a "moderate" flare.

Conclusion: The new SFI is organ system-based. The choice of recommended treatment overrides the clinical definition when the treatment choice is higher.

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Using the CLASI to Assess Disease Severity and Responsiveness to Therapy in Cutaneous Lupus Erythematosus. Rachel Klein, Siamak Moghadam-Kia, Jonathan LoMonico, Joyce Okawa, Katherine Chilek, Elizabeth Gaines, Chris Coley, Lynne Taylor and Victoria P. Werth, University of Pennsylvania, Philadelphia, PA

Purpose: The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) is a clinical tool that quantifies disease activity and damage. The purpose of this study was to determine how the CLASI could be used to classify patients according to disease severity (mild, moderate, and severe) and to identify patients who responded to therapy.

Method: To determine how the CLASI could be used to assess disease severity, subsets of patients were classified as having "mild", "moderate", and "severe" disease based on the principal investigator's subjective assessment. Corresponding CLASI activity scores were also calculated. A crosstabs was done to determine the optimal range of CLASI activity scores that corresponded with each severity group. To determine how the CLASI could be used to identify improvement, the CLASI activity score and the physician's skin score were completed at every visit. A change ≥ 2 in the physician's skin score was considered the gold standard for a clinical improvement. Subjects were divided into severity groups and screened for an improvement between consecutive and non-consecutive visits. The mean change in the CLASI activity score was calculated for patients that improved and patients that did not improve. A ROC analysis was done to determine the sensitivity, specificity, and percentage of patients correctly classified for the severity groups and each change in CLASI activity score.

Results: Disease severity was assessed in 45 clinic visits (n=37 patients). Mild, moderate, and severe disease corresponded with CLASI activity score ranges of 0-9 (sensitivity 93%, specificity 78%), 10-20, and 21-70 (sensitivity 80%, specificity 95%), respectively. 91 subjects were included in the responsiveness analysis for a total of 505 comparisons between clinic visits. For moderate and severe disease, a mean change in the CLASI activity score of 7.5 points ($p<0.0001$, sensitivity 58%, specificity 80%) and 13.8 points ($p=0.0002$, sensitivity 59%, specificity 97%), respectively, corresponded with a clinical improvement. A ROC analysis demonstrated improved sensitivity and similar specificity when changes in CLASI activity scores of 7 points (sensitivity 61%, specificity 79%) and 12 points (sensitivity 65%, specificity 97%) were used to identify improvement in moderate and severe disease, respectively. For mild patients, there was no statistically significant difference in the change in CLASI activity scores for patients who improved versus those who did not improve.

Conclusion: The CLASI can be used to categorize patients into severity groups and to identify a clinical improvement in patients with moderate or severe disease.

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Smoking Is Not Associated with Autoantibodies in Unaffected First-Degree Relatives of SLE Patients. J.A. James[1], S.A. Stewart[2], D. Terrell[3], J.M. Guthridge[4], G.R. Bruner[4], D.L. Kamen[5], G.S. Gilkeson[5], D.R. Karp[6], N.J. Olsen[6], M.L. Ishimori[7], M.H. Weisman[7], V.M. Holers[8], J.B. Harley[9] and J.M. Norris[8], [1]OMRF, OU, Oklahoma City, OK, [2]OMRF, [3]OUHSC, [4]Oklahoma Medical Res Fnd, [5]Medical Univ South Carolina, [6]Univ Texas Southwestern, [7]Cedars Sinai, [8]Univ Colorado, [9]Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: SLE is a complex human autoimmune disease with interacting genetic and environmental risks. Epidemiologic studies have identified an association between smoking and the presence of SLE; however, the mechanism by which smoking is associated with SLE in select individuals is not understood. One working model is that smoking modifies select autoantigens leading to a loss of tolerance and autoimmunity. This model suggests that autoantibody-positive family members should be smokers. This study tests whether smoking is associated with autoantibody production in SLE or unaffected first-degree blood relatives (FDRs).

Method: Detailed clinical, serologic, demographic and treatment information was extracted from a coded database from a diverse collection of 1,242 SLE patients and 981 FDRs [55% EA, 23% AA, 16% HI]. Serum samples from each were tested for standard lupus autoantibodies by immunofluorescence and luminex bead-based assays. ANA positivity and the 13 select autoantibody test results were then analyzed on the basis of smoking status at the time of sample. Categorical values included never-smoker, ever smoker, and current smoker. Statistical analysis was conducted using chi-square and ANOVA methods.

Results: SLE cases were less likely to have ever smoked (49% vs 53%) compared to their blood relatives (p=0.031), but not significantly less likely to be current smokers (18% vs 20%). No association was identified between smoking and having a positive ANA when SLE patients who were current smokers were compared with those who never smoked. Among FDRs, 19.1% of current smokers tested positive for at least one of 10 autoantibodies commonly associated with SLE, while 25.8% of never smokers (p=0.053) and 25.6% of former smokers tested positive for one or more autoantibody (p=0.086). Interestingly, the group of SLE patients who had ever smoked had a lower prevalence of autoantibodies against nRNP 70K (p<0.0012), ribosomal P (p=0.003), and dsDNA (p=0.01) than the group of SLE patients who had never smoked. Similarly, the prevalence of dsDNA positivity is lower in unaffected relatives who are current smokers than in unaffected relatives who are non-smokers (p = 0.045).

Conclusion: SLE patients have no significant association between ANA positivity and smoking; moreover, SLE patients with antibodies against nRNP 70K, ribosomal P and dsDNA, as well as FDRs with antibodies against dsDNA, are more likely not to smoke in this cross-sectional cohort. No other strong correlation between smoking and the production of autoantibodies exists in FDRs. Therefore, the epidemiologic association of smoking with SLE may manifest its risk through mechanisms outside of autoantibody production.

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905

Emergence of Circulating Anti-Double Strand DNA (dsDNA) Antibody-Secreting Cells Predicts Disease Flare in Patients with Systemic Lupus Erythematosus. Hironari Hanaoka, Yuka Okazaki, Takashi Satoh, Yuko Kaneko, Hidekata Yasuoka, Noriyuki Seta and Masataka Kuwana, Keio University School of Medicine, Tokyo, Japan

Purpose: It is increasingly appreciated that circulating B cells are functionally altered and involved in pathogenic process in patients with systemic lupus erythematosus (SLE). In this study, we developed an assay to detect circulating anti-dsDNA antibody-secreting cells and examined for their clinical impact on SLE patients.

Methods: We studied 130 patients with SLE, 49 with non-SLE connective tissue disease (32 rheumatoid arthritis, 15 Sjögren syndrome and 2 systemic sclerosis), and 18 healthy controls. Clinical findings at blood examination, including SLEDAI and SLAM, were obtained from all SLE patients. Disease remission was defined as SLEDAI < 5. Serum anti-dsDNA antibody was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. Anti-dsDNA antibody secreting-cells were quantified by an enzyme-linked immunospot (ELISPOT) assay, in which peripheral blood mononuclear cells (PBMCs) were cultured on lambda phage DNA-coated PVDF membranes, followed by incubation with alkaline phosphatase-conjugated anti-human IgG. To examine identity of anti-dsDNA antibody-secreting cells, PBMCs depleted of CD19+ or CD138+ cells were subjected to the ELISPOT assay.

Summary of the Result: Anti-dsDNA antibody-secreting cells were detected in 29 patients with SLE, but in none of disease controls or healthy controls, resulting in higher specificity (100% vs 90%) and lower sensitivity (22% vs 80%), compared with serum anti-dsDNA antibody detected by ELISA. Circulating anti-dsDNA antibody-secreting cells were either CD19+ B cells or CD138+ plasma cells. The number of circulating anti-dsDNA antibody-secreting cells was significantly correlated with serum anti-dsDNA antibody titers ($r = 0.48$, $p < 0.05$). When clinical findings were compared between SLE patients with and without anti-dsDNA antibody-secreting cells, an increased amount of proteinurea and high SLEDAI and SLAM were associated with the presence of circulating anti-dsDNA antibody-secreting cells (p

< 0.02 for all comparisons). Serial analysis in 22 SLE patients showed that the presence or absence of anti-dsDNA antibody-secreting cells was correlated with disease activity scores. Moreover, we prospectively followed 28 anti-dsDNA antibody-positive patients in remission and found that cumulative disease remission rates were significantly lower in patients with anti-dsDNA antibody-secreting cells, than in those without them ($p < 0.001$, Figure).

Conclusion: In SLE patients, anti-dsDNA antibody-secreting B cells and plasma cells were recruited into circulation in active disease phase. Detection of circulating anti-dsDNA antibody-secreting cells is useful in predicting disease flare in patients with SLE.

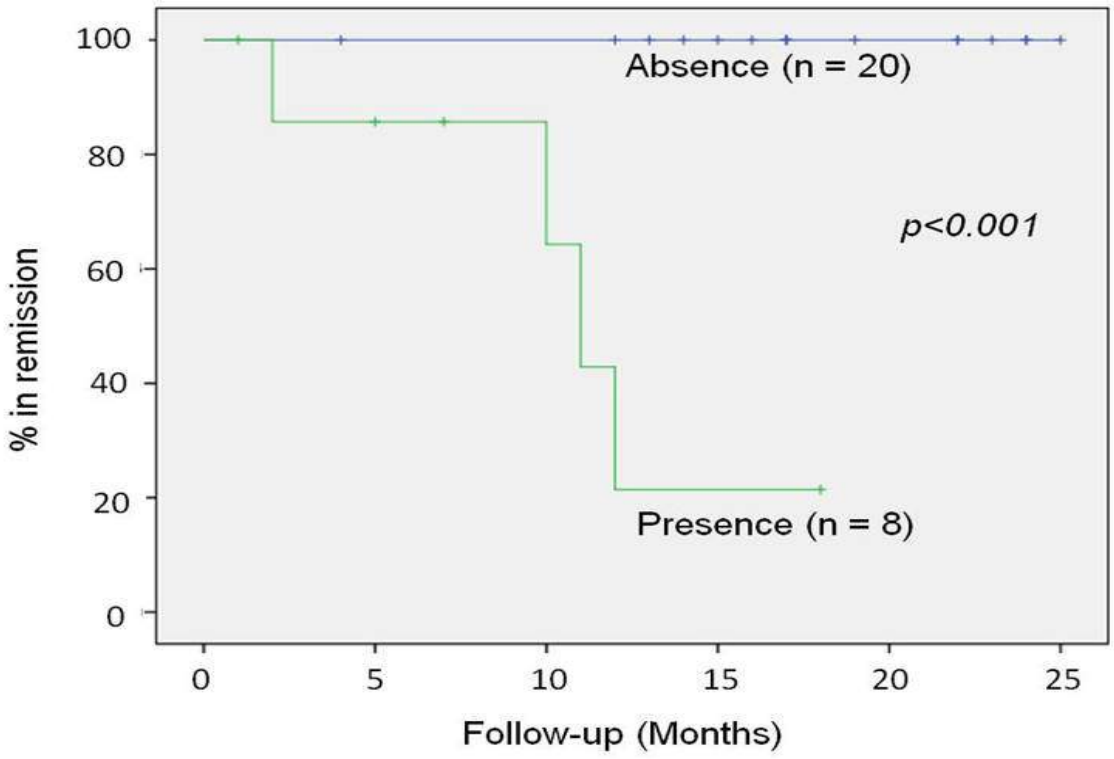

Figure. Cumulative rates for disease remission in patients with anti-dsDNA antibody in the presence or absence of circulating anti-dsDNA antibody secreting cells.

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Urinary Cytology Evaluation in SLE: Implications for Identification of Active Nephritis and Scoring Renal Domains On Activity Indices. Anca D. Askanase[1], David B. Thomas[2], Aspee Chowdhury[1], John Purcell[1] and Jill P. Buyon[3], [1]Hospital for Joint Diseases, New York, NY, [2]Nephrocor, Uniondale, NY, [3]NYU School of Medicine, New York, NY

Purpose: Perhaps with the exclusion of the elusive RBC cast, there is no single laboratory test that can unambiguously predict the presence of active renal disease in patients with SLE. Evaluation of urinary cytology is a valuable tool in identifying early transplant rejection with urinary lymphocytes (>20/10 high power field) preceding the rise in creatinine. This study addressed the value of urinary cytology as a marker of active renal disease in a consecutive sampling of SLE patients.

Method: Seventy spot urine specimens were obtained from the first 50 patients fulfilling 4 ACR criteria seen in an outpatient setting. These were subjected to cytological evaluation in addition to protein/creatinine ratios.

Results: Of the 50 patients, 19 have lupus nephritis defined by a kidney biopsy, 11 of which were active at the time of study as defined by a 24 hour protein excretion of >1 gram. As expected, the average protein/creatinine ratio on the spot urinalysis (UA) of patients with active nephritis compared to patients without active nephritis was 2.71 compared to .41. Clinical data on these patients further substantiated the presence of active renal disease; mean serum albumin (3.3 vs. 4.1), creatinine (1.36 vs 1.11), complement C3 (84 vs. 107), and C4 (16 vs. 21), and anti-dsDNA (228 vs. 52). Examination of the urinary cyto-diagnostic sediments (evaluated per 10 high power fields) revealed that in patients with active nephritis, there were significantly more acantocytes (dysmorphic RBCs), target, and isomorphic RBCs per high powered field compared to inactive patients 8/0, 27/1, 127/7 respectively. However, acantocytes, known to have the highest predictive value for glomerular injury, were only present in 2 patients with active nephritis, whereas all the others had none. The urinary neutrophils were higher in patients with active disease (235 vs. 63) but there was a high incidence of vaginal contamination (substantiated by the presence squamous epithelial cells in 9 of the 17 samples from active nephritis patients, and 33 of 53 inactive), After eliminating the contaminated samples, the PMNs were 131 vs 58 p=NS. The most striking difference between groups was in the number of lymphocytes, 81 vs 3 which remained significant even after removing the contaminated samples (92 vs 5, p=0.008). Of all the patients without active nephritis only 1 had urinary lymphocytes above 20 (21). Since contamination with vaginal fluid can have an impact on the presence of isomorphic RBCs we also examined the average number of RBCs after eliminating the contaminated samples, 62 vs. 12, p=NS.

Conclusion: The presence of increased lymphocytes, not total WBC, on cytological urine exam suggests the diagnosis of active nephritis which may provide insight to activity vs chronicity, a critical clinical dilemma. The value of total RBCs and WBCs is diminished by contamination with vaginal fluid implying caution regarding scoring of renal domains.

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Proteomic Identification of Several Novel Autoantibodies Associated with Systemic Lupus Erythematosus. Yasuhiro Katsumata[1], Yasushi Kawaguchi[1], Sayumi Baba[1], Seisuke Hattori[2], Koji Tahara[3], Kaori Ito[3], Nozomi Yamaguchi[3], Hiroaki Hattori[3], Kinya Nagata[3], Takahisa Gono[1], Kae Takagi[1], Yuko Ota[1], Hisashi Yamanaka[1] and Masako Hara[1], [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Kitasato University, Tokyo, Japan, [3]BML Inc., Tokyo, Japan

Purpose: By using proteomic approach, we aimed to find out novel serum autoantibodies associated with systemic lupus erythematosus (SLE), especially CNS syndromes of SLE.

Method: Autoantigens were screened by 2 methods of proteomic analysis; immunoprecipitation followed by LC-MS/MS shotgun analysis and 2D-PAGE-western blot followed by MALDI-TOF/MS analysis. In immunoprecipitation, total IgG from sera of SLE patients with active CNS syndromes was isolated and purified by using protein G-Sepharose. Total protein extracted from human tumor cell lines and whole human normal brain, was mixed and immunoprecipitaed with isolated IgGs crosslinked to the protein G-Sepharose. Eluted antigens from the immunoprecipitates were analyzed by LC-MS/MS shotgun method and indentified using the MASCOT database search algorithms. Alternatively, after total protein was separated by 2D-PAGE and western blot analysis with the patient's sera, autoantigens were identified by MALDI-TOF/MS analysis. The recombinant proteins of identified antigens were produced in transformed *Escherichia coli*. The IgG reactivities against these recombinant antigens in sera from original SLE patients were confirmed by western blotting. Finally, autoantibodies against the several recombinant human brain antigens in sera of patients with SLE and normal healthy controls were quantified by solid phase direct ELISA.

Results: Among many candidate antigens, these antigens showed positive reactivities against several SLE patients' sera in western blotting: crystallin αB, esterase D, multifunctional DNA repair enzyme (APEX nuclease) 1, nucleophosmin, acidic ribosomal protein P0, proeasome activator subunit 3 isoform 1 (PSME3), YARS, TPI1, PGK1, PEBP1, NFIB, PGAM-B, ERAB, and GFAP. Autoantibodies in serum samples of SLE patients (n = 106) including 32 patients with active CNS syndromes and normal healthy controls (n = 100) were quantitatively examined by ELISAs using these antigens. The O.D. values of SLE patients' serum samples were significantly higher than those of normal healthy controls' in ELSIAs using following antigens: crystallin αB ($p = 0.0002$), esterase D ($p = 0.0002$), APEX1 ($p < 0.0001$), nucleophosmin ($p = 0.0070$), acidic ribosomal protein P0 ($p < 0.0001$), and PSME3 ($p = 0.0005$). Among these results, associations of SLE and autoantibodies against crystallin αB, esterase D, and APEX1 have not been previously reported in literatures as far as we searched. Unexpectedly, none of these autoantibodies were associated with active CNS syndromes.

Conclusion: Associations of SLE with several novel and previously reported autoantibodies were demonstrated. This study shows that our immunoproteomic approach is a reliable method to identify autoantigens in SLE.

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Risk Factors Associated with Development of SLE Among Anti-RNA Helicase A Positive Patients. Jason Y.F. Chan, Yi Li, Eric S. Sobel, Mark S. Segal, Michael R. Bubb, Edward K.L. Chan, Westley H. Reeves and Minoru Satoh, University of Florida, Gainesville, FL

Purpose: Autoantibodies to RNA helicase A (RHA) is a new serological marker of early stage of SLE. Although anti-RHA appears highly specific for SLE among patients with an established diagnosis, some anti-RHA positive individuals do not meet SLE criteria. We evaluated the clinical association of anti-RHA in unselected patients seen in an autoimmune disease clinic, focusing on identifying risk factors associated with the development of SLE.

Method: Sera from the initial visit of patients seen at our autoimmune disease clinic (n = 1542, including 368 SLE, 105 SSc, 72 PM/DM, 56 RA, 61 Sjogren's syndrome: SjS) were screened by immunoprecipitation (IP) of 35S-labeled cell extract and western blot using anti-RHA reference sera. Levels of anti-RHA in sera from sequential visits were measured based on the integrated density (volume) of the protein band acquired with phosphorimager. Clinical information was from a comprehensive database.

Results: Forty-four anti-RHA positive patients (23 Caucasian, 10 African American, 6 Latin, 2 Mixed, 1 Asian, 2 unknown) were identified. Eighty percent (35/44) of cases had SLE (4 or more of criteria), one case each had SSc-PM overlap and SjS. Demographic information and levels of anti-RHA were comparable between SLE vs. non-SLE groups. Among 7 cases that did not meet any disease criteria, 3 cases had 3 items of SLE criteria. Sixty-seven percent (21/32) of anti-RHA positive SLE were within one year of diagnosis consistent with its association with an early stage of SLE. Levels of anti-RHA were reduced over time in 20/23 SLE whose sequential sera were available; however, the correlation between the disease duration vs. levels of anti-RHA at initial visit was not strong. As a whole, the non-SLE group was characterized by lack of other specific autoantibodies by IP (73% vs. 19% in SLE, p = 0.002). Anti-U1RNP (p = 0.008), Sm, ribosomal P (rP), or La (44, 22, 13, and 16%, respectively) were found only in the SLE group whereas anti-Ro and -phospholipid antibodies were found at similar prevalence in both groups. Anti-dsDNA was rare in non-SLE (11% vs 81% in SLE, p = 0.043). In the SLE group when sequential (>6 month apart) sera were tested, 22% (5/23) of patients developed new autoantibody specificities during follow-up (anti-U1RNP+Sm, anti-rP, and anti-Su, one case each, anti-Ro, 2), within 1 year from initial visit in 4/5 cases and within a year of diagnosis of SLE in 3 cases. None of the non-SLE patients with anti-RHA developed new autoantibodies.

Conclusion: Anti-RHA is highly specific for SLE; however, certain anti-RHA positive cases without other coexisting autoantibodies may not fulfill SLE criteria and have a milder/undifferentiated disease. Anti-RHA positive patients who also have anti-U1RNP, Sm, ribosomal P, or dsDNA may have higher risk of developing SLE.

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Detection of Anti-dsDNA in Subjects Referred for Inflammatory Rheumatic Disease Associates with Differing Clinical Phenotypes Depending On the Assay Used. Soren Jacobsen[1], Gunnar Sturfelt[2], Anders Bengtsson[3], Michele Compagno[3], Niels Heegaard[4], Andreas Jönsen[2], Rasmus S. Jacobsen[1], Lennart Truedsson[3], Ole Petter Rekvig[5] and Hans Nossent[5], [1]University Hospital, Copenhagen, Denmark, [2]Inst of Clinical sciences, Lund, Sweden, [3]University Hospital, Lund, Sweden, [4]Statens Serum Institut, Copenhagen, Denmark, [5]University Hospital, Tromsø, Norway

Purpose: Determination of anti-dsDNA antibodies is a serological cornerstone in diagnosis and classification of systemic lupus erythematosus (SLE) but may also be detected in other conditions. Furthermore, there is no present consensus on which assay to use. Purpose of the study was to establish which clinical features regardless of the SLE diagnosis that were associated with anti-dsDNA determined by various assays assays.

Method: In a Scandinavian tri-center study, subjects were recruited from 1082 patients referred due to suspicion of rheumatic disease. 292 were ANA positive and 292 sex- and age-matched ANA negative controls were selected from the original cohort. All 584 subjects were phenotyped according to active manifestations including the current SLE classification criteria and a broad range of other clinical manifestations. In all subjects determination of anti-dsDNA was performed by means of 1-3) Chrithidiae luciliae immunofluorescence test (CLIFT, ImmunoConcept) in 3 different laboratories, 4) solution phase ELISA (SPADE, Tromsø), 5) Varelisa (Pharmacia), 6) EliA (Pharmacia) and 7) ELISA (Pharmacia). Cut-off levels according to instructions of the manufacturer or the performing laboratory were used. Statistical analysis included logistic stepwise regression analysis using dichotomized anti-dsDNA results as the dependent variable and clinical manifestations as explanatory variables.

Results: The prevalence of positivity for the 7 anti-dsDNA tests ranged from 5.3 to 14.2 %. The five most common SLE classification manifestations were non-erosive peripheral arthritis (28%), photosensitivity (10%), oral/nasal ulcers (6.0%), hematuria (3.8%) and proteinuria (3.1%). The five most common other manifestations were arthralgias (58%), morning stiffness (24%), headache (14%), Raynauds phenomenon (13%) and xerostomia (13%). Statistically significant hazard ratios deriving from the regression analyses are shown in the table:

	Butterfly rash	Alo-pecia	Cutaneous vasculitis	Livedo reticul	Morning stiffness	Axial arthritis	Pleuritis	Protein-uria	Oral/nasal ulcers	Lympho-penia	Lymph-adenopathy
CLIFT 1	11	3.9	6.6	4.8	-	-	7.8	4.7	-	-	-
CLIFT 2	-	-	-	-	-	-	17	6.7	-	8.5	-
CLIFT 3	4.3	13	-	-	0.04	12	29	11	-	27	-
SPADE	-	6.1	-	-	0.34	-	25	8.5	-	-	-
VARELISA	3.3	4.1	-	-	0.13	-	24	22	-	-	-
ELIA	-	9.0	-	-	0.15	-	37	23	-	-	-
ELISA	-	-	-	-	0.22	-	48	8.4	5.1	-	-

Conclusion: Positive results in all 7 anti-dsDNA tests associated with pleuritis and proteinuria. However, the remaining clinical manifestations shown in the table had varying associations with the anti-dsDNA tests used. The results indicate that the correlation between clinical features and any anti-dsDNA test may vary depending on the assay used and on the laboratory performing the test, as shown for CLIFT.

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ANA-Positive Healthy Individuals and Autoimmune Rheumatic Patients Present Distinctive Pattern and Titer Profiles at the ANA HEp-2 Assay. Henrique A. Mariz[1], Silvia H. Rodrigues[1], Silvia H. B. Campos[2], Gilda A. Ferreira[3], Emilia I. Sato[1] and Luis Eduardo C. Andrade[1], [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Fleury Health and Medicine, Sao Paulo, Brazil, [3]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Purpose: We sought for distinctive ANA HEp-2 features in ANA-positive healthy controls (HC) and patients with autoimmune rheumatic diseases (ARD).

Method: 918 HC [32.1±10.3 years old; 634 (69.0%) women], from two large cities in the western southern hemisphere were retrieved among workers in a hydroelectric power plant (n=444) and among blood donors (n=474). HC were defined after a clinical questionnaire to

exclude current or past ARD, infections and neoplasia. A subset of the HC group was re-evaluated after 3.6 to 5.0 years (mean 3.9±0.3 years). Sera from 153 randomly selected ARD patients comprised the control group: systemic lupus erythematosus (n=87), systemic sclerosis (n=45), Sjögren's syndrome (n=10), and dermato/polymyositis (n=11). HEp-2 ANA was determined at 1:80 and successive dilutions by two blinded independent observers. ANA-positive sera were screened for antibodies against extractable nuclear antigens (ENA: Sm, U1-RNP, SS-A/Ro, SS-B/La) by double immunodiffusion against calf spleen extract.

Results: ANA was positive in 138 ARD patients (90.2%) and 118 HC (12.8%). ARD patients presented predominantly high titer (≥1:1280) and HC presented essentially low titer (≤1:160) but exceptions did occur (Table 1). ANA pattern profile was distinct in the two groups. Nuclear homogeneous (Ho), nuclear coarse speckled (NCS), centromere, and cytoplasmic dense fine speckled (Cyto DFS) patterns were exclusively observed in ARD patients. Nuclear dense fine speckled (NDFS) pattern was present only in HC. The most frequent ANA pattern in both groups was the nuclear fine speckled (NFS), which occurred at significantly lower titer among HC (median 1:80) as compared to ARD patients (median 1:1280) ($p<0.001$). Anti-ENA was present in 1 HC (SS-A/Ro) and in 35 (25.3%) ARD patients. At follow-up none of the 40 re-evaluated HC developed ARD and 29 (72.5%) remained ANA-positive. All HC that became ANA-negative had baseline ANA titer of 1:80. Table 1 – Distribution of ANA HEp-2 titer and pattern in HC and ARD patients

Titer	**HC (%)**	**ARD (%)**	**P**	**Pattern**	**HC (%)**	**ARD (%)**	**P**
1:80	54 (45.7)	10 (7.3)	< 0.001	NCS	0	36 (26.0)	<0.001
1:160	9 (7.7)	5 (3.7)	0.259	Ho	0	10 (7.2)	0.008
1:320	15 (12.7)	23 (16.7)	0.477	Centromere	0	11 (7.9)	0.005
1:640	21 (17.7)	0	< 0.001	NFS	54 (45.8)	58 (42.0)	0.636
≥1:1280	21 (17.78)	100 (72.5)	0.002	NDFS	39 (33,0)	0	<0.001

Conclusion: The ANA HEp-2 assay offered distinctive titer and pattern profiles for ANA-positive individuals and for ARD patients. ANA pattern seemed to be more reliable than ANA titer for discriminating ANA-positive HC and ARD patients. Some ANA patterns (NCS, Ho, Centromere) were exclusively observed in ARD patients while the NDFS pattern was restricted to HC. The NFS pattern was equally frequent in both groups and showed different titer distribution in HC and ARD patients. ANA-positive HC tended to keep ANA reactivity but did not develop evidence of ARD after a 4-year follow-up period.

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Comparison of Three dsDNA Antibody Tests in a Cohort of Rheumatology Patients. Michael W. Ettore and Melissa R. Snyder, Mayo Clinic, Rochester, MN

Purpose: Autoantibodies to double-stranded DNA (dsDNA Ab) are a serological marker strongly correlated with systemic lupus erythematosus (SLE). Several distinct methodologies are available to laboratories for the quantitative measurement of dsDNA Ab. In this study, we compared the performance of a radioimmunoassay, an enzyme immunoassay (EIA), and a multiplex immunoassay in a population of rheumatic disease patients.

Methods: Serum samples (n=188) were collected for a study on inflammatory biomarkers from patients seen in the Mayo Clinic Division of Rheumatology for evaluation of suspected connective tissue disease. All diagnoses were established based on clinical evaluation; patients diagnosed with SLE and rheumatoid arthritis (RA) fulfilled the diagnostic criteria established by the American College of Rheumatology. Patients without a specific diagnosis, but with evidence of an inflammatory rheumatologic disorder, were classified as having undifferentiated connective tissue disease. Samples were tested for dsDNA Ab using the Anti-dsDNA Radioimmunoassay Kit (Farr method; Diagnostic Products Corporation), the Anti-dsDNA EIA Kit (Bio-Rad), and the dsDNA analyte of the Bioplex 2200 ANA Screen (Bio-Rad), according to respective manufacturer's instructions. A consensus result was determined for each sample, defined as the qualitative interpretation (positive or negative) agreed upon by a majority of the three methods. Sensitivity, specificity, and concordance rates between the three methods were calculated, first using cutoff values specified by the manufacturer, and second using cutoff values empirically chosen to optimize concordance.

Results: Using manufacturer specified cutoff values, the following sensitivity, specificity, and concordance rates with consensus results were observed.

Table 1.

	Farr	EIA	Multiplex
Sensitivity	74.3%	52.2%	35.4%
Specificity	49.3%	84.0%	92.0%
Positive Concordance	100.0%	93.0%	63.4%
Negative Concordance	56.4%	95.7%	99.1%
Overall Concordance	72.9%	94.7%	85.6%

After empirically raising the Farr and lowering the EIA and multiplex cutoff values, the following sensitivity, specificity, and concordance rates with consensus results were observed.

Table 2.

	Farr	EIA	Multiplex
Sensitivity	54.0%	60.2%	47.8%
Specificity	81.3%	82.7%	77.3%
Positive Concordance	87.3%	98.6%	81.7%
Negative Concordance	88.9%	90.6%	88.9%
Overall Concordance	88.3%	93.6%	86.2%

Conclusion: In our cohort of rheumatology patients, using manufacturer's suggested cutoff values, the Farr assay had the highest sensitivity and the Bioplex 2200 ANA Screen had the highest specificity, while the Bio-Rad EIA showed the best concordance with the consensus result. Changing cutoffs resulted in the Bio-Rad EIA attaining the best combination of sensitivity and specificity, while maintaining the best concordance. Laboratories should carefully weigh the clinical needs of their patient populations when selecting a dsDNA Ab method.

Disclosure: M. W. Ettore, None; **M. R. Snyder**, None.

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IgG Anti-Pentraxin 3 Antibodies in Systemic Lupus Erythematosus. Andrea Doria[1], Nicola Bassi[1], Anna Ghirardello[1], Miri Blank[2], Margherita Zen[1], Michele Tonon[1], Yehuda Shoenfeld[3] and Leonardo Punzi[1], [1]University of Padova, Padova, Italy, [2]Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan, Israel, [3]Sheba Medical Center, Ramat Gan, Israel

Purpose: To evaluate the prevalence and correlates of anti-pentraxin 3 (PTX3) antibodies in patients with systemic lupus erythematosus (SLE).

Method: Sera of 130 SLE patients (ACR criteria), 130 healthy subjects (HS), and 130 patients affected with other autoimmune diseases (oARD), including 27 with rheumatoid arthritis, 26 with polymyositis, 27 with systemic sclerosis, 26 with Sjögren's syndrome, and 26 with psoriatic arthritis (all healthy and disease controls were age- and sex-matched with SLE patients), were analyzed by home-made ELISA tests, using as substrate human recombinant PTX3 and 2 peptides obtained from the complete protein, identified as potential antigenic sites using Lasergene DNA program (DNA Star) (PTX3_1 from N-terminal domain, and PTX3_2 from central domain). Inhibition tests were performed to evaluate potential interferences between BSA and anti-PTX3 or anti-PTX3 derived peptides; between C reactive protein and PTX3_2; and between PTX3 or PTX3 derived peptides and anti-PTX3 or anti-PTX3 derived peptides. SLE activity was measured using ECLAM score. Statistics were performed using ROC curves, Fischer's exact test, two-tailed t test and Person's correlations.

Results: All inhibition tests were negative, apart from PTX3 against anti-PTX3 and PTX3_2 against anti-PTX3_2 (maximum optical density reduction: 83%, 82%, respectively). SLE patients had higher prevalence of anti-PTX3, anti-PTX3_1 and anti-PTX3_2 antibodies than healthy controls or patients with oARD (Table). No differences were observed between healthy controls and patients with oARD. A correlation was found between anti-PTX3 and anti-PTX3_2 antibody levels ($r=0.615$, $p<0.001$). No association between these antibodies and disease activity was observed. The prevalence of anti-PTX3, anti-PTX3-1, and anti-PTX3_2 antibodies were lower in patients with glomerulonephritis than in those without (anti-PTX3 11.5% vs. 34.6%; anti-PTX3_1 9.2% vs. 27.7%; anti-PTX3_2 21.5% vs. 39.2%; all $p<0.001$) and higher in patients who were antiphospholipid antibody (aPL) positive than in those aPL negative (anti-PTX3 33% vs. 17.9%, $p=0.041$; anti-PTX3_2 42.5% vs. 21.7%, $p=0.032$). These associations were confirmed by multivariate analyses. No other significant relationship between anti-PTX3 and anti-PTX3 derived peptides and serological or clinical abnormalities, including the drugs taken by the patients, were observed.

	HS		SLE		oARD
	%	p	%	p	%
Anti-PTX3	6.2	<0.001	46.2	<0.001	5.3
Anti-PTX3_1	8.2	<0.001	36.9	<0.001	1.5
Anti-PTX3_2	5.1	<0.001	60.8	<0.001	2.5

Conclusion: Anti-PTX3 antibodies are significantly prevalent in SLE patients where they might provide protection from renal involvement. The antigenic properties of PTX3_2 peptide are similar to those of PTX3 suggesting its potential use for further analysis.

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Prevalence and Clinical Significance of the Anti-p53 Antibody in Systemic Lupus Erythematosus. Kenjiro Yamanaka[1], Soichiro Nakano[2], Yoshinori Kanai[1], Masanao Asano[2], Keigo Ikeda[2], Syouko Thoyama[2], Kentaro Ishiyama[1] and Yoshinari Takasaki[2], [1]Sasaki Institute Kyoundo Hospital, Tokyo, Japan, [2]Juntendo University School of Medicine, Tokyo, Japan

Purpose: p53 is a tumor suppressor protein and plays an important role in controlling cell proliferation and apoptosis by binding to DNA. There have been many reports on anti-p53 antibodies in cancer patients. However, only several studies have reported on the clinical significance of anti-p53 antibodies in patients with connective tissue diseases. The prevalence of serum anti-p53 antibodies in connective tissue diseases is still controversial. Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies against various nuclear components of cells. In this study, we investigated the prevalence and clinical significance of the anti-p53 antibody in patients with SLE.

Method: The anti-p53 IgG titer in the serum of patients with various connective tissue diseases was assayed by using an enzyme-linked immunosorbent assay (ELISA); MESA CUP anti-p53 test (Medical & Biological Laboratories Co. Ltd, Nagoya, Japan). Wild-type human p53 protein produced by a baculovirus was used in this ELISA kit. The minimum detectable true activity value of the anti-p53 antibody is 0.05 U/ml, and the cutoff value is considered to be 1.30 U/ml, as determined from the 95% distribution range of the antibody titer in a physically unimpaired person.

Results: Anti-p53 antibodies were detected in 59.5% of the patients with SLE ($n = 42$), and the prevalence of these antibodies was significantly higher than in patients with other connective tissue diseases such as mixed connective tissue disease ($n = 13$), scleroderma ($n = 16$), polymyositis or dermatomyositis ($n = 9$), Sjögren's syndrome ($n = 15$), and arthritis rheumatism ($n = 16$) (7.7%, 6.3%, 11.13%, 13.3%, and 6.3%, respectively; all $p < 0.001$). The anti-p53 antibody titer was also significantly higher in patients with SLE than in patients with

other connective tissue diseases (SLE, 7.8 ± 15.42; other, 0.56 ± 0.73; $p < 0.0001$). Next, the SLE patients (n = 42; 98% female; mean age, 46.8 ± 15.7 years) were divided into an anti-p53 antibody-positive or -negative group. The frequency of anti-dsDNA antibodies was higher in the anti-p53 antibody-positive group (42.9% vs 4.8%; $p = 0.00043$). The mean anti-dsDNA antibody titer was higher in the anti-p53 antibody-positive group (36.8 ± 50.3 vs 3.2 ± 7.4 IU/ml; $p = 0.00945$), and it was found to correlate positively with the anti-p53 antibody titers ($r = 0.611$; $p < 0.01$; Spearman). The mean value of CH50 was lower in the anti-p53 antibody-positive group (28.5 ± 11.8 vs 36.2 ± 11.8; $p < 0.05$), and the values correlated negatively with the anti-p53 antibody titers ($r = 0.323$; $p < 0.05$; Spearman). The frequency of SLE with flare was higher in the anti-p53 antibody-positive group (38.1% vs 2.4%; $p = 0.0057$). The peripheral blood lymphocyte counts correlated negatively with the anti-p53 antibody titers ($r = 0.349$; $p < 0.05$).

Conclusion: The anti-p53 antibody is a useful marker not only for diagnosing SLE in connective tissue diseases but also for detecting the disease activity of SLE.

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Clinical-Serologic Discordance in An Multicentre Inception SLE Cohort. Murray Urowitz[1], Dafna Gladman[1], Dominique Ibañez[1] and Systemic Lupus International Collaborating Clinics, [1]University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Anti-DNA antibodies and serum complement levels are considered important biomarkers for disease activity in SLE. Despite this many patients present serologically active but clinically quiescent (SACQ) while others present as clinically active but serologically quiescent (CASQ). These states create therapeutic dilemmas for clinicians. We aim to determine the frequency of SACQ and CASQ in a large international inception cohort of patients with SLE.

Method: An international research network comprising 27 centres from 11 countries has followed an inception (within 15 months of diagnosis) cohort of SLE patients yearly according to a standardized protocol between 2000 and 2009. Of these, 232 patients followed for a minimum of 5 years constitute the study population. Anti-DNA antibody levels and serum complement values are assessed at each visit. Clinical disease activity was assessed using SLEDAI-2K minus anti-DNA antibody and complements. SACQ is defined as presence of elevated anti-DNA ± decreased complement variables of SLEDAI-2K only and CASQ as SLEDAI-2K > 0 in the absence of both anti-DNA and complement variables. Descriptive statistics were used.

Results: Of the 232 patients followed for at least 5 years, 86.2% were female, 61.2% were Caucasian, 13.4% were Black, 17.2% were Asian, 6.5% Hispanic and 1.7% Other. 44.4% were married and 59.7% had at least College education. Their age at diagnosis was 36.5 years and SLEDAI-2K at enrolment was 5.63. The duration from diagnosis to enrolment was 5.2 months.

At some point in their 5 visits 121(52.2%) were SACQ and of the 232, 47(20.3%) were SACQ on no medication other than antimalarials. In 17(7.4%) patients this state was sustained for at least 2 consecutive years. At some point in their 5 visits 137(59.1%) were CASQ and in 63(27.2%) this state was sustained for at least 2 consecutive years.

Conclusion: Clinical-laboratory discordance regarding anti-DNA antibodies and complement levels presenting as SACQ or CASQ represent a significant subgroup of SLE patients who require close clinical follow-up. New biomarkers to better reflect disease activity in SLE are required.

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IFN-Driven Genes but Not Chemokines Correlate with Clinical SLE Predictors in ANA Positive Subjects. Hatice Bilgic[1], Patt Carlson[1], Joseph C. Wilson[1], Thearith Koeuth[1], Abby Montague[1], Kevin G. Moder[2], Emily C. Baechler[1] and Erik J. Peterson[1], [1]Univ. of Minnesota, Minneapolis, MN, [2]Mayo Clinic, Rochester, MN

Purpose: Virtually all Systemic Lupus Erythematosus (SLE) patients display ANA positivity. However, ANA positive status in the absence of disease (ANA+) is a poor predictor of a future autoimmunity-related diagnosis. Whole blood "signatures" comprising Type I interferon (IFN) driven transcripts and chemokines were described in a number of autoimmune diseases, including SLE. IFN "signatures" are promising biomarkers for SLE. We evaluated the hypothesis that IFN-driven peripheral blood gene and **chemokine "signature" derived scores** will assist in stratification of ANA+ persons at risk for SLE or other autoimmune disease.

Method: Peripheral blood samples and clinical data were obtained from 124 ANA+ subjects with no autoimmune disease diagnosis. A whole-blood derived IFN gene expression score was defined as the normalized sum of the expression levels of 3 IFN-driven genes (IFIT1, G1P2, IRF7) measured by AB.Taqman Low Density Arrays (n=124). Multiplexed ELISAs were used to quantify serum levels of 3 IFN-driven chemokines (IP-10, MCP-1, MIP-3B, n=67). The IFN chemokine score was defined as the normalized sum of the 3 chemokine levels. Gene expression and chemokine levels were also determined in 23 healthy controls and 168 SLE patients. Subjects with score values 2 standard deviations above the control subject mean were designated "IFN high". We used the Mann-Whitney rank sum test for group comparisons and Spearman`s rank coefficient to determine significance of correlations.

Results: High IFN gene expression scores were observed in 9% of ANA+ individuals, compared to 4.3% of healthy controls and 51.5% of SLE cases. An IFN high **chemokine score was observed in 46.3% of the ANA+ individuals, 0% of healthy controls, and 82.9% of SLE cases. IFN gene scores were significantly higher in ANA+ subjects with immunologic disorder (presence of anti-dsDNA or anti-Sm; p=0.052). No other clinical parameter differences were detected between IFN gene or chemokine score high and low groups. However, IFN gene score high individuals displayed a statistically non-significant trend toward increased number of SLE diagnostic criteria satisfied (p=0.084). IFN chemokine scores did not correlate with presence of any individual diagnostic criterion or the number of diagnostic criteria met. Although the IFN gene score was highly correlated with the chemokine score in SLE patients (r=0.514, p<0.0001), these scores did not correlate in the ANA+ group.**

Conclusion: IFN gene score is elevated in a subgroup of ANA+ subjects, and immunologic disorder correlates with IFN high gene scores. Although a high fraction of ANA+ subjects also show high IFN chemokine scores, the observed correlation between IFN gene and chemokine signatures in SLE patients is lacking in ANA+ persons. Ongoing longitudinal followup of disease-negative ANA+ subjects will shed light on the prognostic utility of IFN gene or chemokine scores in this clinical subset.

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Measurement of Serum Free Light Chains Performs Better Than Known Immunological Biomarkers for Systemic Lupus Erythematosus Disease Activity. Rohit Aggarwal, Winston Sequeira, Rachel Mikolaitis, Rediet Kokebie, Joel A. Block and Meenakshi Jolly, Rush University Medical Center, Chicago, IL

Purpose: To compare serum free light chains (FLC) with total IgG, complement (C3,C4) & double-stranded DNA (Ds-DNA) as a biomarker of disease activity in Systemic Lupus Erythematosus (SLE).

Method: 75 patients with SLE & 41 age and gender-matched control patients with RA were enrolled. Disease activity was assessed using Selena-SLEDAI and physician global assessments (PGA) for SLE and the DAS-28 for RA. PGA was categorized into 'no activity' PGA =0, 'mild' 0< PGA ≤ 1, 'moderate' 1< PGA ≤ 2, 'severe' 2< PGA ≤ 3. For RA subjects, disease activity was dichotomized into inactive (DAS-28 <3.2) and active disease. Finally, SLE flares were defined by Selena-SLEDAI. Serum FLC (Kappa (κ), Lambda (λ) and total FLC (κ + λ)) was measured using nephelometry (Binding site,UK). IgG, C3, C4, Ds-DNA were also measured. Mann-Whitney or Kruskall Wallis test was used to compare a) FLC and IgG in SLE vs. RA, b) FLC, C3, C4, Ds-DNA and IgG in patients with different levels of PGA in SLE as well as patients with and without flares in SLE, c) FLC in active vs. inactive RA. Spearman correlation was used to correlate FLC, C3, C4, Ds-DNA, IgG with SLEDAI and adjusted SLEDAI (adjSLEDAI= SLEDAI – [C3C4 and Ds-DNA score]).

Results: Serum FLC and IgG levels were higher in SLE than RA [FLC: median mg/L (IQR), total FLC in SLE: 46.2 (30.9–64.5) vs. RA: 32.3 (22.0-44.9), p< 0.01; IgG: SLE: 18.4 (14.9-24.1) vs. RA: 15.4 (11.8-18.24), p<0.01]. FLC and IgG in SLE and RA exceeded those of healthy normal controls. Total FLC (median, IQR) were significantly higher in subjects whose PGA was "severe" (179.8, 122.1-211.5) than in those with mild (38.2, 27.7-61.49) or no activity (39.1, 29.5-46.9), P<0.01 for each, and had a non-significant magnitude greater than those with moderate PGA (56.2, 42.7-106.3). Serum total FLC were significantly different between severe flare and no flare [severe flare

(204.3, IQR 122.1-219.2) vs. no flare (37.9, IQR 28.3-49.8), p<0.01]. There were no significant differences in IgG, C4 or Ds-DNA levels among different levels either of disease flare or of PGA, though C3 levels were significantly higher in those with flare or with severe PGA. Table 1 includes correlations. In RA, there was moderate correlation between total FLC and DAS-28 (rho 0.35, P=0.04), though no differences were detected between "active" and "inactive" RA; individually, κ and λ had results similar to total FLC. Finally, controlling for GFR, age and gender did not alter the results.

	Total FLC	Lambda FLC	Kappa FLC	Ds-DNA	C3	C4	CRP	IgG
SLEDAI	Rho: 0.66 P < 0.01	Rho : 0.68 P < 0.001	Rho : 0.58 P = 0.002	Rho : 0.45 P <0.001	Rho : -0.56 P < 0.001	Rho : -0.37 P = 0.001	Rho : 0.29 P = 0.01	Rho 0.27 P=0.06
adjSLEDAI	Rho: 0.45 P < 0.01	Rho : 0.49 P < 0.001	Rho : 0.39 P = 0.002	Rho :0.16 P = 0.20	Rho : -0.32 P = 0.005	Rho : -0.18 P = 0.12	Rho : 0.18 P = 0.10	Rho: 0.14 P=0.23

Conclusion: Serum FLC levels are highly correlated both with disease activity and with flare in SLE. Serum FLC performed better than C3, C4, Ds-DNA and IgG levels as a marker for disease activity in SLE.

Table 1.Spearman correlation (rho) between SLEDAI and biomarkers (C3, C4, dsDNA, Hs-CRP, FLCs)

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Lupus Nephritis: Urinary Biomarkers. Adnan Kiani[1], John Arthur[2], Laurence Magder[3], Jim C. Oates[2] and Michelle Petri[4], [1]Johns Hopkins University, Baltimore, MD, [2]MUSC, Charleston, SC, [3]University of MD, Baltimore, MD, [4]JHU, Baltimore, MD

Purpose: Lupus nephritis (LN) occurs in over 50% of SLE patients and is frequently associated with a poor long-term prognosis. A diseased kidney may lead to the generation of certain proteins in the urine, either in an intact form or, more likely, as peptide fragments. In either case, identifying urine proteins and cytokines would help identify the pathologic process and could lead to future primary or secondary preventive measures. We investigated different potential biomarkers for LN.

Method: Eotaxin, IP-10, GM-CSF, IFNa2, IFNy, IL-1a, MIP1B, PDGF, IL-6, IL-8, MCP-1, OPG, CysC, NAG, NGAL and sIL-2RA were measured by ELISA during 1 to 2 clinic visits in 30 SLE patients (93% female, 43% African-American, 37% Caucasian, and 20% other ethnicity). Ages ranged from 20-64 years (median 51). At each visit, the SLICC renal activity score (RAS) was calculated as proteinuria of 0.5 to 1 gm/day (3 points), proteinuria of 1 to 3 gm/day (5 points), proteinuria of > 3 gm/day (11 points), urine red blood cells ≥5 /hpf (3 points), urine white blood cells ≥10 /hpf (1 points). We looked at the relationship between these urinary biomarkers and the urine Protein/Creatinine Ratio (urine Pr/Cr), the renal activity score, and concurrent renal biopsies.

Results: The Spearman correlation coefficients between biomarkers and renal activity are shown in the table for urinary biomarkers that correlated with both Urine Pr/Cr and SLICC RAS.

Table 1: Spearman Correlation Coefficients between biomarkers and renal activity (p-values are based on a mixed effects model appropriately accounting for the fact that there are multiple measures from the same person)

Variable	IL-1a (n=41)	MIP1B (n=27)	IL-6 (n=42)	IL-8 (n=42)	MCP-1 (n=42)	sIL-2RA (n=42)
Urine Protein/Creatinine	0.62****	0.74****	0.69***	0.56****	0.61***	0.47*

Ratio						
SLICC Renal Activity score	0.56*	0.79*	0.69**	0.50***	0.57**	0.33***

* p<.05, ** p<.01, *** p<.001, **** p<.0001

Eotaxin, GMCSF, IFNy, PDGF correlated well only with the Urine Pr/Cr ratio, where as CysC correlated well only with SLICC renal activity score. We then looked at the association of these biomarkers with concurrent renal biopsies. Table 2: Mean log-transformed, normalized biomarker levels, by biopsy findings among those with concurrent biopsies

Variable	logIL-8 (pg/ml)	logMCP-1 (pg/ml)
ClassIV No(n=11) Yes(n=6)	-1.8* -0.5	2.1 2.7
ClassV No(n=9) Yes(n=8)	-0.5*** -2.2	2.8* 1.9

Urinary IL-8 was significantly higher in Class V, whereas urinary MCP-1 was significantly lower in Class V.

Conclusion: There is an immediate need of non-invasive urinary markers which associate with renal activity and are predictive of renal outcome. Validation of these urine biomarkers in LN patients followed longitudinally and with larger numbers of concurrent biopsies, may allow their eventual use in routine SLE care.

Disclosure: A. Kiani, None; **J. Arthur**, None; **L. Magder**, None; **J. C. Oates**, None; **M. Petri**, HGS, 5, HGS, 2 .

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ADAMTS5 Is a Biomarker for Prediction of the Response to Infliximab in Patients with Rheumatoid Arthritis. Kensei Tsuzaka[1], Yuka Itami[1], Koichi Amano[2] and Tsutomu Takeuchi[3], [1]Ichikawa General Hospital, Tokyo Dental College, Ichikawa, Chiba, Japan, [2]Saitama Medical Center, Saitama Medical School, Kawagoe,Saitama, Japan, [3]Keio University School of Medicine, Tokyo, Japan

Purpose: To identify a biomarker for prediction of the response to infliximab (INF) in rheumatoid arthritis patients, we focused on a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) that seems to play a key role in aggrecan degradation in cartilage.

Method: Fourty-four randomly selected active RA patients were treated with INF. Peripheral blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR.

Results: Baseline ADAMTS5 mRNA levels in the responder (1.461 ± 0.817) was significantly (p=0.0090) lower than that in the non-responder (2.246 ± 1.350) at 62 weeks' treatment with INF. The DAS28 at 62 weeks' treatment was significantly (p=0.0003) lower in the Low-ADAMTS5 group (2.47 ± 1.50) than in the High-ADAMTS5 group (4.46 ± 1.76). The percent reduction of the DAS28 (%DAS28 reduction) was significantly (p=0.0015) higher in the Low-ADAMTS5 group (52.8 ± 7.25) than in the High-ADAMTS5 group (22.5 ± 5.21). Interestingly, significant correlations were observed between the DAS28 and %DAS28 reduction at 62 weeks (p<0.001; r= 0.56 and -0.60, respectively) and the baseline ADAMTS5 mRNA level. Furthermore, ΔHAQ, an estimate of the improvement in the HAQ score, at 62 weeks' treatment was significantly (p=0.0305) higher in the Low-ADAMTS5 group (0.70 ± 0.68) than in the High-ADAMTS5 group (0.25 ± 0.35). The positive predictive value of a low baseline ADAMTS5 level for predicting good response and remission (DAS28<2.6 at 62 weeks) was 80.0% and 73.3%, respectively.

Conclusion: The baseline ADAMTS5 mRNA level is a candidate biomarker for prediction of the response to INF in RA patients.

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VCAM-1 Is a Better Measure of SLE Renal Activity Than NGAL and CXCL16. Adnan Kiani[1], Chandra Mohan[2], Tianfu Wu[2], Laurence Magder[3] and Michelle Petri[4], [1]Johns Hopkins University, Baltimore, MD, [2]Univ of Texas SW Med Ctr, Dallas, TX, [3]University of MD, Baltimore, MD, [4]Johns Hopkins Univ, Baltimore, MD

Purpose: VCAM-1, an adhesion molecule, is involved in the progression of glomerular and tubulointerstitial injury. Lipocalin-2 (NGAL, a member of the lipocalin superfamily) levels have been shown to rise in both acute and chronic kidney damage and in lupus nephritis (LN). CXCL16 is a chemokine whose levels are increased in both murine and human lupus. We investigated these three as potential biomarkers for LN.

Method: VCAM-1, CXCL16 and NGAL were measured during 1 to 3 clinic visits in 81 SLE patients (90% female, 49% African-American, 40% Caucasian, 4% Asian, 5% Hispanic and 2% others, mean age 46, 109 total visits) by ELISA (R&D). At each visit, the SLICC renal activity score was calculated as proteinuria of 0.5 to 1 gm/day (3 points), proteinuria of 1 to 3 gm/day (5 points), proteinuria of > 3 gm/day (11 points), urine red blood cells ≥5 /hpf (3 points), urine white blood cells ≥10 /hpf (1 points). We looked at the relationship between these biomarkers and the urine Protein/Creatinine Ratio (urine Pr/Cr), the renal activity score, and SLEDAI renal descriptors.

Results: The Spearman correlation coefficient between an individual's mean urine Pr/Cr (across visits) and their mean VCAM-1 was 0.60 ($p<.0001$) indicating that those with high mean VCAM-1 tend to have high mean urine Pr/Cr. The Spearman correlation coefficient between the individual's mean SLICC renal activity score and their mean VCAM-1 was 0.43 ($p<.0001$) indicating that those with high mean VCAM-1 tend to have high renal activity scores.

Table : Mean (SD) log-transformed and normalized (by urine creatinine) VCAM-1, NGAL and CXCL16, by clinical variables at each visit

Clinical variables at each visit	NGAL		VCAM-1		CXCL16	
	Mean (SD)	P-value[1]	Mean (SD)	P-value[1]	Mean (SD)	P-value[1]
Physicians Global Estimate	0.05 (0.05)	.41	3.26 (0.87)	.0022	0.25 (0.23)	.37
≥1.5 (n=35)	0.04 (0.04)		2.52 (0.78)		0.20 (0.21)	
< 1.5 (n=74)						
SLICC Renal Activity Score	0.07 (0.06)	.0024	3.54 (0.80)	<.0001	0.28 (0.28)	.041
High (4+ points) (n=21)	0.04 (0.03)		2.54 (0.72)		0.19 (0.13)	
Low (< 4 points) (n=78)						
C3	0.04 (0.03)	.14	2.84 (0.79)	.87	0.14 (0.03)	.052
< 79 (n=23)	0.04 (0.05)		2.69 (0.89)		0.22 (0.18)	
>= 79 (n=77)						
C4	0.05 (0.04)	.96	3.00 (0.84)	.027	0.20 (0.14)	.88
<16 (n=33)	0.04 (0.04)		2.60 (0.85)		0.20 (0.17)	
>=16 (n=68)						
Hematuria	0.08 (0.06)	.0039	3.90 (0.33)	.0021	0.26 (0.17)	.63
Present (n=5)	0.04 (0.04)		2.71 (0.86)		0.22 (0.22)	
Absent (n=104)						

Proteinuria		.047		.0002		.037
Present (n=8)	0.07 (0.07)		4.09 (0.43)		0.38 (0.39)	
Absent (n=101)	0.04 (0.04)		2.66 (0.82)		0.20 (0.20)	
Pyuria	0.04 (0.02)	.88	3.75 (0.17)	.038	0.26 (0.20)	.72
Present (n=3)	0.04 (0.04)		2.73 (0.87)		0.22 (0.22)	
Absent (n=106)						
Anti-dsDNA	0.04 (0.03)	.32	2.98 (0.84)	.24	0.15 (0.06)	.065
Present (n=25)	0.04 (0.04)		2.70 (0.88)		0.24 (0.25)	
Absent (n=84)						
Urine Protein/Creatinine ratio	0.06 (0.06)	.058	3.53 (0.77)	<.0001	0.30 (0.29)	.0036
≥ 0.5 (n=55)	0.04 (0.04)		2.50 (0.70)		0.18 (0.11)	
< 0.5 (n=99)						

[1] P-values are based on a mixed effects model to account for the fact that some patients contributed multiple observations.

Conclusion: Urine VCAM-1 had the greatest association with SLICC renal activity scores. However, all three measures showed significant association with measures of lupus nephritis. Future study of these measures with long-term renal outcomes is justified.

Disclosure: A. Kiani, None; **C. Mohan**, None; **T. Wu**, None; **L. Magder**, None; **M. Petri**, None.

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SLE Patients Show Evidence of Premature Biological Senescence. Sahena Haque[1], Chadi Rakieh[2], Fiona Salway[3], Rachel Gorodkin[4], Pauline Ho[4], Lee-Suan Teh[5], Philip J. Day[3] and Ian N. Bruce[4], [1]arc Epidemiology Unit, Manchester, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom, [3]Univeristy of Manchester, Manchester, United Kingdom, [4]Manchester Royal Infirmary, Manchester, [5]Consultant Rheumatologist, Blackburn, United Kingdom

Purpose: Patients with SLE have premature mortality compared to the general population. The main causes of death include coronary heart disease and infection. These observations suggest a phenotype of premature senescence in SLE. Telomere length can be used to assess overall biological ageing. Our hypothesis is that patients with SLE will demonstrate reduced telomere length compared to a control population.

Method: Telomere length was measured in a cross sectional study using real-time quantitative PCR in females with SLE (4 or more ACR 1997 criteria) and age-matched healthy female controls recruited from the local community. SLE factors and traditional cardiovascular risk factors were noted and assessed against telomere length in a larger cross-sectional SLE population.

Results: We studied 63 SLE patients *vs.* 63 controls with a median (IQR) age of 50.8 (37, 59) and 49.9 (32, 60) yrs respectively. The median relative telomere length was significantly reduced in SLE patients (0.97 *vs.* 1.5, p=0.0017). In our cross-sectional study we assessed 144 SLE patients with a median (IQR) age of 52.6 (44.0, 60.8) years; disease duration of 13.0 (7.8, 23.1) years; SLEDAI 2 (0, 6) and SLICC DI 1 (0, 2). 33 (23%) had renal involvement and 68 (47%) were current steroid users. After correction for multiple testing, factors significantly correlated with telomere length were C3 complement (Spearman's correlation coefficient 0.23, p = 0.0051) and estimated GFR (-0.22, p= 0.0075). Therapy and traditional cardiovascular risk factors were not correlated with telomere length.

Conclusion: Whole blood telomere length, a marker of biological senescence, is significantly reduced in SLE patients. Shorter telomeres associated with low C3 complement may reflect increased replicative senescence with active inflammation. The cross-sectional association of longer telomeres with renal impairment/damage may be a surviving cohort effect. The predictive value of telomere length as a biomarker of future risk of damage/mortality requires prospective evaluation. .

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Expression of CD44 Isoforms Correlates with SLE Disease Activity and Nephritis. Jose C. Crispin[1], George C. Tsokos[1] and Karen H. Costenbader[2], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Brigham & Women's Hospital, Boston, MA

Purpose: T cell CD44 variants v3 and v6 have been associated with increased T cell migration to sites of inflammation and active lupus nephritis. We assessed relationships between T cell CD44 (v3 and v6) levels and SLE disease activity and nephritis.

Method: We recruited 72 subjects with SLE by ACR criteria and 36 age-, race-, and sex- matched controls. Clinical data, including SLE history, autoantibodies and SLE disease activity (SLEDAI) were collected. CD44, CD44v3 and CD44v6 expression on CD4, CD8 and total T cells was quantified by flow cytometry. We examined Pearson correlations between clinical variables, SLEDAI scores and nephritis, and CD44 levels. Wilcoxon rank sum tests and conditional multivariable regression analyses were used to test for differences in CD44 levels in SLE cases compared to controls, controlling for clinical variables.

Results: Mean subject age was 42.1 (± 13.5) years in SLE cases and 43 (± 11.8) years in controls. 94% were female, 68% white, 10% Black, 7% Asian, 13% other/mixed race. Mean SLE duration was 11 (± 0.9) years. Mean SLEDAI score was 2.7 (± 3.4). Of SLE cases, 28 (39%) had antidsDNA antibodies, 22 (31%) were receiving corticosteroids and 18 (25%) immunosuppressive medications. Total CD44 on CD4 and CD8 cells was higher in SLE cases than controls, but no correlations with SLEDAI or nephritis were found. CD44 or its variants did not correlate with age, race, sex, smoking, or recent infection. CD44v3 and v6 on CD3, CD4 and CD8 cells were significantly higher in cases than controls (**Table**). Among SLE cases, strong positive correlations between CD44v3 and v6 levels and SLEDAI, nephritis, anti-dsDNA antibodies were found. In multivariable regression models, adjustment for clinical variables did not affect these relationships.

Conclusion: CD44v3 and v6 levels were strongly correlated with SLEDAI, nephritis and anti-dsDNA antibodies. Future studies will assess these biomarkers longitudinally in relation to SLE disease activity.

		Expression level (MFI)			**Pearson Correlations (cases)**					
Surface marker	**Cell subset**	**SLE**	**Control**	**p***	**SLEDAI**		**Nephritis**		**anti-dsDNA**	
		n=72	n=32		**r**	**p**	**r**	**p**	**r**	**p**
	CD3	**719 ± 59**	**477 ± 68**	**<0.01**	**0.29**	**0.01**	0.19	0.06	0.21	0.07
CD44v3	**CD4**	**805 ± 60**	**514 ± 71**	**<0.01**	**0.28**	**0.02**	0.19	0.06	0.15	0.21
	CD8	**482 ± 53**	**279 ± 50**	**<0.01**	**0.31**	**<0.01**	**0.19**	**0.05**	**0.26**	**0.03**
	CD3	**303 ± 37**	**190 ± 37**	**0.02**	**0.24**	**0.04**	**0.28**	**<0.01**	**0.29**	**0.01**
CD44v6	**CD4**	**418 ± 31**	**287 ± 39**	**<0.01**	**0.29**	**0.01**	**0.27**	**<0.01**	**0.23**	**0.05**
	CD8	**296 ± 41**	**154 ± 31**	**0.03**	0.21	0.07	**0.26**	**0.01**	**0.25**	**0.03**

*Wilcoxon rank sum test

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Clinical Utility of Changes in Cyto/Chemokines as Markers of Disease Activity in Systemic Lupus Erythematosus. Carolina Landolt-Marticorena[1], S. Morrison[2], H. Reich[1], E. Aghdassi[2], A. Herzenberg[1], J. Scholey[1], Dafna Gladman[3], Murray Urowitz[3], Paul. R. Fortin[1] and Joan E. Wither[1], [1]University Health Network, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Lupus patients have elevated plasma levels of a number of cytokine/chemokines suggesting that fluctuations in the concentration of these soluble mediators may mirror changes in SLE disease activity. In a preliminary screen of 20 cyto/chemokine plasma concentrations in SLE patients, IP-10, MCP-1 and sVCAM were found to be elevated in active SLE patients. We therefore examined the relationship between changes in disease activity and alterations in cyto/chemokine plasma levels.

Methods: Patients (n = 74) satisfying 4 or more ACR criteria were recruited from the University of Toronto Lupus Clinic. 21 healthy controls were also recruited. The plasma concentration of the 3 analytes was determined by Luminex assay. All patients underwent at least 2 assessments during the study period. Disease activity was measured by the SLEDAI-2K and used to segregate patients into a high ($\geq$ 7) and low/moderate (< 7) disease activity groups. A modified SLEDAI-2K was calculated by subtracting the contribution of anti-dsDNA antibodies and complement from the global score. The Mann Whitney non-parametric test was used for comparisons between groups. The statistical significance of correlations was determined by linear regression analysis.

Results: IP-10, MCP-1 and sVCAM were significantly elevated in SLE patients versus controls ($p < 0.0001$ for all). The concentration of all 3 analytes was significantly increased in patients with high versus low/moderate disease activity (IP-10; $p = 0.02$: MCP-1; $p = 0.007$: sVCAM; $p = 0.0002$). There was a moderate positive correlation for IP-10 ($r = 0.42$, $p = 0.0002$), MCP-1 ($r = 0.50$, $p < 0.0001$) and sVCAM ($r = 0.48$, $p < 0.0001$) and the SLEDAI-2K at inception. This association was comparable to that seen for traditional biomarkers (anti-dsDNA antibodies or complement (C3)) and the modified SLEDAI-2K (anti-dsDNA ($r = 0.52$, $p < 0.0001$) and C3 ($r = 0.40$, $p = 0.0004$)). There was a moderate positive correlation between the change in concentration of each analyte and the change in SLEDAI-2K, between the first and 12-month visits (IP-10 ($r = 0.56$, $p < 0.0001$), MCP-1 ($r = 0.58$, $p < 0.0001$) and sVCAM ($r = 0.59$, $p < 0.0001$)). This was stronger than the association between the change in the modified SLEDAI-2K and the change in anti-dsDNA ($r = 0.43$, $p = 0.0001$) or C3 ($r = 0.33$, $p = 0.0041$). Longitudinal analysis ($\geq$ 3 or more assessments) of 34 patients showed that changes in IP-10 mirrored changes in disease activity with high fidelity in 50% of cases.

Conclusion: This study suggests that IP-10, MCP-1 and sVCAM may be useful biomarkers to monitor disease activity, functioning as well, if not better, than traditional biomarkers.

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Factors Determining Response in Patients with Active Lupus Nephritis Treated with Glucocorticoids and Mycophenolate Mofetil (MMF). Chi Chiu Mok[1], Shirley Ying[2], Cheuk-wan Yim[3], Chi Hung To[4] and Eric WL Ng[5], [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Princes Margaret Hospital, Hong Kong, China, [3]United Christian Hospital, Hong Kong, Hong Kong, [4]Tuen Mun Hospital, Hong Kong SAR, Hong Kong, [5]United Christian Hospital, Hong Kong

Purpose: To evaluate the clinical variables associated with response after induction treatment of active lupus nephritis with combined prednisolone and MMF.

Method: Data were extracted from an open randomized controlled trial of the efficacy of MMF vs tacrolimus for induction treatment of lupus nephritis. All patients who were recruited into the MMF arm were treated with a standard protocol of prednisolone (0.6mg/kg/day for 6 weeks and then slowly tapered) and MMF (2-3g/day in 2 divided doses). Clinical response and remission was assessed at 6 months and factors associated with the achievement of a good clinical response were studied by logistic regression analysis.

Results: Data from 53 patients who had completed the induction phase of the controlled trial were analyzed. The mean age was 34.2±11.3 years and the mean SLE duration was 56.4±64 months. 33(62%) patients had first time nephritis. The histological classes of lupus nephritis (RPS/ISN) were IVg (36%), IVs (8%), III (19%) and V/V+III/IV (38%). The activity and chronicity scores were 7.6±3.8 and 2.8±1.6, respectively. 21(40%) patients were hypertensive and 23(43%) were nephrotic at presentation of nephritis. The mean daily MMF dosage

administered was 2.23±0.42g (2g in 74% and ≥2.5g in 26%). At the end of 6 months, 31(58%) patients achieved good clinical response (defined as urine P/Cr <1.0, improvement in lupus serology and urinary sediments and no deterioration of creatinine clearance [CrCl]) by ≥10%) and 5(9%) patients achieved ACR renal remission (CrCl ≥90ml/min, urine P/Cr <0.2 and inactive urine sediments). Regression analysis revealed that the presence of membranous component in the renal histology (RR 0.29[0.09-0.93]; p=0.04) and increasing anti-dsDNA titer at presentation (RR 1.01[1.001-1.012]; p=0.03) were unfavorable factors for a good clinical response. More serious proteinuria at onset was also less likely to respond well to the treatment regimen. 25(47%) patients reported ≥1 adverse events. The distribution of these adverse events was: diarrhea / nausea (13%), major infections requiring hospitalization (13%), minor infections including herpes zoster (62%), transient hyperglycemia (5%) and others (8%).

Conclusion: Combined prednisolone and MMF is a reasonably safe and effective regimen for the initial treatment of active lupus nephritis. Patients with histological evidence of membranous nephropathy, lower anti-dsDNA titer and more serious proteinuria at onset are less likely to achieve a good clinical response. Alternative initial regimens may be considered.

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Efficacy of Combination Therapy with Tacrolimus Plus Mizoribine for Early Lupus Nephritis. Hisanori Shimizu, Hiromichi Tamaki, Eishi Uechi, Ken-ichi Yamaguchi, Yukio Matsui and Masato Okada, St. Luke's International Hospital, Tokyo, Japan

Purpose: The ideal treatment of early lupus nephritis remains to be determined. A regimen including cyclophosphamide has been studied intensively for advanced cases with recurrent and chronic courses, but the long-term adverse effects including risk of malignancy or infertility are not acceptable for reproducitve age women. High dose tacrolimus (0.1mg/kg/day) with corticosteroid have been shown to be effective as an induction regimen but the nephrotoxicity is problematic. We examine low dose tacrolimus in conjunction with mizoribine, which shares the mechanism of action as purine production with MMF, as an initial treatment of early lupus nephritis. This case series described remarkable efficacy in induction and maintenance of lupus nephritis.

Method: In our case series, 8 patients with lupus nephritis received a combination therapy with tacrolimus (0.06mg/kg/day), mizoribine (150mg/day) and corticosteroid. Complete remission was defined as a value of proteinuria < 0.1 g/24 h, normal urinary sediment, serum albumin ≥ 4 g/dl, and a normal value of serum creatinine or no more than 15% above baseline values. A secondary efficacy parameter was partial remission, defined as the resumption of normal or at least a 50% improvement in proteinuria and hematuria, serum albumin ≥ 3.0 g/dl, and a normal value of serum creatinine or no more than 15% above baseline values.

Results: At 6 months, seven of the 8 patients receiving the combination therapy had satisfactory early responses. Seven of the 8 patients had complete remission, and partial remission occurred in the rest one of the 8 patients (Table 1).

Conclusion: In this study, the combination therapy of tacrolimus and mizoribine was effective in inducing and also maintaining remission of lupus nephritis without significant adverse events.

Parameter	Baseline	Week 1	1 Month	3 Months	6 Months
Urine protein (g/24h)	0.64	0.64	0.37	0.10	0.06
eGFR (ml/min)	93.9	95.3	97.3	100.7	116.8
Serum albumin (g/L)	3.66	3.83	3.86	4.00	4.18
Trough of tacrolimus (ng/ml)	-	3.62	3.98	2.64	2.90
Prednisolone (mg/day)	21.8	21.4	13.9	12.7	8.8

Table 1. Average of clinical parameters from the beginning of the study to the 6 months follow-up

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Flare Assessment in Systemic Lupus Erythematosus (SLE) Patients Treated with Rituximab in the Phase II/III EXPLORER Trial. Joan T. Merrill[1], J.P. Buyon[2], R. Furie[3], K.M. Latinis[4], C. Gordon[5], H. Hsieh[6] and P. Brunetta[6], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]NYU School of Medicine, New York, NY, [3]NSLIJHS, Lake Success, NY, [4]Univ. Kansas Medical Center, Kansas City, KS, [5]Univ. of Birmingham, Birmingham, United Kingdom, [6]Genentech, Inc., South San Francisco, CA

Purpose: SLE patients (pts) with moderate to severe disease activity (≥ 1 BILAG A or ≥ 2 BILAG B domain scores) despite background immunosuppressives and corticosteroids, were randomized to placebo (PLA) or rituximab (RTX). Although differences in primary and secondary outcome measures were not observed, an exploratory analysis was performed to evaluate the impact of RTX on the intensity and frequency of disease flares. Our objectives were to assess in those pts who achieved response whether RTX affected: 1) time to moderate or severe flares, 2) annualized flare rates, and 3) prednisone usage during flares.

Methods: The BILAG index was scored every 4 wks for 52 wks after the first study drug treatment. Only pts who achieved response (BILAG C, D, or E scores for all domains before wk 52) were included in this analysis. A severe flare was defined as ≥ 1 BILAG A or > 3 BILAG B domain scores in a pt who previously achieved response; an A flare was defined as ≥ 1 new BILAG A domain scores; a moderate flare was defined as 2 BILAG B domain scores following response. Kaplan-Meier estimates were used to assess time to flare. Annualized flare rates were calculated using the number of flares a patient experienced during the study; the p-value was based on Poisson regression model. Only flares that occurred after the protocol-mandated prednisone taper at 12 wks were incorporated into the analysis of prednisone usage during flares.

Results: A response was achieved in 58 (66.0%) of 88 PLA-treated and 127 (75.1%) of 169 RTX-treated pts during the study, and these patients qualified for subset analysis. Whereas the times to first moderate or severe flare were not different in the two treatment groups, there was a trend towards a prolonged time to first A flare in the RTX group (HR=0.612; p=0.052). Annualized severe and moderate flare rates were similar in both groups, but the mean annualized A flare rate in the RTX group was significantly lower than in the PLA group (0.86 vs 1.41; p=0.038). Prednisone was increased in 20 of 101 (20.7%) of the A flares and was not significantly different between the RTX and PLA groups (24% vs 14%; p=0.204). Pts with the highest initial prednisone dosing (> 60 mg/day) had lower treatment rates (14.0%). In one month, 44/81 (54.3%) of the untreated A flare improved to B or better.

Conclusion: There was no difference between PLA and RTX in preventing moderate or severe flares after a response was achieved. However, RTX treatment was associated with a lower annualized A flare rate, and a trend towards prolonging the time to A flare. Prednisone rescue following A flares was low compared to observational cohorts, possibly reflecting a reluctance to reinitiate prednisone, or reduced BILAG A severity, in this trial.

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SLE Transplanted Patients Have Inferior Patient Survival Compared to Matched Controls. Gudrun E. Norby, Torbjoern Leivestad, Jan Tore Gran and Hallvard Holdaas, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Purpose: Cardiovascular disease is a common cause of morbidity and mortality in systemic lupus erythematosus (SLE), including those treated with renal transplantation. Outcome following renal transplantation in SLE patients is still debated, but most studies report similar outcom for SLE patients and patients transplanted for other causes of end stage renal disease.

The aim of the study was to analyse the outcome of renal transplanted SLE patients with special emphazise on patient and graft survival in a large singe transplant centre unit.

Method: Ninety transplantations were performed in 79 SLE recipients from 1972 to 2005. SLE patients were matched for recipients transplanted for glomerulonephritis diagnosis, excluding recipients transplanted for diabetic nephropathy. For each case, 2 controls were matched for age, donor source (living donor/deceased donor), era (date of transplantation) and sex (when possible).

Results: SLE transplanted patients were mainly women (77%) with an age of 37±13 years at transplantation (controls 37±13 years). This age at transplantation is 20 year younger than the general transplant age in Norway. Living donors were 52% in SLE patients versus 53% in the controls. Death censored graft survival was equal for SLE transplanted patients and matched controls with 1, 5 and 10 years graft survival of 89%, 82% and 71% for SLE recipients, and 91%, 83% and 74% for matched controls (p=0.69).

Patient survival at year one was 94% and 96% for SLE recipients and controls respectively. Corresponding survival at 5 years was 83% and 91% and at 10 year 68 % and 84%. (p=0.023). Of deaths occurring in the control group 34% was due to cardiovascular disease versus 58% in the SLE transplanted patients (p=0.103).

Conclusion: Although graft survival are equal in SLE transplanted patients compared to matched controls, SLE patients have inferior patient survival. Cardiovascular causes were numeric more frequent as a death cause in SLE transplanted patients which have to be focused strongly in the future.

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Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Urinary Biomarker of Disease Activity and Severity in Lupus Nephritis. M. Torres-Salido, J. Cortés-Hernández, M. Urquizu-Padilla, A. Pedrosa, E. Balada, M. Vilardell-Tarrés and J. Ordi-Ros, Systemic Autoimmune Diseases Research Unit. Research Institute Vall d'Hebron. Vall d'Hebron Hospital, Barcelona, Spain

Purpose: : To evaluate urinary (uNGAL) and serum (sNGAL) NGAL levels as a biomarker of active lupus nephritis (LN) in SLE patients. To study the association of uNGAL and sNGAL levels in patients with active LN, partial (PR) and complete (CR) response as well as in patients with non-renal flare and inactive SLE. To establish the relationship between uNGAL levels, the clinical and biological parameters in patients with active LN and to calculate the specificity/sensitivity of this biomarker for distinguishing active renal from non-renal lupus.

Methods: All patients fulfilled the ACR classification criteria for SLE. Active renal disease was defined by active renal sediment, a urinary protein:urinary creatinine ratio (uP/C)>0.5 and/or a biopsy-proven renal disease. Complete remission (CR) was defined by an uP/C<0.2 with an inactive sediment and partial remission (PR) by an uP/C between 0.2-2.0. A non-renal flare was defined by a SLEDAIs≥6 and inactive disease by a SLEDAIs<6. This cross-sectional study included 5 groups of patients and one healthy group control (n=35). Groups are as follow: a group of active LN (n=38), a group of patients with PR (n=56), with CR (n=29), with non-renal flare (n=23) and inactive SLE (n=39). For each patient laboratory parameters (anti-dsDNA, C3, C4, FBC, serum creatinine (sCr) and albumin, estimated glomerular filtration rate (eGFR by Cockcroft-Gault equation) and uSLEDAIs were measured. Both uNGAL and sNGAL levels were measured by ELISA kits according to the manufacturer's instructions (Bioporto, Denmark). ROC curves were used to calculate the specificity/sensitivity.

Results: : The uNGAL values were expressed as median (ng/mL), interquartile range (IQR). In patients with renal flare, uNGAL was significantly higher (47.25 (25.08-88.05) than in those with CR (28.00 (17.10-47.50), PR (34.30 (15.63-61.10), non-renal flare (24.00 (16.30-41.60), inactive SLE (20.00 (12.50-37.80) and healthy control subjects (16.30 (9.14-28.70). Whereas, no significant differences in uNGAL values were found between active LN and patients with PR, the differences were statistically significant with the rest of groups ($p< 0.05$). On the other hand, the sNGAL levels only could differentiate the active LN from the inactive SLE group ($p= 0.0084$). The uNGAL values in patients with active LN correlated significantly with uSLEDAIs ($R= 0.3527$, $p< 0.0001$), and uP/C ratio ($R= 0.2282$, $p= 0.0018$), eGFR ($R= -0. 1784$, $p=0.0151$), and serum albumin ($R= -0.2306$, $p= 0.002$). The uNGAL levels showed ROC profiles, with AUC values equal to 0.69, reflecting an acceptable sensitivity and specificity for discerning active LN from non-renal flare SLE patients.

Conclusion: uNGAL is a promising potential biomarker of activity and severity in LN. Our results indicate that uNGAL can be a useful tool in the management of the patients with LN.

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Renal Outcome and Risk Factors for End-Stage Renal Disease in a Cohort of 100 Patients with Lupus Nephritis: A Very Long-Term Follow-up Study. Mikkel Faurschou[1], Anne-Lise Kamper[1], Henrik Starklint[2] and Søren Jacobsen[1], [1]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [2]Vejle Hospital, Vejle, Denmark

Purpose: While the short- and medium-term outcome in lupus nephritis (LN) has been described in a range of studies, data on the very long-term prognosis of LN patients are scarce. The aim of the present study was to describe the renal outcome and identify baseline predictors of end-stage renal disease (ESRD) in an unselected cohort of patients diagnosed with LN between 1971 and 1995 and followed throughout 2007.

Methods: 100 patients with LN (WHO classes I-VI) were included in the study. For all patients, a variety of clinico-pathological variables were recorded at date of first renal biopsy (study baseline). Predictors of ESRD were identified through univariate and multivariate analyses.

Results: The median duration of follow-up was 13.7 years (range: 0.01-36.9 years). In total, 25 patients (25%) progressed to ESRD. New cases of ESRD occurred throughout the follow-up period, and the cumulative renal survival after 5, 10, 15, and 20 years was 86%, 83%, 76%, and 73%, respectively. In univariate analyses, statistically significant baseline predictors of ESRD included: duration of nephritis manifestations before renal biopsy ≥6 months; systolic blood pressure ≥180 mmHg; s-creatinine ≥140 µmol/L; advanced sclerosing (WHO class VI) nephritis; tubular atrophy; and glomerular sclerosis. Duration of nephritis manifestations prior to renal biopsy ≥ 6 months and s-creatinine ≥140 µmol/L emerged as the strongest combination of independent risk factors for ESRD in sex-, age-, and treatment-adjusted multivariate analyses (relative hazard ratios: 4.5 and 4.6, respectively). Patients treated with cyclophosphamide for induction of remission (n=44) did not have a lower risk of progression to ESRD than patients treated otherwise.

Conclusion: In the present LN cohort, new cases of ESRD continued to appear even after prolonged follow-up. The current data confirm the importance of early diagnosis and therapy in LN. However, our findings also underscore the limitations of traditional immunosuppressive regimens used for the treatment of patients with LN.

Disclosure: M. Faurschou, None; **A. L. Kamper**, None; **H. Starklint**, None; **S. Jacobsen**, None.

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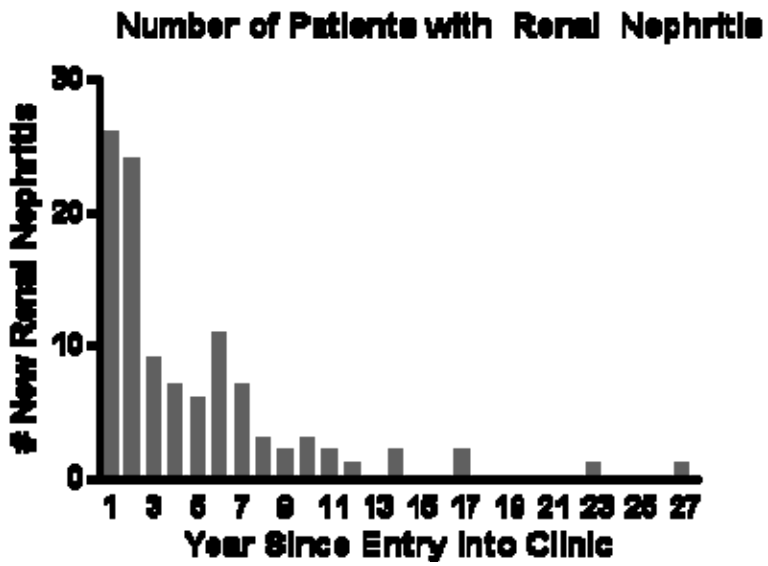
Time to Development of Nephritis in Patients with SLE. Debra Dye-Torrington[1], Dominique Ibañez[1], Murray Urowitz[2] and Dafna Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Lupus nephritis is a frequent and serious complication of SLE and is seen in approximately 50% of patients with SLE. This complication is often present at time of diagnosis but in some patients it may occur later in the course of disease. We investigate the first occurrence of nephritis at inception and over the course of the disease in an inception cohort of patients followed in a single centre and examined predictive factors for late occurrence of nephritis.

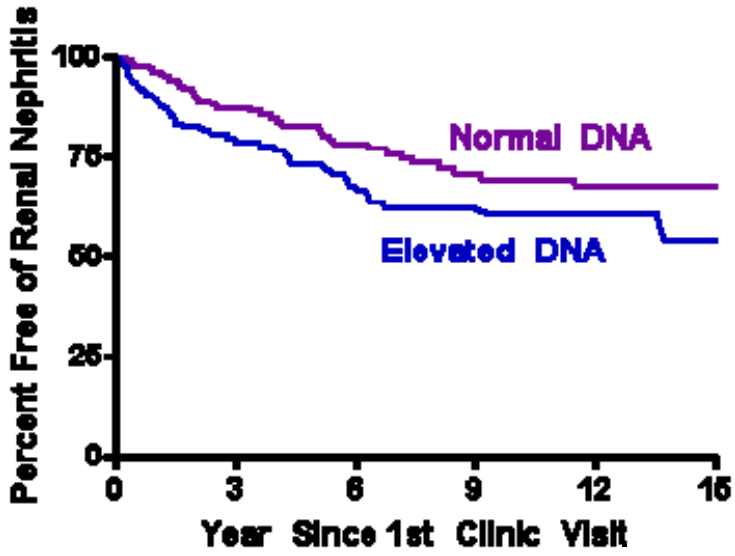
Methods: Inception patients seen in clinic within one year of diagnosis of SLE were selected from a single centre cohort followed in an observational cohort study. Lupus nephritis was defined as sterile hematuria and/or pyuria, granular casts, proteinuria (>500mg/24hr), or elevated serum creatinine (defined as greater than 120µmols/l) on two or more consecutive visits, or dialysis, transplant or WHO renal biopsy ≥ class 2. Incidence of lupus nephritis was determined for each year following entry into the clinic. In patients with no lupus nephritis at entry into the clinic, a Cox survival regression analysis was run, using the values at 1st clinic visit to predict development of future renal nephritis. Included in the model were sex, disease duration, SLEDAI-2K, SLICC/ACR damage index (SDI), steroids, antimalarial, immunosuppressant, race, complement and dsDNA. Selection of variables retained in the model was done through the stepwise approach. Kaplan-Meier curves were done for significant predictors

Results: In a cohort of 633 patients with SLE, 382(57 %) did not have lupus nephritis at inception. These were 87% female, mean age at SLE diagnosis 36yrs. 77% Caucasian, 8% Black, 65% Chinese, 10% Other. Their disease duration at first clinic visit was 0.24 yrs, SLEDAI-2K was 8.63 and SDI 0.07. 46% were taking glucocorticoids, 35% antimalarials and 8% immunosuppressants. The mean serum creatinine

was 73, 46% had low complement and 48% elevated anti-DNA antibodies. Of the 382 patients, 107 (28%) eventually developed lupus nephritis – 77% of them within the first 5 years.



Cox regression analysis revealed that only anti-DNA antibody was a statistically significant predictor with HR = 1.59 (95% CI 1.01, 2.48, p=0.04). Kaplan-Meier curve comparing the development of nephritis between patients with normal vs. elevated anti-DNA antibody at 1st clinic visit showed a statistically significant difference (Wilcoxon p=0.04)



Conclusion: 28% of patients with SLE without nephritis at inception develop lupus nephritis later in their course. The majority occur within the first 5 years, but some patients develop nephritis later. The only predictor for future development of lupus nephritis is the presence of anti-DNA antibody at inception.

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Renal Outcome of Lupus Nephritis Is Different Between Class IV-G (A) and IV-G (A/C). Takashi Kuroiwa, Noriyuki Hiramatsu, Ken Kayakabe, Noriyuki Sakurai, Takayuki Matsumoto, Akito Maeshima, Keiju Hiromura and Yoshihisa Nojima, Gunma University Graduate School of Medicine, Maebashi, Japan

Purpose: We previously reported that in the international Society of Nephrology/Renal Pathologist Society (ISN/RPS) 2003 classification of lupus nephritis (LN), renal outcome was worst in cases in diffuse global LN involving glomerular chronic lesion (class IV-G (A/C)). In contrast, cases in class IV-G with active lesion alone (IV-G (A)) had good renal outcome. In this study, we reevaluated this observation in the cohort of increased patients and extended follow-up period. We also compared difference of clinical characteristics between class IV-G (A) and IV-G (A/C).

Method: A total of 110 patients with LN who underwent renal biopsy during 1986 to 2007 in our hospital were classified according to ISN/RPS 2003 criteria. Outcome was compared across histological classes by Kaplan-Meier analysis with endpoint as survival without end-stage renal disease and doubling of the serum creatinine. Complete or partial remission (CR or PR) was defined as proteinuria <0.5 g/creatinine (g/Cr) or <3.0 g/Cr with >50% decrease, respectively, in the presence of stabilized renal function.

Results: Mean patient age was 36.3 yrs and the median observation period was 7.4 yrs. The relative frequency for each class was as follows: class I (minimal mesangial LN) 0%, class II (mesangial proliferative LN) 13%, class III (focal LN) 17%, class IV (diffuse LN) 59% and class V (membranous LN) 11%. Within class IV, diffuse segmental (class IV-S) was 25% and diffuse global (class IV-G) 75%. Patients who reached endpoint was 14% in class II, 5% in class III, 13% in class IV-S, 14% in class IV-G, and none in class V. Statistically significant difference in outcome by Kaplan-Meier analysis was not observed among all classes and between class IV-S and IV-G. However, when compared between class IV-G (A) and IV-G (A/C), outcome was significantly worse in IV-G (A/C) cases (p=0.014). Response to the therapy was better in class IV-G (A), as ratio of patients who achieved CR/PR 6 months after induction therapy was 89% in IV-G (A) and 63% in IV-G (A/C). There was a trend that treatment was more intensive in IV-G (A), as the use of immunosuppressant was 68% in IV-G (A) and 52% in IV-G (A/C). Ratio of patients who started treatment within 12 months from LN onset was 86% in class IV-G (A) and 48% in class IV-G (A/C), suggesting that the delay in diagnosis/treatment is in part associated with development of glomerular chronic lesions. Coexistence of class V and frequency of renal flare during the observation period were comparable between both groups.

Conclusion: This study confirmed our previous observation that in Class IV-G cases, renal outcome differed in the presence of chronicity. Thus, the revised classification of LN is clinically valuable in identifying different renal outcomes among patients with diffuse L.

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The ISN/RPS Classification of Renal Biopsy as a Determinant of Prognosis in a Prospective Lupus Cohort. D. M. Tulloch-Reid, D.D. Gladman, P. R. Fortin, A. Herzenberg, Edward Cole and M.B. Urowitz, University Health Network, Toronto, ON

Purpose: The International Society of nephrology/renal pathological Society(ISN/RPS)classification system for lupus nephritis was introduced in 2003 to reduce ambiguities and to provide a clearer standardized framework for clinical-pathological correlation. Prognostic studies utilizing this classification have been limited by sample size, follow-up time and methodology producing conflicting results. We aimed to assess the ISN/RPS classification as a determinant of prognosis in a prospective cohort.

Method: Patients followed prospectively in a single centre were studied. All met American College of Rheumatology (ACR) criteria for systemic lupus (SLE) and had a renal biopsy following entry into the cohort and a minimum of 3 years follow-up. Patients had clinical and laboratory assessment at 2-6 month intervals according to a standard protocol. The first available biopsy suitable for ISN scoring was used for each patient. Survival analysis was used to assess patient event-free survival with respect to outcomes of death and sustained renal deterioration (ESRD, sustained creatinine doubling or increase to >200mmol/l from baseline at time of biopsy, dialysis or tranplantation) for each ISN/RPS class.

Results: 189 patients biopsied between 1970 and 2004 were included, 84.1% female and 66.7% Caucasian. The mean age at biopsy was 35.5 years, median disease duration 2.9 years. 49% of patients had purely proliferative classes, 12.7% membranous and 5.9% combined classes,

Over a follow-up period of up to 30 years, 59 patients experienced a composite outcome of death/ESRD. Most cases of renal deterioration occurred in the first 5 yrs and predominantly in classes III and IV, while most deaths occurred later and at a similar rate across classes. No significant difference in median time to event were detected among the individual ISN classes with respect to death, renal deterioration or a composite of the two.

No difference was found between Class III and Class IV compared in the rate of any outcome, or between Class III /IV biopsies occurring with class V vs. those without. However, within class IV, ESRD occurred more frequently (RR 1.31 [1.10, 1.56]) in patients with predominantly global vs. segmental lesions. On crude bivariate analysis ISN classes III & IV together were associated with increased 10 year event rates for ESRD (RR 1.16 [1.06, 1.26]) but not for death, compared with classes I, II and V.

Persons who experienced the outcomes of interest were significantly older, had longer disease duration, higher blood pressure, higher creatinine at time of biopsy, higher chronicity index (CI)and were more likely to have been biopsied prior to 1985.

On survival analysis using the composite outcome, a trend toward decreased survival with class III/IV compared with remaining classes was lost in a multivariate model that controlled for baseline creatinine, age, CI and the presence of hypertension. However, when assessed using ESRD only, Class III/IV was a strong predictor of ESRD [HR 3.4] with only CI significantly influencing the model.

Conclusion: The ISN/RPS classification is a useful independent predictor of renal deterioration but not mortality in our cohort.

Disclosure: D. M. Tulloch-Reid, None; **D. D. Gladman**, None; **P. R. Fortin**, None; **A. Herzenberg**, None; **E. Cole**, None; **M. B. Urowitz**, None.

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Outcomes in Biopsy-Proven Lupus Nephritis. Evaluation of 190 Caucasian Patients From a Single Center. Manuel Ramos-Casals[1], Rafael Belenguer[2], Antoni Siso[3], Albert Bove[1], Pilar Brito-Zeron[1], Candido Diaz-Lagares[1], Marta Perez-de-Lis[1], Myriam Gandia[1] and Antonio Coca[4], [1]IDIBAPS, Hospital Clinic, Barcelona, Spain, [2]Hospital 9 d'Octubre, Valencia, Spain, [3]CAP Les Corts, Barcelona, Spain, [4]ICMiD, Hospital Clinic, Barcelona, Spain

Purpose: To describe the natural history of lupus nephritis (LN) in a historical cohort of 190 Caucasian patients diagnosed with biopsy-proven LN followed in a single reference center.

Method: Six hundred and seventy patients with systemic lupus erythematosus (SLE) consecutively followed in our department from 1970 until 2006 were evaluated. All patients fulfilled the 1997 revised criteria for the classification of SLE. Caucasian patients (white, Spanish-born) with biopsy-proven LN were selected as the study population.

Results: One hundred and ninety patients (170 females and 20 males) were included. The mean age at LN diagnosis was 31 years at diagnosis of LN. Renal biopsy showed type I LN in 8 (4%) patients, type II in 33 (17%), type III in 46 (24%), type IV in 72 (38%), type V in 28 (15%) and type VI in 3 (2%) patients. Induction remission was achieved in 85% of patients with types I and II, in 78% of those with type III, in 70% of those with type IV and in 32% of those with type V. After a mean follow-up of 2391 patient-years, 62 (33%) patients developed chronic renal failure and 18 (9%) evolved to end-stage renal disease. Adjusted multivariate Cox regression analysis identified male gender (HR 4.33) and raised creatinine at diagnosis of LN (HR 5.18) as independent variables for renal failure. After a mean follow-up of 2391 patient-years, 19 (10%) patients died at a mean age of 46.5 ± 4.1 years. Survival was 92% after 10 years of follow-up, 80% after 20 years and 72% after 30 years. The 10-year survival rate according to the LN types was 100% for type II, 91% for type III, 93% for type IV and 95% for type V. Patients who died had received antimalarials less frequently (5% vs 30%, p=0.027) in comparison with survivors.

Conclusion: Our results suggest that biopsy-proven LN in Caucasian patients has an excellent prognosis. Ethnicity should be considered a key factor when the prognosis and therapeutic response to different agents is evaluated in patients with LN.

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Lupus Nephritis: Outcome After Discontinuation of Immunosuppression. Oier A. Barrutia, Shirish.R Sangle, Jose Vargas, David P. D'Cruz and Munther A. Khamashta, Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom

Purpose: Lupus nephritis (LN) remains the strongest predictor of morbidity and mortality in SLE patients. Management of LN involves long term immunosuppression. It is not clear how long and in whom the immunosuppressive therapy should be continued and which are the best predictors for flares after the withdrawal.

Method: We retrospectively reviewed 49 patients, since 1985 in our dedicated lupus nephritis clinic with lupus nephritis patients who received remission maintaining therapy such as azathioprine, mycophenolate mofetil, cyclophosphamide along with prednisolone and antimalarials. All had discontinued the therapy due to stable LN and/or pregnancy desire. All of them were stable when immunosuppressive therapy was stopped. Patients who remained without therapy at least for 6 months were included. Patients' data regarding serology, complement levels, urinary protein creatinine ratio (PCR), estimated glomerular filtration rate (EGFR), antiphospholipid antibody status, previous remission inducing and maintenance therapy, type of renal biopsy (WHO criteria) and other drugs were collected retrospectively and analyzed. Longitudinal regression model was used as multivariate analysis, controlled for age at flare, anti-dsDNA, complement level, serum albumin,PCR ratio and EGFR.

Results: All but 2 patients (4.1%) were female. 59.2% were Caucasian, 30.6% Afro-Caribean and 10.2% Asian. Median age of the patients was 29.33 ± 3.32 years. Median follow up period was 51.67 ± 48.05 months. Nine of 49 (18.4%) patients had renal flare;. There was no correlation between type of LN, previous therapy, complement levels, aPL status and drugs such as hydroxychloroquine. A univariate analysis showed positive correlation between older age at flare, persistent positive anti-dsDNA antibodies, hypoalbuminaemia, high PCR ratio and an EGFR under 85 ml/min. At multivariate analysis, PCR ratio was the best predictor (OR:1.03, CI:1.003-1.05).

Patient (n=49)	**Without flare (n=40)**	**Flared-up (n=9)**	**p value**
Median age (median)	**29.33 ± 3.32**	**36.67 ± 4.93**	**0.03**
Persistent anti-dsDNA	**5 (12.5%)**	**4 (44%)**	**0.046**
Positive aPL	**26 (65%)**	**4 (44%)**	**0.25**
Median Serum albumin (g/L)	**43.20 ± 2.94**	**37.33 ± 3.33**	**0.016**
Median EGFR<85 (mL/min)	**16 (40%)**	**8 (89%)**	**0.007**
Pr/Cr ratio* (median)	**27.93 ± 13.65**	**180.44 ± 113.07**	**<0.0001**
Biopsy (WHO class II – V)	**40**	**9**	**0.61**
Antimalarials	**23 (57%)**	**7 (78%)**	**0.24**
Median duration of immunosuppression (years)	**5.06 ± 1.72**	**5.33 ± 2.69**	**0.68**

Notes. aPL: antiphospholipid antibodies; AZA: azathioprine; CPA: cyclophosphamide; MMF: mychophenolate mofetil; MTX: methotrexate; CYC: cyclosporine; EGFR: estimated glomerular filtration rate; Pr/Cr: Protein/Creatinine. ***:** significant at multivariate analysis.

Conclusion: In patients with LN old age, positive anti-dsDNA antibodies, high protein creatinine ration and low albumin may indicate adverse outcome in whom immunosuppressive therapy was discontinued.

Disclosure: O. A. Barrutia, None; **S. R. Sangle**, None; **J. Vargas**, None; **D. P. D'Cruz**, Aspreva, 5 ; **M. A. Khamashta**, None.

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Comparison of Different Formulas to Estimate Renal Function in Mexican Systemic Lupus Erythematosus Patients. Marco U. Martínez-Martínez, Martín Magaña-Aquino, Jaime A. Borjas-García, Lilia Llamazares-Azuara and Carlos Abud-Mendoza, Faculty of Medicine, Universidad Autónoma de San Luis Potosí and Hospital Central, San Luis Potosí, Mexico

Purpose: The National Kidney Foundation (NKF) and the European Consensus of Lupus Nephritis (ECLN) suggest evaluate the glomerular filtration rate (GFR) with the Modification of Diet in Renal Disease (MDRD) study equation. This formula agrees with the gold standard for GFR mainly in patients with low GFR (< 60 ml/min/1.73 m^2 of body surface index [BSI]); recently the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was published with excellent correlation between iothalamate in low and high GFR. In spite of the NKF and ECLN recommendation, CCl is still used in practice. *Objective:* Assessment of the performance of the simplified MDRD equation (sMDRD), 24 h creatinine clearance (CCl), Cockcroft Gault equation (CG), CG equation calculated with ideal body weight (CGi), Mayo Clinic Quadratic equation (MCQ) and the CKD-EPI to estimate the GFR in Mexican patients with systemic lupus erythematosus (SLE).

Methods&Patients: Cross sectional analysis. In ≥18 years old Mexican patients with SLE (ACR) demographic data, serum and urine creatinine (24 h collection) were taken to calculate GFR using the different equations. We consider the CKD-EPI as the gold standard and this equation was compared with all the others to evaluate bias (differences in median), correlation (r), r square statistic (R^2), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), percentage of measurement of GFR between 70-130% of the GFR measured by the CKD-EPI formula (P30) and computed the receiver operating characteristic (ROC) curves. We evaluated 24 h urine collection for creatinine excretion compared with those calculated for weight (between 80-120% was considered adequate). All the patients were classified into 1-5 NKF stages.

Results: We included 302 SLE patients. With the CKD-EPI, 181 (59.9%) were in stage 1, 71 (23.5%) in stage 2, 37 (12.3%) in 3, 10 (3.3%) in 4 and 3 (1%) were in stage 5. (Table 1).

Formula	GFR (1.73 m^2)	r	R^2	AUC
sMDRD	90.2	0.958	0.918	0.999
CCl	84.5	0.727	0.529	0.865
CG	102.2	0.931	0.866	0.973
CGi	87.9	0.929	0.863	0.968
MCQ	101.5	0.877	0.769	0.913
CKD-EPI	93.48			

The best sensitivity (98%), specificity (98%) and NVP (99.6%) to classify in NKF stages 3-5, were for the sMDRD, best PPV was for CGi (97.1%). P30 was 99.3% for sMDRD, 77.2% for CCl, 91.1% for CG, 96.6% for CGi and 74.5% for MCQ. Only 52% (157/302) were considered to have had adequate urine collections, and when we re-evaluated these 157 patients, the different statistical results improved for CCl (r, R^2, AUC and P30); r, R^2 and AUC was better for sMDRD in low GFR.

Conclusion: In Mexican SLE patients the different formulas had a good global correlation, but the different formulas can misclassify the patients in different stages of renal function, and although the NKF and the ECLN suggests MDRD to estimate GFR, we suggest the new CKD-EPI as the best option to estimate the GFR in SLE patients either in low or high GFR. Moreover CCl should not be considered as safe to calculate GFR. Higher cost of CCI should also be considered.

Disclosure: M. U. Martínez-Martínez, None; **M. Magaña-Aquino**, None; **J. A. Borjas-García**, None; **L. Llamazares-Azuara**, None; **C. Abud-Mendoza**, None.

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No Increase in the Incidence of Malignancy with Immunosuppressive Use in SLE. Michelle Petri[1] and Laurence Magder[2], [1]Johns Hopkins Univ, Baltimore, MD, [2]University of MD, Baltimore, MD

Purpose: SLE itself increases the risk of malignancy, including non-Hodgkins lymphoma. Immunosuppressive drug use has increased the risk of later malignancy in transplant recipients. We determined the risk of malignancy in a prospective SLE cohort, based on use of immunosuppressive drugs, mycophenolate mofetil (MMF), azathioprine (AZA), and methotrexate (MTX).

Method: 1667 SLE patients, with 6849 person-years of follow up were included.

Results: Cancer rates during cohort participation, by age, sex, race, and exposure to immunosuppressive drugs are shown in the table.

Group	Number of person-years observed	Number of incident cases of cancer	Rate (95% CI) per 1000 person-yrs,	Age-adjusted Rate Ratios	Age-adusted P-value
All	9830	92	9.4 (7.6, 11.5)		
Agegroup					
18-39	4932	26	5.3 (3.6, 7.7)		
40-49	2633	30	11.4 (8.0, 16.3)		
50-59	1508	21	13.9 (9.1, 21.4)		
60-69	566	10	17.7 (9.5, 32.8)		
70+	139	5	26.4 (11.0, 3.4)		
Sex					
Female	8108	80	8.8 (7.1, 10.9)	Reference	
Male	722	12	16.6 (9.4, 29.3)	1.8 (1.0, 3.3)	.059
Ethnicity					
African-American	4385	39	8.9 (6.5, 12.2)	Reference	
Caucasian	4975	52	10.5 (8.0, 13.7)	1.1 (0.8, 1.7)	
Other	469	1	2.1 (0.3, 15.1)	Too few	.51
Prior MMF exposure					
None	8671	77	8.9 (7.1, 11.1)	Reference	
Only in last 2 years	487	4	8.2 (3.1, 21.9)	1.1 (0.4, 3.0)	.87
Some 2+ years ago	672	11	16.4 (9.1, 29.6)	1.8 (1.0, 3.4)	.071
Cumulative MMF					
None	8671	77	8.9 (7.1, 11.1)	Reference	.35
< 1 year	433	5	11.5 (4.8, 27.7)	1.5 (0.6, 3.8)	.16

1-3 years	411	6	14.6 (6.5, 32.4)	1.8 (0.8, 4.2)	.69
3+years	313	4	12.8 (4.8,34.1)	1.2 (0.5, 3.4)	
Prior AZA exposure					
None	8768	79	9.0 (7.2, 11.2)	Reference	
Only in last 2 years	392	5	12.7 (5.3, 30.6)	1.6 (0.7, 4.0)	.29
Some 2+ years ago	669	8	12.0 (6.0, 23.9)	1.4 (0.7, 2.9)	.38
Cumulative AZA					
None	8768	79	9.0 (7.2, 11.2)	Reference	
< 1 year	397	4	10.1 (3.8, 26.8)	1.4 (0.5, 38)	.54
1-3 years	319	5	15.7 (6.5, 37.7)	1.9 (0.8, 4.6)	.17
3+years	346	4	11.6 (4.3, 30.8)	1.2 (0.5, 3.4)	.68
Prior MTX exposure				Too Few	
None	9321	88	9.4 (7.7, 11.6)		
Only in last 2 years	203	2	9.9 (2.5, 39.4)		
Some 2+ years ago	305	2	6.6 (1.6, 26.2)		
Cumulative MTX				Too few	
None	9321	88	9.4 (7.7, 11.6)		
< 1 year	208	3	14.4 (4.6, 44.7)		
1-3 years	189	0	0		
3+years	111	1	9.0 (1.3, 64.2)		

Conclusion: Use of MMF or AZA did not significantly increase the risk of malignancy over the reference group of non-users. There was no difference between MMF and AZA. However, MMF exposure 2 or more years in the past did have a non-significant increase (p = 0.071, age-adjusted rate ratio 1.8).

Disclosure: M. Petri, None; **L. Magder**, None.

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Seasonal Variation in the Incidence of Disease Flares in Systemic Lupus Erythematosus (SLE): Relationship with Weather Parameters and Ultraviolet Light Intensity. Chi Hung To[1], Chi Chiu Mok[2], Ling Yin Ho[3] and Carrel Yu[1], [1]Tuen Mun Hospital, Hong Kong SAR, Hong Kong, [2]Tuen Mun Hospital, Hong Kong, Hong Kong, [3]Tuen Mun Hospital, Hong Kong SAR

Purpose: To examine the seasonal variation in disease flares of SLE with regard to individual organ systems and their relationship with weather parameters and environmental ultraviolet light intensity

Method: SLE patients who were followed up in our clinics between 2000 and 2008 were studied. Details of disease flares, defined by the SELENA-SLE flare instrument, were retrieved from review of the electronic medical records. Disease activity scores during the flare episodes were measured by the SELENA-SLEDAI. The monthly rates of disease flares (mild / moderate and severe) and of individual organ systems were calculated. Flares in five organ systems (cutaneous and musculoskeletal, serositis, hematologic flare, renal and neuropsychiatric) were defined by using the individual components of SLEDAI and the SELENA-SLE flare instrument. The rate of SLE

flares was correlated by Pearson's correlation with a number of weather parameters which included mean and maximum temperature, relative humidity, total rainfall, duration of sunshine and mean ultraviolet light intensity index each month as released by the Royal Observatory of Hong Kong.

Results: 452 SLE patients were studied. There were a total of 425 mild / moderate SLE flares (0.87/100 patient-months) and 314 severe flares (0.64/100 patient-months) recorded. There were a total of 300 cutaneous and musculoskeletal flares (0.61/100 patient-months), 51 serositis flares (0.11/100 patient-months), 196 hematologic flares (0.41/100 patient-months), 196 renal flares (0.41/100 patient-months) and 49 neuropsychiatric flares (0.10/100 patient-months). The monthly rate of severe SLE flare was lowest in June and highest in January and the difference was statistically significant (p=0.042). Renal flare was significantly more frequent in the months January to March compared to June (p=0.041, 0.048, 0.043, respectively). The monthly rates of severe lupus flare and renal flare were negatively associated with the mean daily temperature (r=-0.73, p<0.01; r=-0.68, p=0.015, respectively), mean daily maximum temperature (r=-0.72, p<0.01; r=-0.67, p<0.016), total monthly rainfall (r=-0.73, p<0.01; r=-0.75, p<0.01) and mean ultraviolet light intensity index (r=-0.63, p=0.03; r=-0.69, p=0.012). The monthly total duration of sunshine was associated positively with cutaneous and musculoskeletal flare (r=0.62, p=0.03), but negatively with neuropsychiatric flare (r=-0.65, p=0.021).

Conclusion: Seasonal variation in lupus flares in different organ system exists. Skin and joint lupus flares were more frequent in periods of more prolonged sunshine but were not associated with environmental ultraviolet light intensity. Severe lupus flare and renal lupus more commonly occurred during the winter months which were associated with lower temperature, humidity and ultraviolet light intensity.

Disclosure: C. H. To, None; **C. C. Mok**, None; **L. Y. Ho**, None; **C. Yu**, None.

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A Role for APRIL in the Development of SLE- and RA-Associated Lymphomas? Ingrid E. Lundberg[1], Björn Löfström[2], Carin Backlin[3], Christer Sundström[3], Tom Pettersson[4], Anders Ekbom[5] and Eva Baecklund[6], [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Uppsala University, Sweden, [4]Helsinki University Hospital, Helsinki, Finland, [5]Karolinska Institutet, Stockholm, Sweden, [6]Rheumatology clinic, Uppsala, Sweden

Purpose: Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) are associated with an increased lymphoma risk, in particular diffuse large B cell lymphoma (DLBCL). Involved biologic mechanisms are still unknown. A PRoliferating-Inducing Ligand (APRIL), a cytokine of the TNF superfamily, regulates B-cell activation and survival. It is overexpressed both in lymphomas like DLBCLs and in RA/SLE-patients. We hypothesise that APRIL may have a role in the development of DLBCL in RA and SLE.Investigate APRIL expression in lymphoma tissue from RA/SLE patients with DLBCLs using general population DLBCLs as controls and correlate to clinical characteristics.

Method: Linked, previously presented, registry studies of the Swedish Hospital Discharge Register and the Swedish Cancer Register between 1964 and 1995 yielded 98 patients with RA and 13 with SLE who developed DLBCL. (One SLE-DLBCL Helsinki patient also included). Diagnoses were verified using current ACR criteria for RA and SLE and the WHO classification of lymphoma. General DLBCL patients from Uppsala Region without chronic inflammatory disease were used as controls (n=63). Lymphoma specimens were sectioned and stained with Aprily-2 (Alexis). Percentage APRIL positive staining lymphoma cells were counted in light microscope. The results of the controls were divided in quartiles and the result of the RA/SLE lymphomas compared to the controls using the χ^2test. Cumulated disease activity (from clinical data abstraction) in RA was scored and measured as area under the curve (AUC).

Results: Mean percentage of stained cells in SLE-, RA- and control-DLBCLs was 25, 11 and 12 %. The quartile distribution of the stainings was significantly different in RA DLBCLs (45,14,11,28) and SLE DLBCLs (1,0,0,13) compared to controls. In RA, an association was seen between high cumulated disease activity and high % APRIL positive cells (mean AUC in quartile 1= 636, quartile 4=968).

Conclusion: Our data reflect the heterogeneity of the DLBCL subtype and suggest that APRIL could be of particular importance in the development of lymphoma in SLE and in development of lymphoma in a subset of RA patients with high cumulated disease activity.

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Assessment of Lupus (SLE) Mortality in a Patient-Based Community Data Bank. Frederick Wolfe[1], KD Michaud[2], Tracy Li[3] and RS Katz[4], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]U Neb Med Cntr and NDB, Omaha, NE, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Rheumatology Associates, Chicago, IL

Purpose: SLE studies usually derive from the clinic where the emphasis is on physician and laboratory assessments. Although patient-based assessments may be ideal for assessment of patient reported outcomes and mortality, there have been only rare and small systematic, longitudinal studies of SLE patient outcomes. We have reached into rheumatology practices to develop a community SLE databank to assess SLE outcomes, to determine the risk and predictors of mortality, and to confirm the utility of patient-based databanks in SLE.

Methods: We studied 1,324 patients with SLE, 2,809 with fibromyalgia (FM), 3,825 with non-inflammatory rheumatic disorders (NIRD), and 14,444 with rheumatoid arthritis (RA). Patients were assessed semi-annually by questionnaires that included detailed demographics, all patient-reported outcomes, treatments, and comorbid conditions. The risk of mortality was assessed by age and sex adjusted time-varying Cox regression analyses, expressed as hazard ratio (95% confidence interval). The discriminatory ability of baseline predictors was assessed by Harrell's c (C).

Results: At entry, median age and disease duration of SLE patients was 48.9 and 11.8 years, and 94% were women. Lifetime treatments included corticosteroids (CS) 81.3%, hydroxychloroquine, 82.9%, methotrexate 28.6%, azathioprine 26.0%, and cyclophosphamide 13.0%. During a mean follow-up of 2.5 years, range (0.5 to 10.1 years), 30 of the 1,324 SLE patients died. The resultant estimated 5-year survival was 94.9% (91.5% to 97.0%). Compared with patients with NIRD, FM, and RA, the hazard ratio (HR) for mortality was 2.8 (1.9, 4.1), 3.6 (2.4, 5.4), and 2.1 (1.5, 3.1). In general, the strength of comorbidity predictors was similar across all rheumatic disorders. The HR for stroke was 7.7 (1.7, 31.3), for myocardial infarction 3.3 (0.4, 25.1), and for GI ulcer 3.6 (1.1, 12.2). But confidence intervals overlapped between SLE and the other disorders, and no definite differences among disorders could be identified. Using baseline predictors in patients with SLE, we found that age (HR 1.5 (1.1, 2.1)) per 10 years and being male (HR 3.5 (1.4, 8.8)) increased mortality risk. After adjustment for age and sex, only household income (HR 1.2 per $US 10,000 reduction in income), among demographic predictors, was significantly associated with mortality. In particular, education, ethnicity, and marital status were not significant in this model. Mortality was best predicted by baseline HAQ-II (HR 3.9 (2.1, 7.3), C=0.82), compared with HAQ (HR 1.7 (1.0, 2.7), C=0.67), and SF-36 PCS (HR 0.95 (0.92, 0.99), C=0.75). In multivariable analyses only HAQ-II was significant. Other significant multivariable predictors of mortality included age sex, household income, preexisting renal, cardiovascular and GI ulcer conditions, and azathioprine (HR 1.9 (1.4, 2.6)), prednisone (HR 1.7 (1.0, 2.9)), and hydroxychloroquine (HR 0.5 (0.3, 0.7)). C for the combined model was 0.89.

Conclusion: Patient-based outcomes are highly discriminative for mortality, and functional assessment (HAQ-II) is the best overall predictor of SLE mortality. Patient-based databanks are effective in assessing lupus mortality and other outcomes.

Disclosure: F. Wolfe, Bristol-Myers Squibb, 2 ; **K. Michaud**, None; **T. Li**, Bristol-Myers Squibb, 3 ; **R. Katz**, None.

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Effects of SLE Activity On Lymphoma Risk: Preliminary Results of a Case-Cohort Study. S. Bernatsky[1], R. Ramsey-Goldman[2], Murray Urowitz[3], Dafna Gladman[4], G. Ruiz-Irastorza[5], S C. Bae[6], P. R. Fortin[4], S. Manzi[7], Y. St. Pierre[1], J. L. Lee[1], E. Turnbull[1], A. E. Clarke[1] and Systemic Lupus International Collaborating Clinics, [1]MUHC, Montreal, QC, [2]SLICC, Chicago, IL, [3]U of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]Universidad del País Vasco, Bizkaia, Spain, [6]Hanyang Univ, South Korea, [7]University of Pittsburgh, Pittsburgh, PA

Purpose: It is increasingly recognized that persons with autoimmune rheumatic diseases have heightened risks for certain cancers, particularly lymphoma. The role of immune system activity in driving cancer risk is incompletely understood. Our purpose was to examine if, in systemic lupus erythaematosus (SLE), disease activity increases lymphoma risk.

Methods: A case-cohort study was performed within a multi-site international SLE cohort; subjects were linked to regional tumour registries to determine lymphoma cases occurring after entry into the cohort. Controls represented a sub-cohort randomly selected at cohort entry. Disease activity was assessed using the adjusted mean SLE Disease Activity Index (AMS) scores in each case-control set, as of the index time for each event. We calculated the hazard ratio (HR) for lymphoma related to AMS scores (as a continuous variable), in models that

controlled for drugs (immunosuppressive medications, anti-malarial drugs, glucocorticoids), smoking, age, sex, race/ethnicity, geographic location, and SLE duration. Drug exposures were treated categorically (ever/never) and as time-dependent.

Results: Preliminary results are presented for 13 lymphoma cases and 152 cancer-free controls. The proportion female were similar in cases (85%) versus controls (86%). The average age at time of lupus diagnosis for cases was 38.5 (standard deviation, SD=17.7) and 34.5 (SD=14.0) in controls. The lymphoma cases occurred a mean of 8.7 years after SLE diagnosis (5.8 years after cohort entry). The adjusted HR for the effect of AMS on lymphoma risk was 1.19 (1.04, 1.36). Increasing age was also an independent risk factor for lymphoma risk.

Conclusion: These preliminary findings suggest the importance of disease activity in influencing lymphoma risk in SLE. However, more in-depth analyses are required to establish the relationship definitively. These further efforts are in progress, and will help define the independent influences of medication exposures and disease activity on the risk of malignancy in SLE.

Variable	**Adjusted HR (95% CI)**
Residence outside North America	1.33 (0.11, 16.2)
Male sex	0.58 (0.07, 4.55)
Age (Continuous, time-dependent)	1.05 (1.00, 1.11)
Disease duration (Continuous)	0.99(0.81, 1.21)
Tobacco use (ever/never)	3.22(0.64, 16.2)
White race	0.85(0.05, 13.3)
Corticosteroids	0.07(0.01, 1.21)
Immunosuppressive agents*	7.3 (0.62, 85.2)
Anti-malarial agents	2.49(0.34, 18.0)
Adjusted mean SLEDAI	1.19 (1.04, 1.36)

***Exposure to azathioprine, methotrexate, or cyclophosphamide prior to lymphoma diagnosis**

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Plasma Myeloperoxidase Predicts Mortality in Women with Systemic Lupus Erythematosus. Kimberly P. Liang[1], Abdus Sattar[2], Stanley Hazen[3], Jennifer R. Elliott[4], Linda C. Santelices[5], Amy H. Kao[2], Susan Manzi[2] and Kathleen Maksimowicz-McKinnon[2], [1]Univ of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Cleveland Clinic, Cleveland, OH, [4]Rheumatology & Osteoporosis Se, Lincoln, NE, [5]Magee-Womens Hospital UPMC, Pittsburgh, PA

Purpose: Patients with systemic lupus erythematosus (SLE) are at increased risk of cardiovascular disease (CVD), in part related to excess inflammation. Myeloperoxidase (MPO), an abundant leukocyte enzyme, is elevated in persons with angiographically documented CVD and within culprit lesions prone to rupture, and previous studies suggest mechanistic links between MPO and both inflammation and CVD. Single initial measurement of plasma MPO has been shown to independently predict the early risk of cardiovascular (CV) events in patients presenting with chest pain. The objective of our study was to determine whether plasma MPO levels, a potential novel marker of plaque vulnerability, are associated with CV events and/or mortality in patients with SLE.

Method: We performed a longitudinal study of 213 SLE women with no prior CV events. Cox models were used to estimate the influence of baseline plasma MPO levels on time to CV events, including cardiac arrest, myocardial infarction (MI), angina, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), cerebrovascular accident (CVA); and time to death. Multivariable Cox models were used to adjust for traditional CV risk factors, SLE disease activity measures, and disease duration.

Results: At baseline, the median age was 44 years and the majority was Caucasian (89.9%). Mean lupus disease duration was 10 years, mean Systemic Lupus Activity Measure (SLAM) score was 6.5, and 42.3% were on steroids (median 8.9 years duration). Median follow-up was 10.1 years. Thirty-seven percent were hypertensive, 65% had hypercholesterolemia, 5.5% had diabetes, and 42% were ever smokers. There were 24 CV events (cardiac arrest, angina, MI, PTCA, CABG), 6 CVA events, and 22 deaths. While plasma MPO levels did not predict time to non-fatal MI or need for revascularization (CABG or PTCA) in women with SLE ($p>0.05$), plasma MPO levels did predict time to fatal events (all-cause mortality) with hazard ratio (HR) 2.01 (95% CI 1.17, 3.46, $p=0.01$). This association remained significant even after adjusting for age, CV risk factors, inflammatory markers and disease activity measures (C-reactive protein, low-density lipoprotein, duration of steroid use, and creatinine), with HR 2.32 (95% CI 1.14, 4.72, $p=0.02$).

Conclusion: These findings indicate that plasma levels of MPO predict increased risk of overall mortality in SLE even following adjustments for CVD risk factors. However, no significant association was noted between MPO and non-fatal MI or need for revascularization in SLE women. Further studies are needed to determine whether MPO levels may be pathophysiologically linked to causes of death in SLE.

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ACR/ARHP Poster Session B

Rheumatoid Arthritis Clinical Aspects: Cardiovascular co-morbidity

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Preclinical Atherosclerosis Is of Similar Severity in Rheumatoid Arthritis and Diabetes Mellitus Despite Differential Impact of Traditional Risk Factors and Systemic Inflammation. Kimon S. Stamatelopoulos[1], George D. Kitas[2], Christos M. Papamichael[1], Elda Chryssochoou[1], Christina G. Katsiari[3], George Georgiopoulos[1], Athanasios Protogerou[1], Vasileios F. Panoulas[2], Aamer Sandoo[2], Nikolaos Tentolouris[3], Myron Mavrikakis[1] and Peter P. Sfikakis[3], [1]Vascular Laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece, [2]Dudley Group of Hospitals NHS Foundation Trust, Dudley, and Arthritis Research Campaign Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [3]First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece

Purpose: The extent to which atherosclerosis is accelerated in chronic inflammatory diseases is not established. We compared preclinical atherosclerosis in rheumatoid arthritis (RA) with diabetes mellitus (DM), a known coronary heart disease (CHD) equivalent.

Method: Vascular studies were performed in 84 RA patients without overt cardiovascular disease or DM vs 84 matched (1:1 for age, gender and classical CVD risk factors) healthy controls. In addition, 48 DM patients matched for age, gender, and disease duration with 48 RA patients were studied. Vascular studies included measurements of endothelial function (flow-mediated dilatation - FMD), arterial stiffness (pulse wave velocity - PWV), carotid intima-media thickness (cIMT) and analysis of atheromatous plaques.

Results: All markers of preclinical atherosclerosis were significantly worse in RA patients compared to controls. RA duration associated with arterial stiffening, whereas RA activity associated with carotid plaque vulnerability. The prevalence and severity of functional and structural vascular abnormalities was similar in RA and DM of equal duration (mean of 10 years), despite the fact that DM patients had a worse classical CVD risk profile. Both RA and DM were associated independently with increased IMT; RA, but not DM, was independently associated with decreased FMD.

Conclusion: Preclinical atherosclerosis appears to be of equal frequency and severity in RA and DM of similar duration. RA activity impacts upon endothelial function, and disease duration upon arterial stiffness. Modifiable CVD risk factors may need to be targeted as aggressively in RA as is currently recommended for DM, but this may need to be accompanied by sustained control of systemic inflammation. These strategies require prospective evaluation in RA.

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Infraclinical Atherosclerosis Is Correlated to Hypertension and Parameters Reflecting Systemic Inflammation (CRP, CD40L and oxydative stress) in a Cohort of Very Early Inflammatory Rheumatisms (VErA). Thibault Vandhuick[1], Yannick Allanore[2], Jean Pierre Louvel[1], Philippe Dieudé[3], Elisabeth Flipon[4], Patrice Fardellone[4], Gaelle Clavel[4], Patrick Boumier[4], Jean Daniel Allart[5], Corinne Lesage[1], Sophie Pouplin[1], Catherine Krzanowska[1], Jean-François Ménard[1], Mary Jan[6], Xavier Le Loët[7] and Olivier Vittecoq[1], [1]CHU Rouen, Rouen, France, [2]Paris Descartes Univ, Paris, France, [3]Bichat hospital APHP, Paris, France, [4]Hopital Nord Amiens, Amiens, France, [5]Pauchet Hospital, Amiens, [6]CHU, Rouen, France, [7]CHU Rouen - INSERM U 905, France

Purpose: Rheumatoid arthritis (RA) is an independent cardiovascular risk factor (CVRF). However, the link between RA and cardiovascular events has only been proven in active and severe forms of RA, but not in early inflammatory rheumatisms. The objectives of our study were: (i) to assess infra-clinical atherosclerosis in a cohort of early RA and undifferentiated arthritis; (ii) to identify specific parameters likely to predict the development of atherosclerosis.

Methods: Patients, prospectively recruited from 1998 to 2002 in a cohort (VErA) of untreated early inflammatory rheumatisms evolving for less than 6 months, accepted to undergo a carotid sonography, measuring the intima-media thickness (IMT), at 7 years of the first symptoms. Clinical, biological and radiological parameters have been notified at the inclusion and every 6 months: Disease Activity Score (DAS44), ESR, CRP, Rheumatoid Factors (RF), anti-CCP2 antibodies, markers of oxydative stress and endothelial dysfunction, van der Heijde modified Sharp score… Traditional CVRF were collected for each patient. RA treatment was standardized at the onset of the disease and corticosteroids were avoided if possible.

Results: One hundred and five patients were included in our study (80 RA fulfilling the ACR criteria). At the inclusion mean age was 51.7 ± 12.8 years, DAS44 3.23 ± 1.25, ESR 25.9 ± 23.6 mm/h, CRP 22.0 ± 32.2 mg/l; 38 % of patients had RF and 36 % antiCCP2 abs. Mean number of CVRF after a 7-year follow-up was 1.67 ± 1.09 with a mean carotid artery IMT measured at 0.67 ± 0.12 mm. Increased IMT was correlated with age ($p<10^6$), swollen joint count ($p=0.01$) and DAS44 ($p=0.048$) at the inclusion. It was also associated with persistent elevated CRP during the first three years ($p=0.005$). Hypertension and android obesity were the only classical CVRF significantly correlated with elevated IMT (respectively $p=0.006$ and $p=0.03$). Mean levels of advanced oxidation protein end products (AOPP) and CD40L during the first 2 years were both specific biological markers associated with increased IMT (respectively $p=0.041$ and $p=0.02$). On the other hand the presence of antiCCP2 abs (related to erosions in this study) is associated with a significant reduced carotid IMT ($p=0.009$). No relationship was found between IMT and genetic background or structural damages.

Conclusion: In this very early arthritis cohort, the 2 events, structural damages and infraclinical atherosclerosis, usually observed in RA, seem to be related to different mechanisms: the first one to the presence of antiCCP abs and the second one to baseline as well as mean levels over the first years of parameters reflecting inflammatory process (AOPP, CD40L and CRP)

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Systolic Blood Pressure Is An Independent Modifiable Risk Marker Associated with Subclinical Atherosclerosis in Early Inflammatory Polyarthritis- Results From the Norfolk Arthritis Register (NOAR). H. Mirjafari[1], T. Farragher[1], P. Pemberton[2], V. Charlton-Menys[3], D. Bunn[4], T. Marshall[4], P. Wilson[4], D. P. Symmons[1] and I. N. Bruce[1], [1]arc Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom, [3]The University of Manchester, Manchester, United Kingdom, [4]Norfolk and Norwich University Hospital, Norwich, United Kingdom

Purpose: Patients with inflammatory polyarthritis (IP) experience excess cardiovascular (CVD) mortality due to accelerated atherosclerosis. It is important to have accessible and reliable predictors of subclinical atherosclerosis, as early as possible in the disease process. The aim of this study was to identify markers of subclinical atherosclerosis in patients with IP

Methods: Consecutive patients aged 18-65 years with early IP (≥2 joints swollen for ≥4 weeks) within 24 months of symptom onset were recruited as part of a primary-care-based inception cohort. Patients completed a questionnaire including history of diabetes, smoking and family history of MI. Clinical examination included joint count and measurement of blood pressure and BMI. Blood was taken for rheumatoid factor (RF), C-reactive protein (CRP), anti-cyclic citrullinated peptide antibodies (ACPA), fasting glucose and lipid profile. Patients underwent B mode Doppler ultrasound examination of the carotid arteries to assess intima-medial thickness (cIMT). In univariate analyses we identified factors associated with a cIMT above the median; after age and gender adjustment. We then entered the significantly associated parameters into a multivariable model.

Results: 326 patients were recruited, of whom 226 (70%) were female. Median (IQR) age at study entry was 50 (41-57) years and median symptom duration was 6 (4-11) months. Mean (SD) blood pressure was 134/ 84 (16/10) mmHg. The median (IQR) cIMT was 0.6 (0.5-0.7) mm. Age, male gender, family history of MI, systolic blood pressure (SBP) and BMI were significantly associated with above median cIMT in the univariate analysis (Table). In a multivariable model age, male gender, family history of MI and SBP remained significant independent predictors of above median cIMT (OR (95% CI) 1.1 (1.1, 1.2), 1.9 (1.0, 3.4), 3.4 (1.3, 9.0), 1.0 (1.0, 1.0) respectively). These results were revalidated using linear regression with cIMT as a continuous variable as outcome. The relationship between SBP and cIMT was linear and no threshold effect was found.

Table: Univariate association with above median cIMT at baseline

Variable	**OR (95% CI)** (age and gender adjusted)
Age (years)	1.1 (1.1, 1.2) *
Male gender	1.9 (1.1, 3.4) *
Smoker	1.5 (0.8, 3.0)
Diabetes	1.3 (0.5, 3.3)
SBP (mmHg)	1.0 (1.0, 1.0) *
Family history of MI	3.6 (1.4, 9.2) *
LDL (mmol/l)	1.2 (0.9, 1.6)
HDL (mmol/l)	0.6 (0.3, 1.2)
BMI	1.1 (1.0, 1.1) *
IP disease duration (months)	1.0 (1.0, 1.0)
Steroid therapy	0.6 (0.3, 1.1)
DAS28	1.1 (0.9, 1.3)

RF	1.1 (0.6, 1.8)
ACPA	1.0 (0.6, 1.7)
HAQ score	1.1 (0.7, 1.5)
CRP (mg/l)	1.0 (1.0, 1.0)

*Statistically significant

Conclusion: In our dataset SBP was the only modifiable risk factor for subclinical atherosclerosis (as assessed by cIMT). This underlines the importance of regular measurement of BP in patients with early IP with a view to starting and adjusting anti-hypertensive therapy in accordance with national guidelines.

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Determinants of Hypertension in Rheumatoid Arthritis. Siriporn Manavathongchai[1], Young-Hee Rho[1], Annette M. Oeser[1], Joseph F. Solus[1], Ginger L. Milne[1], Aihua Bian[1], Tebeb Gebretsadik[1], Ayumi Shintani[1], Yu Asanuma[2] and C. Michael Stein[1], [1]Vanderbilt University, Nashville, TN, [2]Saitama Medical University, Saitama, Japan

Purpose: Hypertension (HT) is one of the most common modifiable cardiovascular risk factors and is associated with increased atherosclerosis and cardiovascular risk. HT is more common in patients with rheumatoid arthritis (RA) and inflammation is postulated to play a role. In the general population, oxidative stress, insulin resistance, homocysteine (Hcy), osteoprotegerin (OPG), C-reactive protein (CRP) and leptin (all of which are elevated in RA) have been associated with HT. The contribution of these factors to HT in RA is not known. The aim of this study was to define the contribution of these factors to HT in RA.

Methods: We studied 169 patients with RA enrolled in a study of cardiovascular risk factors and outcomes. HT was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or currently receiving antihypertensive therapy. We measured inflammatory markers (serum CRP, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6)), insulin resistance (homeostasis model assessment (HOMA) index), oxidative stress (serum myeloperoxidase (MPO) and urinary F_2-isoprostane excretion), Hcy, leptin and OPG concentrations. Factors were compared between patients with and without HT using Wilcoxon rank-sum tests and Pearson's chi-square tests. The association of each factor of interest on HT status was examined using separate multivariable logistic regression models. Covariates for adjustment include age, sex, race, smoking status, body mass index (BMI), and corticosteroids and non-steroidal antiinflammatory drugs (NSAIDs) use.

Results: The prevalence of HT in patients with RA was 53.3%. Hypertensive patients (n=90) were significantly older than those without HT (n=79) (median [IQR] 58.5 [51.2-67.0] years vs. 46.0 [41.0-56.0] years) and had longer disease duration (11.0 [2.0-20.0] years vs. 2.0 [1.6-11.5] years) (P<0.001). BMI and smoking history did not differ significantly between patients with and without HT (P>0.05). Concentrations of Hcy (11.1 [8.5-13.5] µmol/L vs. 9.3 [7.8-11.0] µmol/L and OPG (1778 [1300-2602] pg/ml vs. 1304 [961-1626] pg/ml) were significantly higher in hypertensive patients (P<0.001). After adjustment for age, sex, race, smoking status, BMI, and corticosteroids and NSAIDs use, increased concentrations of Hcy (OR 2.9, CI 1.5-5.5, P<0.001), OPG (OR 2.1, CI 1.2-3.7, P=0.01) and leptin (OR 2.0, CI 1.0-3.8, P=0.046) remained associated with HT. DAS28, HOMA, MPO, F_2-isoprostane excretion, IL-6, CRP and TNF-α were not significantly associated with HT among RA patients (all P values >0.05).

Conclusion: HT in patients with RA is not associated with insulin resistance, oxidative stress or non-specific markers of inflammation, but with increasing concentrations of Hcy, OPG and leptin. The pathogenesis of HT in RA may involve pathways more usually associated with the maintenance of bone, fat and vascular homeostasis.

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Assessment of Cardiac Involvement in Rheumatoid Arthritis Using a Comprehensive Cardiac Magnetic Resonance Approach: Association of Myocardial Abnormalities with Disease Activity. Hitomi Kobayashi[1], Jon T. Giles[2], Isamu Yokoe[3], Masaharu Hirano[4], Tsubasa Onishi[3] and Yasuyuki Kobayashi[5], [1]Itabashi Chuo Medical Center, Itabashi-ku, Tokyo, Japan, [2]Johns Hopkins University, School of Medicine, Baltimore, MD, [3]Itabashi Chuo Medical Center, Japan, [4]Tokyo Medical University, Tokyo, Japan, [5]St. Marianna University, Kawasaki, Japan

Purpose: Rheumatoid arthritis (RA) is a multi-organ inflammatory disorder associated with high cardiovascular morbidity and mortality. Using contrast enhanced cardiac magnetic resonance imaging (cMR) with pharmacologic stress, we sought to identify microvascular impairment and myocardial inflammation/fibrosis in a group of RA patients and explore the association of these outcomes with RA disease characteristics.

Methods: RA patients with no history and/or clinical findings of systemic hypertension, coronary artery disease, severe valvular heart disease, atrial fibrillation, diabetes mellitus, or echocardiographic abnormalities underwent contrast-enhanced cMR on a 1.5T scanner. Adenosine triphosphate was used to assess perfusion defects due to microvascular impairment or ischemia, and delayed enhanced imaging was obtained for the assessment of myocardial inflammation/fibrosis. We evaluated the associations of cMR abnormalities with RA disease activity and severity measures.

Result: Eighteen patients (72% female) with a mean age of 57 ± 10 years were studied. The mean DAS28 for the cohort was 3.96, with 6 participants (33.3%) falling into the low disease activity category (DAS28<3.2) and 6 participants (33.3%) falling into the high disease activity category (DAS28>5.1). Eight patients (45%) demonstrated a myocardial abnormality. Stress perfusion defects were seen in two patients (11%), one of whom had a circumferential subendocardial perfusion defect and one had a non-segmental subendocardial perfusion defect. Seven patients (39%) were found to have delayed enhancement (indicating myocardial inflammation or fibrosis), only one of whom also demonstrated a perfusion defect. Mean DAS28 was significantly higher in the group with delayed enhancement compared to the group without by an average of 1.32 DAS28 units (4.77 vs. 3.44 units, respectively; p=0.011). Corresponding trends to statistical significance were noted in systemic inflammatory markers, with both CRP and ESR quantitatively higher in the group with delayed enhancement. Despite higher disease activity overall, TNF inhibitors were prescribed in only one participant with delayed enhancement (14.3%) compared to 6 without delayed enhancement (54.6%); however, this difference was not statistically significant (p=0.15). Other RA characteristics were not significantly associated with myocardial abnormalities.

Conclusion: Myocardial involvement, as detected by cMR, was frequent in RA patients without known cardiac disease. Myocardial inflammation/fibrosis was observed more frequently than microvascular impairment and, combined with its association with higher RA disease activity, suggests a mechanistic connection between articular and myocardial inflammation in RA.

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Methotrexate Reduces Cardiovascular Risk in Rheumatoid Arthritis: A Systematic Review. J. Gupta[1], W.F. Harvey[1] and D.H. Solomon[2], [1]Tufts Medical Center, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

Purpose: Rheumatoid arthritis (RA) is known to be associated with an excess of cardiovascular (CV) risk. RA and atherosclerosis both have important inflammatory underpinnings and may share a common etiopathogenesis. Methotrexate (MTX) effectively decreases inflammation in RA and therefore may have similar effects on the inflammatory aspect of CV disease, thereby decreasing CV risk. Our goal was to conduct a systematic review of the literature analyzing the effects of MTX on CV outcomes.

Method: We searched Medline (Jan 1950-May 2009) using the terms (rheumatoid arthritis and methotrexate) and (cardiovascular or stroke or atherosclerosis or myocardial infarction (MI) or coronary disease or congestive heart failure or mortality). Inclusion criteria were that the population studied had a diagnosis of RA, reported exposure to MTX, and reported a CV outcome, including MI, stroke, congestive heart failure, CV mortality or CV intervention rates.

Results: Our search yielded 340 articles, and an initial screen of the abstracts resulted in 17 articles chosen for detailed review. Ultimately, 6 articles were chosen that fulfilled our inclusion and exclusion criteria. All were observational designs and their heterogeneity prevented a meta-analysis. The included studies are described in the table. The studies ranged in size from 623 to 107,908 patients. In three of the studies, data were collected from outpatient clinics and three (Suissa, Prodanovich, and Bernatsky) used large administrative databases. Median follow up time was reported in only three studies (Choi, Suissa, and Bernatsky). Only Choi reported mean weekly MTX dosage (13mg). Studies did not uniformly report or adjust for RA severity, disease activity or traditional CV risk factors. Despite this heterogeneity, all of the studies showed a reduction in CV risk for patients using MTX, though not all results were statistically significant.

Conclusion: While multiple limitations with the observational nature of this literature exist, our systematic review reveals a decreased CV risk associated with MTX use in RA patients. It is not clear whether this association would hold true across all DMARDs.

Author, year, Country	**N, years studied, source of data**	**Mean follow-up (SD)**	**Comparison**	**Endpoint**	**Key Outcomes (95% CI)**
Choi 2002 US	n=1240 1981-1999 Outpt Clinic	6 yrs (5)	MTX vs. No MTX	CV death	HR 0.3 (0.2-0.70)
Suissa 2006 Canada	n=107908 1999-2003 Insurance claims	14 mo (11) Min 1 year	MTX only vs. No DMARD	First MI requiring hospitalization	RR 0.84 (0.6-1.1)
Van Halm 2006 Holland	n=613 1953-2002 Outpt clinics	Not reported	MTX only vs. Never used HCQ, SSZ, MTX	First CV event: MI, Coronary bypass, Angioplasty, Ischemia on ECG, Stroke, TIA, or Carotid endarterectomy	OR 0.16 (0.04-0.7)
Naranjo 2007 Multinational	n=4363 2005-2006 QUEST-RA Outpt clinics	Not reported	MTX vs. No MTX	MI or stroke	HR 0.85 (0.8-0.9)
Prodanowich 2005 US	n=6707 1998-2003 Veterans database	Not reported	MTX vs. No MTX	CV disease, Cerebrovasc disease or Atherosclerosis	OR 0.83 (0.7-1.0)

Bernatsky 2005 Canada	n=41885 1998-2001 Insurance claims	328 d (244)	MTX only vs. no DMARD	First hospitalization for congestive heart failure	RR 0.8 (0.6-1.0)

Disclosure: J. Gupta, None; **W. F. Harvey**, American College of Rheumatology, 2 ; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 .

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Formal Cardiovascular Risk Determination in Rheumatoid Arthritis Suggests Suboptimal Use of Statins. Tracey Toms[1], Vasileios F. Panoulas[1], Karen.M.J. Douglas[1], Helen Griffiths[2], Naveed Sattar[3], Deborah Symmons[4] and George D. Kitas[1], [1]Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [2]Aston University, Birmingham, United Kingdom, [3]BHF Glasgow Cardiovascular Research Centre, Glasgow, United Kingdom, [4]arc Epidemiology Unit, University of Manchester, United Kingdom

Purpose: Rheumatoid arthritis (RA) associates with an excess cardiovascular morbidity and mortality. This can partially be attributed to traditional risk factors. Thus, the risk of developing cardiovascular disease (CVD) can be reduced if traditional risk factors are identified and managed aggressively. Several algorithms have been developed to calculate CVD risk and guide treatment with lipid lowering agents, including the Framingham Risk Score (FRS). In this study we aimed to identify the degree of CVD risk in an RA population, and whether patients identified at risk were optimally managed.

Method: 400 well-characterised RA patients were recruited from outpatient clinics held at the Dudley group of Hospitals NHS Foundation Trust. Patients with a prior history of CVD were excluded, leaving a total of 314 patients for subsequent analysis. Patients at high risk of developing CVD were identified, by applying the FRS and statin use was then assessed amongst those in the at risk category. **Results:** Of the patients without a history of CVD 17/314 (5.4%) had a FRS 10 year risk of greater than 20% and required primary prevention as per current UK guidelines. Of the 17 high risk patients, only 3 (17.6%) were recieving lipid-lowering therpay (statins/fibrates), leaving a total of 14 (82.3% of the at risk patients or 4.5 % of the total population) untreated and at risk.

Conclusion: Many RA patients are at high risk of developing CVD. Despite this, the use of lipid lowering agents remains suboptimal. We would recommend that all patients undergo annual screening for CVD risk and are managed agressively if deemed to be at high risk.

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Raised Traditional Cardiovascular Risk Factors in Indians with Rheumatoid Arthritis. Firdaus Fatima[1], Rao RK Uppuluri[2], Robert J. Moots[3] and Nicola Goodson[4], [1]Dr, Hyderabad, India, [2]Director, Srideepti Rheumatology Centre, Hyderabad, India, [3]University Hospital Aintree, Liverpool, United Kingdom, [4]Liverpool, United Kingdom

Purpose: The increased cardiovascular disease (CVD) in rheumatoid arthritis (RA) is thought to be mediated by elevated traditional CVD risk factors, and the effects of inflammation. South Asian populations have a high prevalence of traditional CVD risk factors and CVD events[1]. We have investigated the prevalence of CVD risk factors in South Asian patients with RA.

Method: 800 consecutive RA patients (fulfilling ACR classification criteria) and 800 age matched controls without RA were identified. Subjects on therapy for CVD or lipid lowering agents were excluded. The prevalence of individual traditional CVD risk factors and 10 year coronary heart disease (CHD) risk score[2] were compared between cases and controls using age and gender adjusted logistic regression.

Results: 83.5% of RA cases were female Vs 83.3% controls. Mean age of cases was 46.2 yrs SD (11.3) Vs controls 46.1 yrs SD (12.1). RA cases had a 4 fold increased odds of having an elevated CVD risk score (Table 1). Individual risk factor analysis revealed that this was predominantly due to elevated diastolic BP, total cholesterol (TC) and a trend for lower High Density Lipoprotein Cholesterol (HDL C) in

RA. There was a high prevalence of diabetes mellitus (DM) in this population but RA cases had higher triglycerides (trig) and higher fasting blood sugar (FBS) compared to controls.

Table 1 Comparing CVD risk factors between RA cases and controls

CVD Risk factor	RA n	Non RA n	OR	95% CI
DM	252	242	1.06	0.86, 1.32
Smoking	12	5	2.58	0.88, 7.54
Systolic BP ≥140	219	201	1.13	0.89, 1.44
Diastolic BP ≥ 95	91	29	3.46	2.25, 5.34
Waist : Hip ratio>0.9	451	443	1.04	0.85, 1.28
BMI>25	481	514	0.82	0.67, 1.02
TC >200mg/dl	203	84	2.96	2.23, 3.91
HDL C<40mg/dl	47	31	1.56	0.98, 2.48
Trig >150mg/dl	319	176	2.38	1.91, 2.97
FBS >100mg/dl	220	91	3.07	2.34, 4.03
CHD risk score(>15% 10 yr risk of CHD event)	45	13	4.01	2.10, 7.67

OR: Odds ratio (adjusted for age & sex)

Conclusion: We have observed that this young, predominantly female, South Asian population has a high prevalence of CVD risk factors. However, there was a 4 fold increase in elevated CHD risk associated with RA. This was predominantly due to increased risk factors associated with the metabolic syndrome. Screening and treating modifiable CVD risk factors in South Asian patients with RA is strongly recommended.

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A-SAA Levels in Inflammatory Arthritis Patients Prior to Biologic Therapy Are Associated with Increased Cardiovascular Events in Longterm Follow-up. Chin Teck Ng, Ronan Mullan, Mary Connolly, Oliver FitzGerald, Barry Bresnihan, Ursula Fearon and Douglas J. Veale, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Purpose: The acute phase apoprotein Serum Amyloid A (A-SAA) is elevated in serum and is the best marker to correlate with disease activity in inflammatory arthritis. Several studies show that atherosclerotic cardiovascular (CV) disease is the primary cause of premature death in RA patients. A-SAA has been proposed as a potential prognostic biomarker for RA disease activity, however it may also be relevant as a biomarker for cardiovascular disease, possibly comparable to hs-CRP. The collagen cleavage neo-epitopes, C2C and C1-2C are specific for the destruction of type I and II collagens by the collagenases MMP-1, MMP-8 and MMP-13 and are elevated in arthritis and may be associated with CV remodelling. Aim: To determine serial serum A-SAA levels, collagen neoepitopes and CV events in a follow-up cohort

of inflammatory arthritis patients, 4 years after starting on biologic therapy. **Method:** Patients were assessed at baseline, 1, 3, 6, 9, 12 and 48-months (m) after commencing anti-TNFα therapy. Twenty eight tender and swollen joint count (28-TJC, -SJC), CRP, DAS28-CRP score, and HAQ were measured at each assessment. Cardiovascular (CV) events were recorded at 48m. A-SAA levels were measured by ELISA at baseline, 1m and 3m. C2C and C1-2C were measured at baseline, 1, 3, 6, 9, and 12m. Statistical analysis was performed using SPSS 12 statistical software. **Results:** RA (n=45) and PSA (n=17) were followed up. At 48m, 8 patients developed one or more cardiovascular events since starting on anti-TNF therapy. Baseline A-SAA levels were significantly higher in patients with new CV events (CV+) at 48m follow-up compared to patients without CV events (CV-) [927.01ug/ml (285.88-3524.67) vs. 137.51ug/ml (2.44-1648.29), $p< 0.05$]. High A-SAA levels persisted at 1m and 3m post therapy in CV+ compared to CV-, where A-SAA levels decreased significantly after treatment at 1m and 3m ($p<0.05$). In contrast, there was no significant difference in CRP at baseline between the two groups. In addition, C2C and C1-2C levels remained higher at all time points in CV+ patients, and were associated with lower clinical responses (DAS28-CRP and HAQ) to anti-TNF therapy. **Conclusion:** High A-SAA levels at baseline, but not CRP, were associated with CV events in this long-term follow-up cohort. A-SAA may be a biomarker, but may also reflect a mechanism of action of CV disease in inflammatory arthritis.

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Do Rheumatoid Arthritis (RA) Patients without Cardiovascular Disease (CVD) Have More Metabolic Syndrome Than Subjects without RA? Cynthia S. Crowson, Elena Myasoedova, Veronique Roger, Richard J. Rodeheffer, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: Patients with RA suffer from an excess burden of CVD. Metabolic syndrome and its components are known to significantly increase risk of CVD. The purpose of our study was to examine whether RA patients without CVD have a higher prevalence of metabolic syndrome than subjects without RA and no history of CVD.

Method: A sample from a population-based cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1-1-1980 and 1-1-2008 were studied, as were a sample of subjects from the same underlying population who did not have RA. Data on waist circumference, body mass index [BMI], blood pressure [BP] and current medications were obtained during the study visit. Data on CVD (physician diagnosis of coronary artery disease, heart failure, hospitalized myocardial infarction, revascularization, or angina), lipids and glucose measures were ascertained by review of medical records. Metabolic syndrome was defined based on AHA criteria as 3 or more of: high waist circumference (≥102 cm in men, ≥88 cm in women), elevated triglycerides (TG ≥150 mg/dL or treatment), reduced high-density cholesterol (HDL<40 mg/dL in men or <50 mg/dL in women or treatment), elevated BP (≥130 mmHg systolic or ≥85 mmHg diastolic or treatment) or elevated fasting glucose (FG ≥ 100 mg/dL or treatment). Subjects with CVD were excluded from both samples. Logistic regression models adjusted for age and sex were used to examine differences between the RA and non-RA cohorts.

Results: The study included 232 RA patients (mean age [SD] 58.8 [13.0] years, 75% women) and 1235 subjects without RA (mean age [SD] 62 [9.2] years, 55% women) who had no CVD. The median duration of RA was 7.0 years (range: 0.7 – 27 years) and 50% were rheumatoid factor positive. RA patients were more likely to have a high waist circumference than non-RA subjects (odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.7, 3.0; $p<0.001$), even though BMI was similar in both groups (mean 29 vs 28 kg/m^2 in RA and non-RA, respectively; $p=0.22$). RA patients were more likely to have elevated BP (OR: 1.4; 95% CI: 1.1, 2.0; $p=0.02$) and somewhat more likely to have elevated FG (OR: 1.4; 95% CI: 1.0, 1.9; $p=0.05$). The proportion of patients with low HDL was similar in both groups ($p=0.8$). However, RA patients were less likely to have high TG levels (OR: 0.7; 95% CI: 0.5, 0.9; $p=0.02$). More RA patients were classified as having metabolic syndrome (32% vs. 25% in non-RA). This difference remained significant after adjustment for age and sex (OR: 1.6; 95% CI: 1.2, 2.3; $p=0.002$).

Conclusion: Among subjects without CVD, RA patients are more likely to have metabolic syndrome than non-RA subjects. This suggests a potential impact of RA disease and/or treatment on the development of metabolic syndrome in RA. More research is needed to understand the reasons for these metabolic changes in RA and the impact of metabolic syndrome on development of CVD in RA patients.

Disclosure: C. S. Crowson, None; **E. Myasoedova**, None; **V. Roger**, None; **R. J. Rodeheffer**, None; **T. M. Therneau**, None; **S. E. Gabriel**, None.

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Is Brain-Type Natriuretic Peptide (BNP) Associated with Left Ventricular Diastolic Dysfunction (LVDD) in Rheumatoid Arthritis (RA) Patients without Cardiovascular Disease (CVD)? Cynthia S. Crowson, Elena Myasoedova, John M. Davis III, Veronique Roger, Barry L. Karon, Richard J. Rodeheffer, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: Patients with RA are at increased risk of CVD. Elevated BNP is associated with CV abnormalities in the general population. We compared BNP levels in RA and non-RA subjects without CVD, to evaluate whether BNP is associated with LVDD in RA.

Method: In a population-based incident cohort of RA patients (1987 ACR criteria fulfilled between 1-1-1980 and 1-1-2008) and a cohort of non-RA subjects from the same underlying population, we assessed BNP, C-reactive protein (CRP) and body mass index (BMI). LVDD was assessed by 2D/Doppler echocardiography using a validated algorithm and categorized as none, mild, moderate/severe or indeterminate. For RA patients, RA characteristics (health assessment questionnaire, interleukin-6, tumor necrosis factor α, rheumatoid factor [RF] and anti-cyclic citrullinated peptide antibody) were collected. Subjects with CVD (diagnosis of coronary disease, heart failure, hospitalized myocardial infarction, revascularization, or angina), ascertained from medical records, were excluded from both cohorts. Linear regression models were used to assess differences in log-transformed BNP for RA compared to non-RA cohort adjusting for age, sex, BMI and CRP. Proportional odds models evaluated the association between LVDD and BNP in the RA patients.

Results: The study included 232 RA patients (mean age 58.8 years, 75% women) and 1730 non-RA subjects (mean age 61.3 years, 55% women) who had no CVD. The median RA duration was 7.0 yrs (range 0.7 – 27 yrs); 50% were RF positive. Among the RA patients, 121 (52%) had normal, 48 (21%) mild, 16 (7%) moderate/severe LVDD and 47 were indeterminate. Among the non-RA subjects, 1172 (68%) had normal, 286 (17%) mild, 82 (5%) moderate/severe LVDD and 190 were indeterminate. More RA patients had elevated BNP (above the upper limit of normal) than non-RA subjects (18% vs. 9%, respectively, $p<0.001$). RA patients without LVDD had higher BNP than non-RA subjects without LVDD (fold change 1.9; $p<0.001$). Similarly, BNP was higher in RA compared to non-RA subjects with mild LVDD (fold change 2.0; $p<0.001$) and with moderate/severe LVDD (fold change 2,2; $p=0.04$). RA patients with elevated BNP were more likely to have LVDD (OR 2.7; 95% CI 1.1, 6.5 adjusted for age, sex and BMI) as compared to those with normal BNP. This association persisted after adjustment for CRP and RA characteristics (OR 3.5; 95% CI 1.3, 9.2).

Conclusion: Among subjects without CVD, RA patients were more likely to have elevated BNP than non-RA subjects and abnormal BNP was associated with LVDD, even after adjustment for RA characteristics, including inflammatory markers. This suggests BNP may be a useful marker of LVDD in RA patients without CVD. More research is needed to understand the mechanisms influencing BNP levels in RA and the role of this molecule in myocardial dysfunction in RA.

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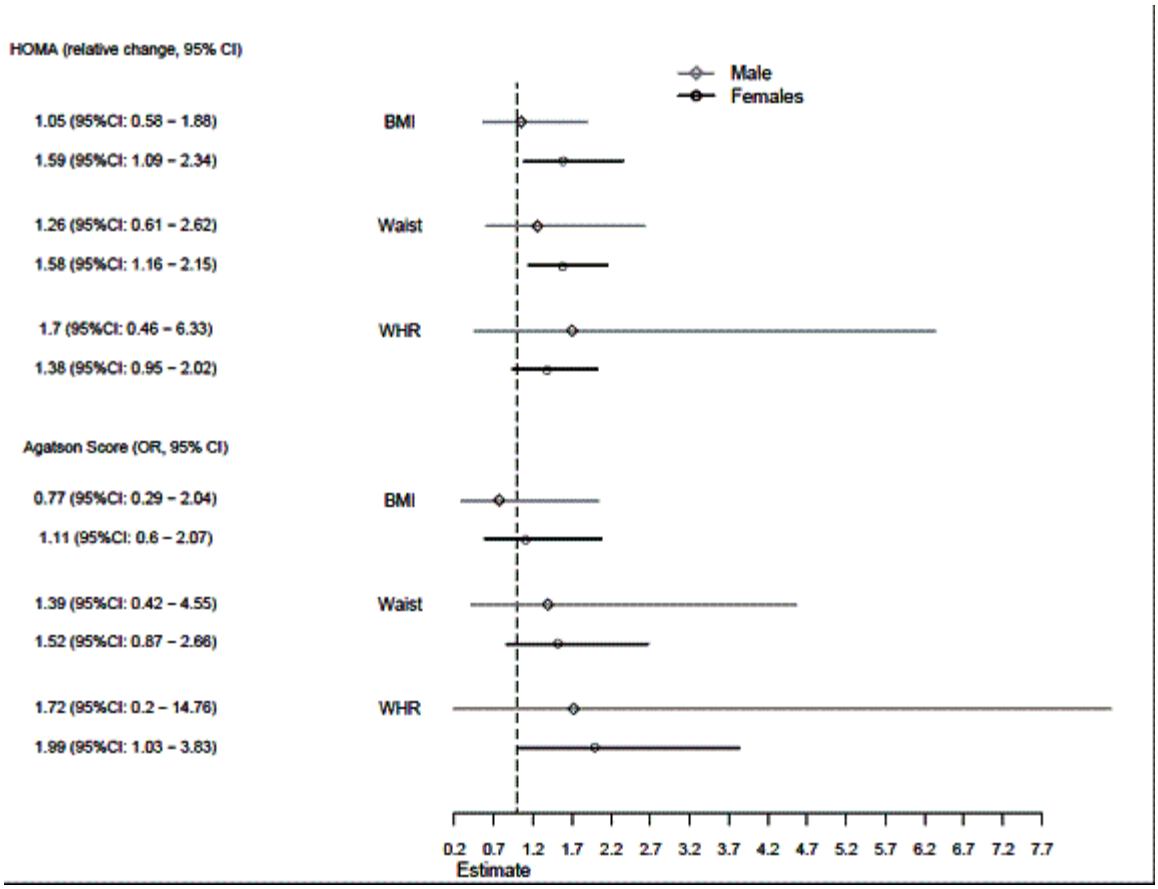
Effects of Body Fat Distribution On Insulin Resistance and Coronary Atherosclerosis in Rheumatoid Arthritis. David Brey[1], Young-Hee Rho[1], Annette M. Oeser[1], Joseph Solus[1], Paolo Raggi[2], Tebeb Gebretsadik[1], Ayumi Shintani[1] and C. Michael Stein[1], [1]Vanderbilt University, Nashville, TN, [2]Emory University, Atlanta, GA

Purpose: Rheumatoid arthritis (RA) is associated with insulin resistance and increased coronary atherosclerosis. In the general population, it is known that body mass index (BMI) is associated with insulin resistance and cardiovascular risk, whereas waist circumference (WC) and waist-to- hip-ratio (WHR), measures of abdominal adiposity, better predict adverse metabolic and cardiovascular outcomes. We examined the hypothesis that in patients with RA, anthropometric measures that encompass abdominal adiposity are more strongly associated with insulin resistance and coronary atherosclerosis than BMI.

Methods: We studied 169 patients with RA who are part of an ongoing cohort to define the relationship between RA and cardiovascular disease. Height, weight, hip circumference, and WC were measured, and BMI and WHR were calculated. Insulin sensitivity was measured by the homeostasis model assessment (HOMA). Patients underwent chest computed tomography, and Agatston coronary artery calcium scores (CAC) were calculated. Gender specific effects of anthropometric measures on HOMA and CAC were assessed using multivariable regression adjusting for age and race.

Results: There were 52 men (age 54.6±11.2 yrs, BMI 28.1±6.82 kg/m^2, WC 101.1±17.2 cm, WHR 0.94±0.07) and 117 women (age 54.1±12.1 yrs, BMI 29.6±6.7 kg/m^2, WC 93.1±16.8 cm, WHR 0.85±0.09). In women, BMI (p = 0.02) and WC (p = 0.004) were associated with HOMA; WHR (p =0.04) alone was associated with CAC. In men, there was no significant association between BMI, WC, and WHR and the outcomes of HOMA and CAC (Figure).



The Figure shows adjusted means ratio for HOMA, or the odds ratio for Agatston scores for a change of one interquartile range of BMI, Waist, and WHR with 95% CI for men (◊) and women (○).

Conclusion: In women with RA, WHR is significantly associated with coronary calcification, and BMI and WC with insulin resistance. Anthropometric measures of obesity may provide information additional to that provided by BMI about the metabolic and cardiovascular consequences of obesity in RA.

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Risk of Tuberculosis in Patients with Rheumatoid Arthritis in Hong Kong- a Multi-Center Study. Lai-Shan Tam[1], Chi-Chiu Leung[2], Shirley Ying[3], Gavin K. Lee[4], Cheuk-wan Yim[5], Ying Y. Leung[6], Emily W. Kun[6] and Edmund K. Li[7], [1]The Chinese University of Hong Kong, Hong Kong, China, [2]Department of Health, Hong Kong, China, [3]Princes Margaret Hospital, Hong Kong, China, [4]Union Hospital, Hong Kong, China, [5]United Christian Hospital, Hong Kong, Hong Kong, [6]Tai Po Hospital, Hong Kong, China, [7]Chinese University of Hong Kong, Hong Kong

Purpose: Data on risk of TB in patients with RA exposed to TNF blockers from countries of high TB burdens are lacking. The aim of this study is to elucidate the incidence rate and relative risk of active TB in patients with RA compared to the general population in Hong Kong between 2004-2008, and to assess whether this risk is associated with exposure to TNF blockers after adjusting for other known risk factors.

Method: We used the mean incidence rate of TB in the general population from 2004 to 2008. To determine the relative risk of TB in RA patients with or without TNF blockers versus the general population, we reviewed all the medical records of RA patients. In order to ascertain the independent explanatory variables associated with active TB in RA, potential explanatory variables (including socio-demographic, co-morbidity, disease severity and immunosuppressive treatment) in RA patients with and without active TB were compared.

Results: A total of 2442 RA patients followed at 5 centers were recruited. The female to male ratio was 4.3 (1979 female, 81%) to 1 (463 male, 19%). Majority (96.5%) of the patients were Chinese. The mean age at the diagnosis of RA and at the start of follow up was 50 +/- 15 and 56 +/- 14 years respectively, with a median disease duration of 3.0 (0.1-8.8) years. The TNF naïve cohort consisted of 2425 patients, including 64 patients who were subsequently started on TNF blockers. Altogether, 2361 patients had never been exposed to TNF blockers, and 81 were treated with at least one TNF antagonists. The total treatment exposure rate for the TNF naïve and TNF treated cohorts was 6,617 and 185 patient-years respectively. Active TB developed in 21/2442 (0.9%) RA patients, including 17/2425 (0.7%) TNF naive patients and 4/81 (4.9%) TNF treated patients. Compared to age- and sex-matched population controls, the standardized incidence ratio (SIR) of active TB was significantly increased (SIR for all RA: 2.6, 95% CI 1.4-5.0, p=0.003; SIR for TNF naïve cohort: 2.0, 95% CI 1.0-4.3, p=0.053; SIR for TNF treated cohort: 34.9, 95% CI 8.9-137.2, p<0.001). Independent explanatory variables associated with an increase risk of active TB in RA patients included older age at study entry (RR 1.04, 95% CI 1.01-1.08, p=0.025), a past history of pulmonary TB (RR 9.53, 95% CI 3.51-25.84, p<0.001), extra-pulmonary TB (RR 20.09, 95% CI 4.84-83.35, p<0.001), chronic renal failure / dialysis (RR 47.0, 95% CI 8.36-264.13, p<0.001), prednisolone > 10mg daily (RR 4.11, 95% CI 1.27-13.36, p=0.019) and the use of TNF blockers (RR 12.53, 95% CI 3.67-42.77, p<0.001).

Conclusion: There was at least a 2 fold increased risk of active tuberculosis in Chinese RA patients. Exposure to TNF blockers remained to be an independent risk factor after adjusting for other known risk factors.

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How Reliably Can Rheumatoid Arthritis Patients Calculate DAS28? A Comparison Study with Ultrasonography, Physician and Nurse. P. Cheung[1], A. Ruyssen-Witrand[1], L. Gossec[1], S. Paternotte[1] and Maxime Dougados[2], [1]Cochin Hospital, Paris, France, [2]Hospital Cochin, Descartes University, Paris, France

Purpose: Evaluation of swollen (SJC) and tender (TJC) joints are an integral part of indices measuring disease activity such as the DAS28 in rheumatoid arthritis (RA). Until now, health professionals are in charge of this data collection. Whether this can be optimally performed by patients is uncertain. SJC/synovitis can also be detected by ultrasonography (US), which is more sensitive than clinical examination. The purpose is to:

1. Evaluate the inter-observer reliability of patient self-assessed SJC ie. comparing to SJC assessed by the physician, nurse and B-mode US (gold standard)
2. Evaluate the inter-observer reliability of patient self-assessed TJC ie. comparing to TJC assessed by the physician (gold standard) and nurse
3. Assess the level of correlation of DAS28 derived by patients, comparing this to physician, nurse and US-derived DAS28

Method: Forty two RA patients (76% female, 64% RF positive, mean disease duration 16 ± 8 years, age 57 ± 12 years) were recruited to self-assess 28 joints (shoulders, elbows, wrists, MCPs, PIPs, knees) for swelling and tenderness in a question/mannequin format, with a short training session by a nurse prior to starting. Joints were then evaluated independently by a physician, another nurse and an ultrasonographer (B-mode and Power Doppler). Intra and inter-observer reliability was assessed at the patient level (28 joints) by the intra-class correlation coefficient (ICC). The Kappa test evaluated the level of agreement at the joint level. ICC was used to express correlation of the patient-derived DAS28 with those derived by US, physician and nurse.

Results: Intra-observer reliability for TJC was excellent for patient, physician and nurse (ICC 0.95 [0.87; 0.98], 0.98 [0.95; 0.99], 1 [0.99; 1] respectively), but for SJC, ICC ranged from 0.45 [0.02; 0.75] to 0.85 [0.65; 0.94]. Inter-observer reliability of self-assessed TJC was good when compared to physician and nurse (ICC 0.83, 0.73 respectively). However, inter-observer reliability of self-assessed SJC was poor when compared to physician and nurse (ICC 0.47, 0.36). There was poor agreement of SJC in all groups when compared to B-mode US, especially with self-assessed SJC (ICC 0.29). However, excellent correlation was reported in patient-derived DAS28 when compared to US-derived DAS28 (ICC 0.95 [0.88; 0.98]).

Table 1

	TJC		SJC		DAS28
	ICC [IC95%]	Kappa [IC95%]	ICC [IC95%]	Kappa [IC95%]	ICC [IC95%]
Patient vs Physician	0.82 [0.61;0.93]	0.47 [0.41;0.53]	0.47 [0.03;0.76]	0.30 [0.24;0.37]	0.90 [0.76;0.96]
Patient vs Nurse	0.73 [0.42;0.89]	0.46 [0.40;0.52]	0.36 [-0.11;0.69]	0.30 [0.23;0.38]	0.87 [0.69;0.95]
Physician vs Nurse	0.85 [0.65;0.94]	0.48 [0.41;0.55]	0.40 [-0.06;0.72]	0.29 [0.22;0.35]	0.90 [0.75;0.96]
Patient vs US	-	-	0.29 [-0.19;0.65]	-	0.95 [0.88;0.98]
Physician vs US	-	-	0.38 [-0.08;0.71]	-	0.98 [0.94;0.99]
Nurse vs US	-	-	0.47 [0.02;0.76]	-	0.98 [0.96;0.99]

Conclusion: Patient-derived DAS28 is at least as reliable as the other modalities despite poor intra and inter-observer reliability in SJC.

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Economic Aspects of Treatment Options in Rheumatoid Arthritis (RA). Results of a Systematic Literature Search. M. Schoels[1], J. Wong[2], D. L. Scott[3], A. Zink[4], P. Richards[5], R. Landewé[6], J. S. Smolen[7] and D. Aletaha[7], [1]KH Hietzing, Vienna, Austria, [2]Division of Clinical Decision Making, Tufts University School of Medicine, Boston, MA, [3]Kings College, London, United Kingdom, [4]Deutsches Rheuma-Forschungszentrum, Berlin, Germany, [5]University of Bristol, Bristol, United Kingdom, [6]University Hospital, Maastricht, Netherlands, [7]Medical University, Vienna, Austria

Purpose: Recommendations for the management of RA with synthetic and biologic drugs have been elaborated by a Task Force of the European League Against Rheumatism (EULAR). Initialized in November 2008, the consensus finding for these guidelines also addresses the cost effectiveness of therapeutic options.

Method: To comprise the available health-economic evidence on RA drug treatments, a systematic literature search of the Medline, Embase and Cochrane databases was undertaken, followed by an additional handsearch of retrieved papers. Relevant studies in English language up to December 2008 were included.

Results: Cost-effectiveness analyses (CEA) are a rapidly expanding field of interest in RA, as reflected by a majority of recent publications evaluating new therapies, as compared to the era before biologicals. We incorporated results of 54 CEA, among them, 40 papers dealt with biologic treatment. Despite very diverse methodological approaches, the main results of the analyses are, with some exceptions, concordant.

At onset of disease, DMARD therapy is cost effective, i.e., positive treatment effects outweigh drug costs. Alike, when encountering DMARD failure, treatment escalation with biologics is cost effective. Among the licensed TNFα-inhibitors (TNFi), cost-effectiveness is fairly comparable, with the relative exception of Infliximab treatment when used at increased doses or frequencies after insufficient response to the standard treatment schedule. When a TNFi fails, the implementation of Rituximab or Abatacept is cost effective for both.

Employment of biologics in DMARD naïve patients, as has been shown to be clinically effective in recent RCTs, is a matter of ongoing debate, and the appraisal of cost-effectiveness is controversial mainly due to scarce clinical data evaluating the intensive treatment of defined high risk patient groups in randomised trials. Alike, there is little evidence on cost-effectiveness of switching TNFi after failure of the first substance of this group.

Conclusion: The financial burden of rheumatoid arthritis is substantial, and new biologic therapies have further increased treatment costs. On the contrary, their clinical effectiveness has a large positive impact on indirect costs, by maintaining function and work ability for a high proportion of patients. Furthermore, quality of life is improved at cost levels that are commonly accepted by society for the treatment of chronic diseases. (Usually, these levels refer to thresholds of incremental cost effectiveness ratios between 50000 and 100000 US$). Especially in the light of the very costly late sequela of insufficiently controlled RA, new expensive drug treatments still appear to be cost effective and a prudent employment of resources.

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Respiratory Symptoms and Disease Characteristics as Predictors of Pulmonary Function Abnormalities (PFT) in Patients with Rheumatoid Arthritis (RA). Dimitrios A. Pappas, Jon T. Giles, Geoffrey Connors, Noah Lechtzin, Joan M. Bathon and Sonye K. Danoff, Johns Hopkins University, School of Medicine, Baltimore, MD

Purpose: Timely recognition of the pulmonary manifestations of RA is critical given that respiratory involvement is identified as the second leading cause of mortality in patients with RA. We attempted to identify which respiratory symptoms, patient and disease characteristics are most highly predictive of PFT abnormalities in an RA patient cohort.

Method: A total of 159 individuals with RA were evaluated. Respiratory symptoms were assessed with the Lung Tissue Research Consortium (LTRC) questionnaire and all patients underwent evaluation with PFTs. Demographic, lifestyle, RA disease and treatment characteristics were collected. Multivariable regression analysis was used to identify pulmonary symptoms and non-pulmonary parameters predictive of PFT abnormalities. Receiver operator characteristic (ROC) curves were constructed to examine the ability of our models to predict PFT abnormalities.

Results: Of the 159 patients, 45 (28%) demonstrated at least one predefined PFT abnormality. Restrictive lung disease was observed in 12 (7.6%), obstructive lung disease in 18 (11.3%) and isolated impaired diffusing capacity in 31 (19.8%). Only seventeen patients (37.8%) of the 45 patients with abnormal PFTs reported a prior diagnosis of emphysema, asthma or rheumatoid lung disease. Among RA characteristics, seropositivity for RF (p=0.011) and anti-CCP (p=0.003), and current use of glucocorticoids (p=0.018) were significantly higher in patients with PFT abnormalities. Pulmonary symptoms were reported in 78 patients (42%). For any PFT abnormality the predictors retained in the final multivariable model included two pulmonary symptoms (chronic phlegm and breathlessness with walking 100 yards), and four other characteristics (BMI, current smoking, seropositivity for anti-CCP antibodies, and current prednisone use). AUC=0.773 (95% CI 0.679 – 0.857)

For restriction, one symptom (breathlessness with level walking) and two patient characteristics (BMI and current prednisone use) were retained in the final prediction equation AUC=0.786 (95% CI 0.585 – 0.918). For obstruction, 8 predictors were retained in the final model, including one symptom (chronic cough), and six other characteristics (gender, exercise, BMI, current smoking, RF seropositivity, and current prednisone use). AUC=0.905 (0.784 – 0.978).

For isolated impaired diffusion, six predictors were retained in the final model, including one symptom (chronic phlegm), and four other characteristics (age, BMI, current smoking, and current prednisone use). AUC= 0.852 (95% CI 0.749 – 0.934).

Conclusion: Assessment of respiratory symptoms along with a limited number of clinical parameters may serve as a useful and inexpensive clinical tool for identifying RA patients in need of further pulmonary investigation.

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Being in Remission or in Low Disease Activity in Rheumatoid Arthritis: Different Meaning with the Use of Different Composite Scores. R. Koevoets[1], N.B. Klarenbeek[1], Désirée M.F.M. van der Heijde[2], M. V. van Krugten[3], D. van Schaardenburg[4], B. Dijkmans[5], T.W.J. Huizinga[1], P. Kerstens[6] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Ziekenhuis Walcheren, Vlissingen, Netherlands, [4]Jan van Breemen Intitute, Amsterdam, Netherlands, [5]VUMC, Amsterdam, Netherlands, [6]JBI, Amsterdam, Netherlands

Purpose: To compare the proportions of patients categorized in different levels of disease activity based on 6 composite scores and relate that to radiological progression and physical function among these categories.

Method: In the current analysis, 214 patients with complete data for all scores were analyzed who participated in the BeSt trial, a randomized controlled trial in recent onset RA comparing four DAS steered treatment strategies. At t=1 and t=4 years, percentages of patients in remission, low disease activity (LDA), moderate disease activity (MDA) or high disease activity (HDA) were calculated for 6 different composite scores according to published cut-offs. Mean HAQ scores were calculated at t=1 and t=4 years per category and percentages of patients with radiographic progression (Sharp van der Heijde score (SHS)) in the next year were calculated with two cut-offs: >0 and >5 units/year. Here, MDA and HDA patients were combined because of limited patient numbers.

Results: The percentages of patients in remission, LDA, MDA en HDA for the various composite scores are illustrated in the figure. CDAI and SDAI scores show the lowest % remission with a larger proportion of patients in LDA both at the 1st and 4th year visit.

In general, the progression percentages (>5 SHS) increased with higher disease activity levels at 4 years, with the best 'dose response' for SDAI and CDAI (table). Overall, few patients show progression > 5 units/year if categorized as remission. The same pattern was found for mean HAQ scores with the lowest mean HAQ in the CDAI en SDAI remission group (table).

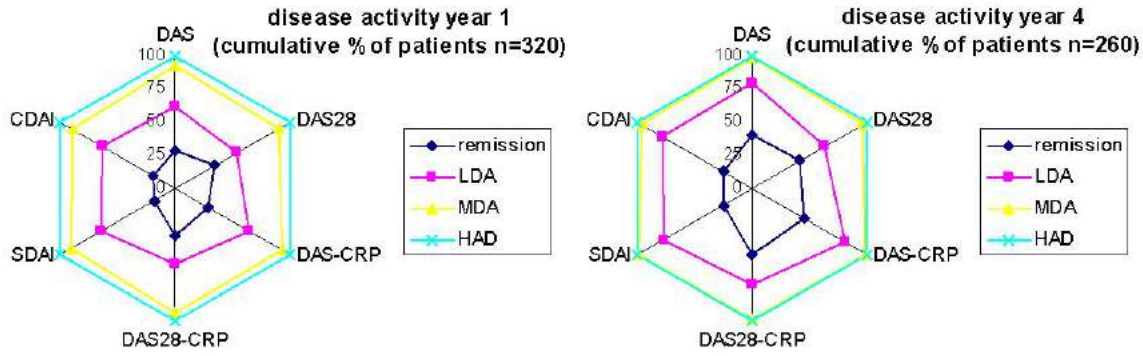

Figure: Cumulative percentage of patients in the different disease activity categories

	DAS		DAS28		DAS-CRP		DAS28-CRP		SDAI		CDAI	
Progression												
>5/year	**n (%)**	**HAQ**	**n (%)**	**HAQ**	**n (%)**	**HAQ**	**n (%)**	**HAQ**	**n (%)**	**HAQ**	**n (%)**	**HAQ**
Remission	8/88 (9.1)	0.38	7/94(7.4)	0.38	8/98(8.2)	0.39	5/108(4.6)	0.42	0/55(0)	0.30	2/55(3.6)	0.27
LDA	8/83 (9.6)	0.56	3/41(7.3)	0.52	9/77(11.7)	0.60	6/52(11.5)	0.56	13/111(11.7)	0.58	14/113(12.4)	0.60

MDA + HDA	9/43(20.1)	1.13	15/79(19.0)	0.90	9/39(23.0)	1.14	14/54(25.9)	1.01	12/48(25.0)	1.00	9/46(19.6)	1.00

Table: Mean HAQ scores and percentage of patients showing progression between year 4 and 5, based on the disease activity status at year 4 (n=214).

Conclusion: The six disease activity indices select different patients for the various levels of disease activity. This has also an impact on the percentage of patients showing radiological progression and mean HAQ scores. SDAI and CDAI scores are the most strict in categorizing remission with the lowest mean HAQ scores and percentage of patients showing radiological progression.

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The Effect of a Change in DAS Level On the HAQ Level During 5 Years Follow-up in the BeSt Study. E. van der Kooi[1], N.B. Klarenbeek[1], P.J.S.M. Kerstens[2], P.A.H.M. van der Lubbe[3], P.B.J. de Sonnaville[4], T.W.J. Huizinga[1], B. A. C. Dijkmans[5] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]JBI, Amsterdam, Netherlands, [3]Vlietland Hospital, Schiedam, Netherlands, [4]Oosterschelde Hospital, Goes, Netherlands, [5]VUMC, Amsterdam, Netherlands

Background: Previous studies suggest that functional ability of patients with RA is related to their disease activity. It remains unclear whether any decrease in disease activity will improve functional ability.

Purpose: To assess the influence of a decrease in Disease Activity Score (DAS) on functional ability (Health Assessment Questionnaire, HAQ) during five years DAS-steered treatment in patients with recent onset RA.

Methods: Data of the BeSt study were used, a randomized controlled trial in which medication was adjusted based on threemonthly DAS measurements, aiming at DAS≤2.4. HAQ was measured every three months. A linear mixed model was performed to assess the effect of DAS changes on the outcome $HAQ_{time\ a+1}$ during 5 years follow-up. Covariates were $DAS_{time\ a}$, deltaDAS (=$DAS_{time\ a+1}$ - $DAS_{time\ a}$), logarithm of time, the two way interactions ($DAS_{time\ a}$*deltaDAS, $DAS_{time\ a}$*log time and deltaDAS*log time) and the three way interaction ($DAS_{time\ a}$*delta DAS*log time) corrected for $HAQ_{time\ a}$.

Results: Corrected for age, gender, baseline BMI, rheumatoid factor, symptom duration, treatment strategy, Sharp-van der Heijde Score, baseline CRP and CCP2, the three way interaction (p=0.27) and the two way interaction between log time and deltaDAS (p=0.08) and log time and $DAS_{time\ a}$ (p=0.82) were not significantly related to the outcome HAQ and were omitted from the analysis. Only the $DAS_{time\ a}$ (p<0.001), deltaDAS (p<0.001), log time (p<0.001), $DAS_{time\ a}$*deltaDAS (p<0.001) and the $HAQ_{time\ a}$ (p<0.001) significantly predicted the outcome HAQ. This results in the following regression formula:

Outcome $HAQ_{time\ a+1}$ = -0.042 + (0.199*$DAS_{time\ a}$) + (0.177*deltaDAS) + (0.043*log time) + (0.024*$DAS_{time\ a}$*delta DAS) + (0.290*$HAQ_{time\ a}$)

A larger decrease in DAS is associated with a lower outcome HAQ (p<0.001). This positive relationship did not significantly change over time (p=0.08). A decrease in a high DAS improved the HAQ more than a similar decrease in a lower DAS. However, corrected for the previous HAQ, this effect is the other way around (p<0.001), but still a DAS decrease is associated with a lower HAQ.

Conclusion: A decrease in DAS is significantly associated with a decrease in HAQ at every time point during 5 years of DAS-steered treatment in patients with recent onset RA and a larger decrease in DAS level is significantly associated with a larger decrease in HAQ. These results indicate that at any time during treatment, if the DAS is lowered, patients will benefit with better functional ability.

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Assessing the Diagnostic Accuracy of a 3-Component Synovitis Score and Its Components with Receiver Operating Curve (ROC) Analysis. Elisabeth Slansky[1], Jialiang Li[2], Thomas Häupl[3], Lars Morawietz[3], Veit Krenn[4] and Frank Pessler[1], [1]Technical University Dresden Children's Hospital, 01307 Dresden, Germany, [2]National University of Singapore, Singapore, [3]Charite Berlin, Berlin, Germany, [4]Univ. of Trier, Germany

Purpose: To assess the diagnostic accuracy of a 3-component synovitis score and its components (intimal hyperplasia, stromal cellularity, inflammatory infiltration) with receiver operating characteristic (ROC) curve analysis and multi-category ROC analysis.

Method: The histological grade of synovitis was scored in 666 synovial specimens carrying the following clinical diagnoses: normal synovium, n=33; post-traumatic arthropathy (PtA), n=29; osteoarthritis (OA), n=221; psoriatic arthritis (PsA), n=42; and rheumatoid arthritis (RA), n=341. The discriminatory abilities of the complete score and each of its components were quantified with the area under the ROC curve (AUC) in each of the 10 possible paired comparisons. Multi-category ROC analysis was used to rank the complete score and each of its components according to their overall discriminatory abilities.

Results: The score differentiated all arthropathies accurately from normal tissue (AUCs: 0.87-0.98), and RA from OA or PtA (AUCs: 0.85 for both), but could not distinguish well between pairs of inflammatory (RA vs PsA, AUC 0.63) or degenerative (PtA vs OA, AUC 0.59) arthropathies. AUCs of the intimal hyperplasia and stromal cellularity components (r=0.94 and 0.91, respectively) correlated with the AUCs of the complete score markedly more strongly than the inflammatory infiltration component (r=0.60). Multi-category ROC analysis ranked the score and its components in the following order of overall diagnostic accuracy: complete score>stromal cellularity>intimal hyperplasia>inflammatory infiltration, with the complete score being clearly superior to any of its components (Table 1).

Conclusion: This 3-component synovitis score is an accurate tool for differentiating diseased from normal synovium and inflammatory from degenerative arthropathies. Its high discriminatory ability stems more from measuring proliferative than infiltrative aspects of synovitis. The data also suggest that multi-component synovitis scores may be superior to single component scores.

Table. Diagnostic ranks of the synovitis score and its components according to multi-category ROC analysis

Rank	Test	HUM[1]
1	Synovitis score	0.0620
2	Stromal cellularity	0.0140
3	Intimal hyperplasia	0.0075
4	Infiltration	0.0005
5	Nondiscriminatory marker[2]	0.000076

[1]Values represent hyper volumes under the ROC manifolds (HUMs), calculated according to ref. 1.

[2]Hypothetical marker corresponding to the null hypothesis.

Reference

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Comparison Between Resection and Arthrodesis of the First MTP Joint in the Same Patient (Internal Control) for Rheumatoid Forefoot Deformity. Masahiro Tada[1], Tadashi Okano[1], Yuko Sugioka[1], Shigeyuki Wakitani[1], Akira Shimazaki[2], Kentaro Inui[2], Hiroaki Nakamura[1] and Tatsuya Koike[1], [1]Osaka City University Medical School, Osaka, Japan, [2]Higashisumiyoshi Morimoto Hospital, Osaka, Japan

Purpose: Most of patients with rheumatoid arthritis have problems with their feet. The painful, deformed rheumatoid forefoot may be treated with resection of the lesser metatarsal heads combined with either arthrodesis or resection of the first metatarsophalangeal (MTP) joint. Good results have been observed in previous surgical procedures. Recurrent deformity of both the hallux valgus (HV) and lesser toes were reported, when the HV deformity was managed by resection. This criticism, however, was based on historical observation from previous studies. There was no prospective or randomized study. So we performed the prospective, randomized, internal-controlled clinical study. To compare the clinical results of arthrodesis and resection of the first MTP joint in simultaneous operation for same patient who had the painful, deformed rheumatoid forefoot.

Method: We performed resection of the lesser metatarsal heads for bilateral and arthrodesis of the first MTP joint for one side and resection (LeLievre method) for opposite side in same patient. Between April 2004 and December 2008, 20 patients with severe painful deformed rheumatoid forefoot were operated. We investigated 15 patients (30 feet) who received at least 6 months of follow-up. All patients were assessed for American Orthopaedic Foot and Ankle Society (AOFAS) score, HV angle, M1M2 angle, and M1M5 angle at the point of pre-operation and final follow-up. We evaluated callosities and recurrence at final follow-up.

Results: At the operation, patients were, on average, 64.1 years old, mostly female (86.7%). Patients had mean disease duration of 14.9 years, with DAS28 of 4.33. The mean follow-up period was 36.7 (8~76) months. We found excellent satisfaction and a significant improvement of AOFAS score, HV angle, M1M2 angle, and M1M5 angle. There were no statistically significant differences between the groups, except HV angle. HV angle of arthrodesis side was significantly less than that of resection side at follow-up (table). Two patients in the each groups had callosities at final follow-up, but there was no patient that have recurrence of HV deformity. In the arthrodesis side, there were no complications of pseudoarthrosis and breakage.

Conclusion: In our prospective, internal-controlled clinical study, it revealed that arthrodesis of the first MTP joint provide better results in maintenance of HV angle, although there was no significant difference in AOFAS score. Arthrodesis of the first MTP joint should be reliable option for the treatment of rheumatoid forefoot deformity.

	Arthrodesis	**Resection**	**P-value**
AOFAS* score			
Pre-operation	33.27	33.60	0.86
Final follow-up	86.07	84.60	0.34
HV angle (°)**			
Pre-operation	40.56	43.30	0.47
Final follow-up	10.13	16.09	<0.01
M1M2 angle(°)			
Pre-operation	15.01	14.71	0.72
Final follow-up	9.55	10.34	0.55
M1M5 angle(°)			
Pre-operation	35.64	33.66	0.05
Final follow-up	29.10	28.08	0.50

*:AOFAS=American Orthopaedic Foot and Ankle Society **:HV=Hallux Valgus

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Rheumatoid Arthritis (RA) Is Associated with Increased Mortality in Patients Undergoing Total Joint Arthroplasty. Kaleb D. Michaud[1], Edward V. Fehringer[2], Kevin Garvin[2], James R. O'Dell[3] and T. R. Mikuls[3], [1]University of Nebraska Medical Center and NDB, Omaha, NE, [2]University of Nebraska Medical Center and Omaha VA, Omaha, NE, [3]U Nebraska, Omaha, NE

Purpose: Although total joint arthroplasty (TJA) is a commonly used procedure in RA, risks and benefits of TJA in this specific population have not been well defined. The purpose of this study was to examine the association of RA with post-operative mortality following total hip, knee, shoulder and elbow arthroplasty.

Methods: Study subjects were enrolled in the Veterans Affairs (VA) National Surgical Quality Improvement Program (NSQIP) undergoing TJA from fiscal years 1999 through 2006. Dispensed medications and ICD9 codes were indentified using links to the VA Pharmacy Benefits Management (PBM) database. Patients were classified as having RA if they had ICD9 code 714.0 plus use of a DMARD within 1 year before TJA. The osteoarthritis (OA) control group had ICD9 code 715. The association of RA with overall mortality was examined using multivariate Cox proportional hazards regression, adjusting for age, gender, TJA type, calendar year, race, select baseline comorbidity / health behaviors (diabetes, COPD, dyspnea, congestive heart failure, cerebrovascular disease, renal insufficiency, anemia, alcohol use and current smoking), pre-operative functional status, and ASA class. The effects of specific RA medications were examined using sequential models.

Results: There were 37,103 patients (n = 888 with RA) undergoing TJA, with total knee arthroplasty being most common (64%), followed by hip (33%), shoulder (2%), and elbow (0.2%). Patients were predominantly men (96%) and had a mean (SD) age of 64.4 (10.7) years. Glucocorticoid use was much more common in RA cases vs. OA (41% vs. 2%). There were a total of 4,093 deaths over a mean follow-up of 3.7 (2.3) years. After multivariate adjustment, RA was associated with a significantly higher mortality (HR = 1.48; 95% CI 1.24 to 1.76). This risk was attenuated after further adjustment for glucocorticoid use (HR = 1.23; 95% CI 1.02 to 1.49). Factors significantly associated with mortality in patients with only RA are shown in the Table. There was no association of other biologic or non-biologic DMARDs with mortality in RA-only sub-analyses.

Patient factor	**Hazards Ratio (95% CI)**
Glucocorticoid use	1.81 (1.28 to 2.53)
Age (year)	1.06 (1.04 to 1.08)
Chronic obstructive pulm disease	2.10 (1.39 to 3.19)
Congestive heart failure	4.05 (1.62 to 10.12)
Anemia, Hematocrit < 38%	1.57 (1.10 to 2.24)
Current smoking	2.03 (1.39 to 2.96)

Conclusion: RA patients have a higher long-term mortality risk than OA patients following TJA, a risk that is most pronounced among glucocorticoid users in addition to current smokers and those with select comorbid conditions. Perioperative interventions that target high risk patients with RA need to be evaluated and implemented with a goal of reducing postoperative mortality following TJA.

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Rheumatoid Arthritis (RA) Patients Are Not at Increased Risk for 30-Day Cardiovascular Events or Infections Following Total Joint Arthroplasty. Kaleb D. Michaud[1], Edward V. Fehringer[2], Kevin Garvin[2], James R. O'Dell[3] and T. R. Mikuls[3], [1]University of Nebraska Medical Center and NDB, Omaha, NE, [2]University of Nebraska Medical Center and Omaha VA, Omaha, NE, [3]U Nebraska, Omaha, NE

Purpose: Although serious infection and cardiovascular disease are increased in patients with RA, it is not known whether RA impacts the risk for these complications following total joint arthroplasty (TJA). We examined whether RA was associated with the occurrence of 30-day postoperative complications in a large population of patients undergoing TJA.

Methods: Analyses included data from the VA National Surgical Quality Improvement Program (NSQIP) for fiscal years 1999-2006. ICD9 codes and medication dispensing data were obtained from the VA Pharmacy Benefits Management (PBM) database. RA was defined for those with a corresponding ICD9 (714.0) plus receipt of at least one DMARD within 1 year before TJA. All other patients had an ICD9 (715.x) corresponding to osteoarthritis (OA). 30-day complications (major cardiovascular event, infection, and return to the operating room) were compared by diagnosis (RA vs. OA) using multivariate regression. Post-operative infections included systemic sepsis, pneumonia, urinary tract infection, superficial and deep wound surgical site infections. Cardiovascular events included cardiac arrest, myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis. All analyses were adjusted for age, sex, and clustering by site (n = 104 sites). Additional covariates included sociodemographics, comorbidities, health behaviors, and well defined operative risk factors (up to 44 covariates examined).

Results: There were 37,103 patients (n = 888 with RA) undergoing TJA, with total knee arthroplasty being most common (64%), followed by hip (33%), shoulder (2%), and elbow (0.2%). Patients were predominantly men (96%) with a mean (SD) age of 64 (11) years. Among RA patients, the most frequently used DMARDs included methotrexate (59%), hydroxychloroquine (40%) and sulfasalazine (23%) while 41% were taking glucocorticoids and 24% biologic DMARDs. The frequency of select complications based on diagnosis is summarized in the table below. Compared to OA patients, those with RA were significantly more likely to require a return to the operating room but had similar rates of postoperative infection and cardiovascular events.

Table: The frequency of select complications following TJA in patients with RA and OA

	RA (n = 888)	OA (n = 36,215)	RA OR (95% CI)
Infection	4.17%	4.12%	1.02 (0.72, 1.47)
Cardiovascular event	1.24%	1.98%	0.69 (0.37, 1.28)
Return to operating room	4.50%	3.01%	1.45 (1.08, 1.94)

Conclusion: : RA patients are not at an increased risk for short-term infectious complications or cardiovascular events following TJA. RA patients did have an increased rate of return to the operating room. Reasons for this difference and strategies to address it require further study.

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Work Instability in Argentinean Patients with Rheumatoid Arthritis: Prevalence and Associated Factors. M. Tamborenea[1], C. Pisoni[1], E. Mysler[2], G. Tate[2], D. Pereira[3], J. Quintero[4], A. Cappuccio[5], O. Rillo[6], A. Baños[7], P. Arturi[8], Jl Velazco Zamora[9], A. Alvarellos[10], J. Ceccatto[11], B. Pons Estel[12], M. Gallo[13], A. Catalan Pellet[14], J. Cavallasca[15], G. Gomez[16], P. Tate[17], V. Malah[18], M. Lazaro[19], D. Sohn[20], J. Moreno[21], M. Larroude[22], S. Toloza[23] and C. Graf[24], [1]OMI, Buenos Aires, Argentina, [2]OMI, [3]HIGA, [4]Hospital de Clinicas, [5]Hospital Cesar Milstein, [6]Hospital Tornu, [7]IMAI, [8]IREP, [9]CER, [10]Hospital Privado, [11]Hospital Cullen, [12]Sanatorio Parque, [13]OSEP, [14]Hospital Rivadavia, [15]Hospital Iturraspe, [16]Instituto Lanari, [17]Hospital Carrillo, [18]CPR, [19]Hospital San Isidro, [20]Instituto Roche, [21]CER, San Juan, [22]Tiempo, [23]Hospital San Juan Bautista, [24]Centro Medico Mitre

Purpose: To determine the prevalence and associated factors to work instability (WI) in Argentinean patients with rheumatoid arthritis (RA) currently working.

Methods: Employment status of RA patients from 31 rheumatology clinics was assessed using a standardized data collection form and a patient questionnaire. RA patients currently working answered the validated Spanish version of RA WIS questionnaire. High risk WI was considered when RA WIS was ≥17 (Total score from 0-23). The association among socioeconomic, demographic, clinical features and comorbidities (diabetes, hypertension, cardiac failure, myocardial infarction, depression and fibromyalgia) with WI was examined by standard statistical tests.

Results: A total of 172 patients answered the RA WIS. Mean age was 49.3±10.8, 81.3% were female; mean disease duration was 8.1±7.2 years. Forty six percent of patients were doing manual work. The mean RA WIS score for the total population was 11.4±6.8 and 40.9 % had a high risk WI.

Univariate analysis:

Variable	Low risk WI N=121	High risk WI N= 84	*p* value
Female, (%)	84.5	79.3	0.347
Manual work, (%)	42.6	50.6	0.270
< 12 years education, (%)	19.8	27.3	0.206
Lack of health insurance, (%)	20.6	29.7	0.137
Below poverty line*, (%)	9.9	19	0.061
Age, mean ± SD	49.9±10.8	48.5±10.6	0.345
Disease duration years, mean ± SD	8 ± 7.5	8 ± 6.7	0.869
Functional class 3 and 4, (%)	7.4	8.3	0.814
Radiological erosions, (%)	**27.2**	**52.3**	**<0.001**
HAQ≥ 1, %	**17.3**	**59.5**	**<0.001**
Rheumatoid factor positive, (%)	84.8	90	0.239

*Monthly household income < 800 pesos/month

None of the extraarticular manifestations, neither any comorbidity was associated with high risk WI.

Multivariate analysis: predictors of high risk WI

Variable	OR	95% CI	*p* value
HAQ≥ 1	**12.31**	**5.38 - 28.18**	**<0.001**
Functional class 1 and 2	**0.151**	**0.036 - 0.632**	**0.010**
Radiological erosions (yes)	**4.848**	**2.22 - 10.54**	**<0.001**
Manual work (yes)	1.429	0.652 - 3.132	0.372
Disease duration> 5years	0.989	0.937 - 1.045	0.713
Below poverty line (*)	**0.301**	**0.096 - 0.943**	**0.039**

Education < 12 years	0.715	0.279 - 1.83	0.485
Extraarticular features (yes)	1.130	0.526 - 2.427	0.752

*Monthly household income < 800 pesos/month

Conclusion: Forty one percent of our patients with RA currently working have high risk WI. The predictors of high RA WIS score in multivariate analysis were HAQ ≥ 1 and radiological erosions; functional class 1-2 and living above the poverty line were protectors for high risk WI.

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The Proportion of Patients with Work Disability (WD) Is in Early Inflammatory Arthritis: Results From the CATCH Cohort. L. Mussen[1], V. Bykerk[2], B. Haraoui[3], C. Hitchon[4], S. Jamal[5] and J. Pope[6], [1]University of Western Ontario, London, ON, [2]Mt Sinai Hospital, Toronto, ON, [3]Institut de Rhumatolgie de Montreal, Montreal, QC, [4]University of Manitoba, Winnipeg, MB, [5]St. Michael's Hospital, Toronto, [6]St Joseph Health Care, London, ON

Purpose: It is known that WD is high in established RA and ranges from 30 to 50%. The prevalence of WD in early RA (ERA) and early inflammatory arthritis (EIA) has not been well established.

Method: Data from 655 patients enrolled since July 2007 were collected from the Canadian Early Arthritis Cohort (CATCH) study, a multi-centre observational prospective cohort of patients with EIA. Inclusion Criteria: age >16, symptom duration of 6-52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP or PIP + ≥1 of: positive RF, positive anti-CCP, morning stiffness >45 mins, response to NSAIDs, or a painful MTP squeeze test. 69% are identified as having RA (CRA criteria). At their first visit, patients were asked about employment status with possible answers including employed, retired, unemployed, on sick leave (SL), work disabled, on maternity leave, in school or a homemaker. The Dictionary of OccupationalTitles (DOT) was used to determine the physical demands of each type of employment.

Results: 54% were employed, 22% retired, and 6% reported WD or SL, with the remaining 18% homemakers, students or on maternity leave. Patients who were neither employed nor on WD/SL were excluded from analysis, and baseline characteristics of the remaining 391 are given in the table below. 86% of the employed were in jobs with sedentary or light physical demands. Patients were further classified according to those who met the ACR criteria for ERA and those who did not (designated as EIA). WD/SL was not significantly different in EIA vs ERA (3.9% vs 7.1%, p=0.1). Factors associated with WD/SL in the group of 391 as a whole included TJC, DAS28 and SF-12, whereas SJC, RF and anti-CCP did not differ significantly between the WD/SL and the employed. Factors associated with WD in subgroup analysis were similar to the group overall with the exception of DAS-28, which differed significantly between the employed and WD/SL in ERA only.

	Employed	WD/SL
N	351	40
Age (SE)	47 (0.6)	47 (2.3)
% female	74%	68%
% positive RF	57%	58%
% meeting ACR criteria for RA	68%	80%
DAS-CRP	4.7 (0.1)	5.4 (0.2)

TJC (0-28)	8.3 (0.4)	11.9 (1.1)
SJC (0-28)	7.3 (0.4)	8.2 (1.0)

Standard Error of mean reported in brackets.

Conclusion: WD is low at entry into an ERA cohort and thus there is a chance to intervene effectively in the care of patients early to prevent WD from occuring. As in established RA, WD was related to patient factors, HAQ, damage and disease activity. Both in patients meeting ACR criteria for ERA and those whose disease activity classifies as EIA, WD is especially related to TJC, DAS-28 and SF-12, and elevation in these parameters may indicate a point at which intervention may prevent WD. Although, p=NS, there appears to be more baseline WD in those who met ERA criteria and as the cohort grows, this may become significant.

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Validation of Rheumatoid Arthritis Disease Activity Index (RADAI) in a North American Cohort of Patients with Early Rheumatoid Arthritis (RA). Xiuying Li, Maggie H. Chen and Claire Bombardier, University Health Network, Toronto, ON

Purpose: The RADAI is a patient self-administered index measure of RA disease activity. It is easy to complete in a practice setting. The SONORA (Study of new-onset Rheumatoid Arthritis) study was used to validate the RADAI against the DAS28-CRP and HAQ as a measure of change over time in early RA.

Methods: Patients diagnosed as having new onset RA (symptoms≥3 but ≤12 months) by a board-certified rheumatologist across North America were recruited in this study. The correlations between RADAI, DAS28-CRP and physical function (Health Assessment Questionnaire-Disability Index, HAQ-DI) were calculated. The agreement of classification of patients into mild, moderate and severe categories for RADAI and DAS28-CRP was determined at baseline, and year 1. Finally, the change in RADAI, DAS28-CRP and HAQ were compared in patients that achieved ACR20 and ACR50

Results: A total of 936 patients were analyzed at baseline, and year 1. Patients were female (73%), with mean age 53 years (19 to 85 years) and mean duration of RA signs and symptoms of 170 days at the time of baseline evaluation. The correlations between RADAI and DAS28-CRP at baseline and 1 year were 0.44 and 0.45 respectively (both $p<0.0001$), between RADAI and HAQ-DI at baseline and 1 year were 0.64 and 0.65, respectively (both $p<0.0001$). The classification of patients into mild, moderate, and severe categories showed a 52% agreement of RADAI and DAS28-CRP at baseline, and 51% at year 1. At baseline, 31% RADAI were classified better than DAS28-CRP and 17% were classified worse. The change in RADAI, DAS28-CRP and HAQ scores of patients achieving ACR20 and ACR50 is shown in Table 1: For both ACR 20 and 50 the changes in RADAI were similar to the changes in DAS-CRP..

Conclusion: The data shows low agreement in classifying patients as mild, moderate and severe for both patient and physician measures cross-sectionally at one point in time. However, the RADAI shows remarkable similar change over time when compared to DAS28-CRP and HAQ-DI, We conclude that the RADAI is a valid measure of disease progression over time , and therefore, it could be a practical tool in daily practice.

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Table 1:

Measures (possible range)	Baseline Mean (SD)	Year 1 Mean (SD)	Mean changes from baseline mean (SD)		
			All	ACR20 achieved	ACR50

			N=936	N=221	achieved N=103
RADAI (0,10)	4.55(1.9)	3.12(2.2)	-1.20(2.2)	-2.54(1.7)	-3.00(1.5)
DAS28-CRP (0.57, 9.58)	4.36(1.3)	3.37(1.4)	-1.03(1.4)	-2.21(1.1)	-2.59(1.1)
HAQ ¨C DI (0,3)	1.00(0.7)	0.82(0.7)	-0.17(0.6)	-0.6(0.5)	-0.75(0.5)

Disclosure: X. Li, None; **M. H. Chen**, None; **C. Bombardier**, None.

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Usefulness of Transient Elastography (Fibroscan) in Assessing Hepatic Fibrosis in Rheumatic Patients Under Long Term Methotrexate Treatment. Dimitrios Vassilopoulos, Spilios Manolakopoulos, Hariklia Kranidioti, Anna Kandili, Maria-Vasiliki Papageorgiou and Athanasios Archimandritis, Athens University School of Medicine, Athens, Greece

Purpose: Liver fibrosis is an infrequent complication of long-term methotrexate (MTX) treatment in rheumatic patients. Current guidelines for MTX monitoring include the periodic measurement of serum aminotransferases (AST/ALT) which do not accurately reflect the degree of liver fibrosis. Liver biopsy which is the current gold standard for the assessment of hepatic fibrosis is an invasive procedure that is rarely used in clinical practice. Transient elastography (TE) is a new, promising, non invasive technique for the evaluation of hepatic fibrosis. The aim of our study was to evaluate the degree of liver fibrosis by TE (FibroScan, Echosens) in rheumatic patients treated with MTX.

Method: This was a prospective study that included consecutive patients with various rheumatic diseases treated with MTX (n=53) and a control group which consisted of age and sex matched patients with rheumatic diseases that had not received MTX (n=11) and patients with osteoarthritis (OA, n=11). Demographic and clinical data, duration and cumulative MTX dose were obtained for all patients. Liver stiffness was assessed blindly using TE by a single experienced operator in all patients. The cut-off point for significant liver fibrosis was set at 7.1 kPa, according to previous publications.

Results: Only patients with valid measurements of liver stiffness by TE were included in the study: 45 rheumatic patients treated with MTX (RA=29, spondyloarthropathies=12, other rheumatic diseases=4) and 19 controls (11 patients not on MTX and 8 with OA). No differences in concurrent liver diseases, alcohol use, BMI, glucose or lipid levels were noted between the two groups. The mean age of MTX treated patients was 55 ± 14 years while the mean cumulative MTX dose was 1349 ± 1036 mg (median=1220 mg). The median duration of MTX therapy was 24 months while 38 % (17/45) of patients had received > 1.5 gm of MTX. 3 patients (7%) and 2 controls (10%) had elevated ALT levels while no patient or control had clinical or imaging evidence of cirrhosis. The mean liver stiffness of patients on MTX was 5.6 ± 1.8 kPa compared to 6.5 ± 3.2 kPa (p=0.6) of the control group. Liver stiffness > 7.1 kPa indicating significant liver fibrosis was observed in 17% of patients (8/45) and 42% of controls (8/19, p=0.06 by Fisher exact test). No correlation between liver stiffness and the cumulative MTX dose was observed (Spearman rho p=0.816 r=-0.136). There was also no difference in liver stiffness between patients that had received > 1.5 gm of MTX (5.7± 2.0 kPa) compared to those treated with < 1.5 gm (5.5 ± 1.3 kPa, p=0.9).

Conclusion: Our data show that long-term MTX administration is not associated with significant liver fibrosis in rheumatic patients. Fibroscan is a useful non-invasive technique to assess liver fibrosis in these patients that should be further investigated as a monitoring tool for MTX-induced liver toxicity.

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Level of Gastrointestinal Discomfort in Patients with Rheumatoid Arthritis Is Associated with Indicators of Health Status and Other Measures of Disease Activity. Cathrine Persson, Tore K. Kvien and Till Uhlig, Diakonhjemmet Hospital, Oslo, Norway

Purpose: Patients with rheumatoid arthritis (RA) commonly use anti-inflammatory medication and many suffer from gastrointestinal (GI) side effects. Our aim was to investigate factors other than use of non-steroidal anti-inflammatory drugs (NSAIDs), both non-selective (ns) NSAIDs and selective COX-II inhibitors (Coxibs) that may influence the level of self-reported GI discomfort on a 100 mm visual analogue scale (VAS).

Methods: From the population based Oslo Rheumatoid Arthritis Registry, 914 patients aged 20-79 years responded to a questionnaire in April 2004, prior to withdrawal of rofecoxib. Assessed variables were demographic information, SF-36 with mental (MCS) and physical (PCS) component scores, Arthritis Impact Measurement Scales2 (AIMS2) pain, Health Assessment Questionnaire (HAQ), self efficacy scales, VAS for general and joint pain, GI discomfort, global disease activity and fatigue, past and present use of NSAIDs and Coxibs, and whether or not the patient had experienced a previous gastroduodenal (GD) ulcer. Descriptive statistics, Student t-tests, correlation and linear regression analysis (uni- and multivariate) were applied to identify associations to degree of current GI-discomfort, adjusting for age, gender and disease duration in linear regression analyses.

Results: The 914 respondents had mean age (SD) 58.7 (13.4) years, disease duration 13.6 (10.5) years, 78.8% were females. Level of GI discomfort (VAS) was moderately correlated to VAS fatigue/ patient global/ general pain/ joint pain (r=0.38/0.38/0.35/0.33), and to AIMS2 pain (r=0.32), self-efficacy pain (r=0.20) and MCS (r=-0.30), p<0,001 all variables. Previous/current users of Coxibs had more GI discomfort than non-users (26.0 vs 19.2mm, p<0.001) / 24.7 vs 20.6mm, p<0.05) on VAS. There was no significant difference between past or present users of nsNSAIDs. In a multivariate model adjusting for age, gender and disease duration (table 1) several variables were independently associated with GI-discomfort (R^2= 0.24).

Table 1. Dependent variable: GI discomfort on 100mm VAS.

	B	95% CI for B
VAS fatigue (0-100)	0.18***	0.11 - 0.24
HAQ (0-3)	5.69***	2.72 - 8.65
MCS (0-100)	-0.40***	-0.55 - -0.24
GD ulcer	14.21***	8.22 - 20.21
Previous Coxib user	1.79*	0.05 - 3.54

* p<0.05, *** p<0.001

Conclusion:

GI discomfort in RA patients is independently related to use of anti-inflammatory medications, to earlier GD ulcer, physical and mental function and fatigue. Clinicians should be aware that in RA patients the level of GI discomfort is influenced by indicators of health status in addition to anti-inflammatory medication.

Disclosure: C. Persson, None; **T. K. Kvien**, None; **T. Uhlig**, None.

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Evidence That Vasculitis Complicating Rheumatoid Arthritis (RA) May Be Becoming Less Common. An Analysis of Extra Articular Features (ExRA) in Two Early RA Inception Cohorts. Gouri Koduri[1], Adam Young[1], Richard Williams[2], Patrick D. Kiely[3], Josh Dixey[4], Sam Norton[5] and Peter Prouse[6], [1]Early RA Study, St. Albans, United Kingdom, [2]Early RA Study, Hereford, United Kingdom, [3]St Georges Hospital, London, United Kingdom, [4]Oswetry, United Kingdom, [5]Hertfordshire, United Kingdom, [6]North Hampshire Hospital, Basingstoke Hampshire

Purpose: Extra articular manifestations have been well documented in RA and previous reports suggest that the presence of ExRA is associated with worse outcomes, measured by erosive disease, physical function and mortality. The aim of this study was to compare baseline prevalence and cumulative incidence of ExRA in two inception cohorts, one started in 1986, the other in 2002.

Method: The Early Rheumatoid Arthritis Study (ERAS) recruited 1460 patients from 1986 to 1998 from 9 centres in England. The Early RA Network (ERAN) has recruited 1060 patients from 21 centres in the UK & EIRE since 2002. Both cohorts recruited patients within 2yrs of disease onset and prior to use of disease modifying drugs. Both have collected the same standardised clinical, laboratory & x-ray measures at baseline, 6 months & yearly. This includes extra articular features and complications of RA, and major co morbid conditions.

Results: For this analysis only patients followed for at least 12 months were included (n=2299). Baseline demographic features in the 2 cohorts were similar: mean age at onset was 55 and 56 respectively for ERAS and ERAN, 66% and 68% were women, rheumatoid factor positive in 65% & 66%, erosions on x-ray of hands & feet in 26% & 29%. Onset of RA to rheumatology consult was median 6 months in both, but time to 1st DMARD was median 3 months & 2 weeks respectively. At least one ExRA feature was recorded at baseline or within 1yr in 264 (19%) & 187 (21%) in ERAS & ERAN respectively. The numbers and baseline prevalence & 5yr cumulative incidence figures (with 95% confidence intervals) for rheumatoid nodules, Sjogren's syndrome, Raynauds, Feltys, rheumatoid lung, neuromyopathy, vasculitis and systemic features (e.g. weight loss) will be displayed graphically. Severe ExRA features were uncommon: baseline prevalence for Interstitial Lung Disease (ILD) was 0.8 for both cohorts, but 5yr cumulative incidence was 2.6 & 1.4 for ERAS & ERAN respectively. Baseline prevalence for vasculitis was 1.1 & 0.4, & 5yr cumulative incidence 3.0 & 2.2 respectively. The 1st drug of choice was sulphasalazine in 73% and 34% in ERAS and ERAN respectively, and methotrexate in 7% and 49%.

Conclusion: Severe ExRA features were uncommon. Vasculitis was more common in the earlier cohort, suggesting that this is becoming less frequent. This could not be explained by smoking history, but may be related to different and the more intensive DMARD use in the later cohort.

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What Should We Have to Aim for RA Patients: Remission or Low Disease Activity? Violaine Foltz[1], Frédérique Gandjbakhch[1], Fabien Etchepare[1], Marie Laure Tanguy[2], Agnes Monnier[1], Carole Rosenberg[1], Cecile Poulain[1], Sylvie Rozenberg[1], Pierre Bourgeois[3] and Bruno Fautrel[3], [1]MD, Paris, France, [2]Paris, France, [3]MD, PhD, Paris, France

Low disease activity or Remission: is this the question? Progression of structural damage in a cohort of RA patients in remission or low disease activity

Purpose: Low disease activity (LDA) and remission (REM) are the therapeutic objectives in rheumatoid arthritis (RA). However, studies have shown that structural damage may progress in such patients. **Objective:** To assess the risk of radiographic progression at 1 year in patients in either LDA or REM.

Method: Patients with established RA, satisfying to 1987 ACR criteria, were included between February 2007 and February 2008. Inclusion criteria were: RA diagnosis made after 2000, LDA or REM defined as DAS 44 $\leq$ 2.4 or < 1.6 respectively. All patients were assessed clinically every three months for 12 months. Hand and forefoot X-rays were performed at baseline and 12 months. At baseline, all patients underwent high resolution ultrasonography of the hands and forefeet (ESAOTE technos) and low-field dedicated MRI of the dominant hand (ESAOTE C-scan 0.2T). Structural damage was assessed with the van der Heijde-modified Sharp score (SHS), performed blindly by 2 trained readers aware of X-ray sequence. Progression was defined as a variation of the total SHS of at least 1 point.

Results: 85 patients were included, 38 in LDA and 47 in REM. Main characteristics were: mean age 51 years; mean disease duration 2.9 years without significant differences between groups. At baseline, the main difference between LDA and REM groups was the presence of positive power Doppler on ultrasonography[1].

The structural progression during the 12-month follow-up was not different between the 2 groups (table 1). There was a trend for higher number of progressors in the LDA than in the REM group (64.9 % versus 50%) although not significant.

Table 1 Radiographic, US and MRI parameters (PD: power Doppler; BMO: bone marrow oedema, n : number)

	LDA (n=47)	REM (n=38)	p
Characteristics at baseline			
- Patients with □ 1 synovitis on US, (%)	86.5	89.4	ns
- Patients with positive PD, n (%)	44.4	17.0	0.01
- Patients with □ 1 synovitis on MRI, (%)	95.7	97.0	ns
- Patients with □ 1 BMO on MRI, (%)	34.2	29.8	ns
Radiographic progression			
- Total SHS variation	3.3	3.0	ns
- Progressors, n (%)	31 (64.9)	17 (50.0)	ns

Conclusion: Patients in LDA or REM don't seem to progress differently over a 1-year period. Further analyses are in progress to determine the impact of PD signal and BMO on radiographic progression.

[1] Foltz V et al. Arthritis and rheum 2008;9 suppl:S468.

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Obesity and RA Disease Severity: A Comparison Between European and American RA Patients. A. Finckh[1], A. Scherrer[2], G. Reed[3], J. Greenberg[4], A. Lubbeke[1], H. Schwarz[2], C. Gabay[1] and J. Kremer[5], [1]University of Geneva, Geneva, Switzerland, [2]SCQM Foundation, Zurich, Switzerland, [3]University of Massachusetts, Worcester, MA, [4]NYU, New York, NY, [5]Albany Medical College, Albany, NY

Purpose: Obese individuals experience elevated levels of circulating proinflammatory cytokines. While obesity might be associated with an increased risk of developing RA and with impaired quality of life, the role of obesity in RA disease severity is not well established. The aim of this study was to examine if obesity is associated with more severe RA disease outcomes, in particular with higher levels of disease activity and higher functional disability.

Method: We included all RA patients from a European (SCQM-RA) and a North-American (CORRONA) RA registry with available Body Mass Index (BMI). Patients were categorized according to the WHO BMI categories as “underweight” (BMI < 18.5), “normal weight” (BMI ≥ 18.5, < 25), “overweight” (BMI ≥ 25, < 30), “obese class I” (BMI ≥ 30, < 35) and “obese class II” (BMI ≥ 35). The study’s primary outcomes were functional disability as measured by HAQ-DI (SCQM-RA) or mHAQ (CORRONA) and RA disease activity as measured by DAS-28 (SCQM-RA) or CDAI (CORRONA). We used simple descriptive statistics to analyze the study outcomes in the 5 BMI categories and multivariate regressions to examine potential trends after adjustment for potential confounders.

Results: 3’952 European and 18’640 US RA patients were included. Overall, obesity (BMI ≥ 30) was more prevalent among US patients (38% in CORRONA compared to 15% in the SCQM), and the mean BMI was 25.1 (95% CI: 25.0 – 25.4) in the SCQM versus 29.1 (95% CI: 29.0 - 29.2) in CORRONA. Disease characteristics at inclusion, categorized by BMI categories:

European patients (SCQM-RA):

	BMI<18.5	**BMI 18.5-25**	**BMI 25-30**	**BMI 30-35**	**BMI≥35**
N patients	178	1992	1185	447	149

age	50.4	56.3	56.3	57.0	55.4
% Female	94	81	65	73	77
% RF+	71	71	68	67	60
DAS28(ESR)	**4.54** (4.3-4.8)	**4.34** (4.3-4.4)	**4.46** (4.4-4.6)	**4.59** (4.5-4.7)	**4.6** (4.4-4.8)
HAQ-DI	**1.11** (1.0-1.2)	**0.97** (.9-1)	**1.04** (1.0-1.1)	**1.15** (1.1-1.2)	**1.31** (1.2-1.4)
% Steroid	53	51	51	60	57
% DMARDs	74	81	82	83	82
% Biologics	31	29	27	29	32

North American patients (CORRONA):

	BMI<18.5	**BMI 18.5-25**	**BMI 25-30**	**BMI 30-35**	**BMI≥35**
N patients	284	5524	6012	3550	3270
age	59	58	59	589	56
% Female	89	82	68	73	82
% RF+	77	67	68	68	65
% anti-CCP+	67	63	62	62	58
CDAI	**16.3** (14.5-18.0)	**13.1** (12.7-13.4)	**13.1** (12.7-13.4)	**14.1** (13.7-14.6)	**15.5** (15.1-16.0)
mHAQ	**0.43** (.36-.49)	**0.32** (.31-.33)	**0.33** (.32-.35)	**0.39** (.38-.41)	**0.47** (.46-.49)
% Steroid	41	39	37	38	41
% DMARDs	86	90	89	90	91
% Biologics	42	39	37	38	41

After adjusting for potential confounders, a significant trend existed for patients with higher BMI to have higher disease activity and greater functional disability in both cohorts. This trend had a quadratic shape, with higher levels of disease outcomes at both extremes of BMI.

Conclusion: Obesity is more prevalent in North-American than in European RA patients, differences which need to be further explored. In both populations, higher BMI scores were associated with somewhat higher disease activity and greater functional disability. Obesity could have pro-inflammatory effects in RA, however further research is needed to understand the impact of obesity on human immunity and identify the effects of BMI on RA disease outcomes.

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Increased Prevalence of Erectile Dysfunction in Rheumatoid Arthritis. Barry J. Sheane[1], Donough G. Howard[2] and Gaye Cunnane[1], [1]St James Hospital, Dublin, Ireland, [2]St James's Hospital, Dublin, Ireland

Purpose: The risk of cardiovascular disease (CVD) is elevated in patients with rheumatoid arthritis (RA), who tend to present with sudden events or atypical disease, resulting in poor outcomes. Increased clinical vigilance may result in early detection of covert atherosclerosis. Separate studies have demonstrated a correlation between erectile dysfunction (ED) and vascular disease, but little is known about such

associations in chronic inflammatory conditions. This study was undertaken to ascertain if erectile dysfunction is more common in RA compared with other forms of arthritis

Methods: Consecutive male patients from rheumatology out-patient clinics were interviewed regarding risk factors for vascular disease and for ED, in addition to their routine medical assessment. The presence of ED was determined using the previously published Sexual Health Inventory for Men (SHIM or IIEF-5) where scores ranged from high (22 – 25 = normal erectile function) to low (< 7 = severe ED). Laboratory tests, including acute phase response, blood count, lipids, glucose and testosterone levels were recorded. Ethics approval was obtained. Data were analysed using SPSS for Windows. Associations between categorical and continuous variables were assessed with chi-square and Fisher's exact test and Student's t-test, respectively.

Results: Fifty-seven patients were entered into the study: 33 had RA while had other forms of arthritis (9 psoriatic arthritis, 8 ankylosing spondylitis, 3 osteoarthritis, 2 connective tissue disorder, 1 gout and 1 undifferentiated inflammatory arthritis). Mean age was 59.5 ± 13.5 years. Thirty-nine patients (68%) had ED. Mean ED score was 17.9 ± 5.4 (range 5 – 25). Twenty patients (35%) had mild ED, 12 had moderate ED and 4 had severe ED. Twenty-six patients (67%) with RA had ED versus 13 (33%) patients with other types of arthritis. Of the eighteen patients with known CVD and any form of arthritis, ED was present in 17 (98%). Conversely, in those without identified CVD, ED was present in 15 RA patients (71%) as compared with 8 (42%) of the non-RA cohort. There was no association between ED and disease duration, methotrexate use, smoking or dyslipidemia.

Conclusion: Erectile dysfunction was more common in patients with RA compared with other forms of arthritis, particularly in those with known CVD. Standard ED scoring should be included in the holistic assessment of RA and may be valuable in the early detection of sub-clinical vascular disease in patients with RA

Disclosure: B. J. Sheane, None; **D. G. Howard**, None; **G. Cunnane**, None.

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Comorbidities Correlates Better Than Age with CDAI Improvement in RA Patients Using the CORRONA Registry. Veena K. Ranganath, Paul Maranian, David Elashoff, D.E. Furst and Harold E. Paulus, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: To evaluate the effect of age and comorbidities on disease activity in rheumatoid arthritis (RA) patients who start a new DMARD, using a community based cohort, the Consortium Of Rheumatology Researchers Of North America (CORRONA).

Methods: An analysis cohort of 1333 RA subjects enrolled in the CORRONA database (Oct 2001-Aug 2007) met the following inclusion criteria: started a disease modifying anti-rheumatic drug (DMARD) or biologic agent, maintained on the same therapeutic regimen for at least 3 months, and were not in clinical remission at baseline. Subjects were categorized into 3 groups: less than 45 years, between 45-65 years, and greater than 65 years of age. Baseline demographic and clinical characteristics were assessed across age categories using one-way ANOVA (Table 1). We then used linear regression (forward stepwise model) to assess predictors of change in the clinical disease activity index (CDAI) to assess the effect of age and comorbidities.

Results: Many of the baseline characteristics were clinically similar across the three age categories (Table 1). However, ESR, number of patient comorbidities and disease duration increased with increasing age, and the male to female ratio decreased with increasing age. Although CDAI change from baseline to follow-up correlated well with age, disease duration, and baseline CDAI in the univariate analyses, only the number of comorbidities, race and baseline CDAI were statistically significant in the multivariate analysis (Table 2).

Conclusion: In the CORRONA database, a large prospective community based cohort of "real-life" RA, increasing number of comorbidities, non-Caucasian race, and lower baseline CDAI correlates with less improvement over time for the CDAI. Age in itself did not predict improvement in CDAI when accounting for other variables.

Table 1: Baseline Characteristics of Older and Younger RA Patients

	Age < 45 (N=197) Mean (SD)	Age 45-64 (N=711) Mean (SD)	Age >=65 (N=488) Mean (SD)	p-value
Age	37 (6.2)	55 (5.6)	73 (5.9)	

Disease Duration	5.5 (4.7)	11.1 (9.4)	13.7 (11.9)	<.001
Female (%)	88.3	76.5	71.8	<.001
Comorbidities	3.7 (2.5)	5.5 (3.2)	6.6 (3.3)	<.001
ESR	23 (17)	28 (23)	35 (27)	<.001
Patient Pain VAS	41 (25)	43 (26)	42 (27)	NS
CDAI	21 (14)	22 (13)	21 (13)	NS
mHAQ	0.45 (0.5)	0.52 (0.5)	0.43 (0.5)	<.001

CDAI= clinical disease activity index, mHAQ= Modified HAQ

Table 2: Univariate and Multivariate Models for Change in CDAI (Baseline to Follow-up)

Outcome: CDAI Change	Estimate	P-Value	Estimate	P-Value
	UNIVARIATE		MULTIVARIATE	
Age	-0.06653	0.02	-0.015	NS
Comorbidities	-0.16459	NS	-0.46	<0.001
Disease Duration	-0.07457	0.03	-0.037	NS
Caucasian Race	0.82	NS	0.97	0.01
Baseline CDAI	0.64612	<.0001	0.66	<0.001

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Comparison of Morning Stiffness Assessment by Severity with Duration for Rheumatoid Arthritis Activty Assessment. Nasim A. Khan, Kashif A. Mufti, Rachel L. Wayne, Fatima Khan and Zainab Siddiqui, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR

Purpose: Morning stiffness is a common symptom of rheumatoid arthritis (RA) and is clinically used for RA activity assessment. We compared MS assessment by duration (MS duration) with MS assessment by severity (MS severity) for disease activity assessment in US Veterans with RA.

Method: We did cross-sectional assessment of 315 patients with RA evaluated at a single VA Medical Center. MS severity, pain, fatigue and patient's assessment of general health (GH) were assessed by a 21-point numeric rating scale (NRS) with a 0-10 score range on a self-report questionnaire. The anchors for MS severity scale were "none" and "very severe". MS duration was assessed (in minutes) from time of waking to time of maximal improvement. Physical function was assessed by Health Assessment Questionnaire II (HAQII). RA activity was assessed by Disease Activity Score based on assessment of 28 joints and erythrocyte sedimentation rate (DAS28-ESR). Correlation of two methods of MS assessment with ACR core data measure and DAS28-ESR was used to assess their utility for RA activity assessment.

Results: The patients were mostly men (92%) with mean (SD) age of 64(8.6) and median (IQR) RA duration of 8.5 (5-18) years. The median (IQR) of MS duration and MS severity were 45 (15-120) minutes and 5 (3-7.5) respectively. Both MS duration and MS VAS had non-normal distribution by Kolmongrov-Smirnov test and hence non-parametric tests were used for analysis. MS severity had good

correlation with MS duration (spearman's rho = 0.66, p < 0.001). Compared to MS duration, MS severity had stronger correlation with patient reported outcomes (pain, physical function, patient global and fatigue) and inflammatory markers (ESR and C-reactive protein). Both methods of MS assessment had almost similar correlation with DAS28-ESR (Table).

Conclusion: MS severity has stronger correlation with patient reported outcomes and inflammatory markers than MS duration. Both MS severity and duration have comparable correlation with a RA severity as assessed by DAS28-ESR.

	Morning stiffness severity		Morning Stiffness duration	
Characteristic	Spearman rho	p Value	Spearman rho	p Value
HAQII	0.64	< 0.001	0.47	< 0.001
Pain	0.72	< 0.001	0.45	< 0.001
Patient global	0.69	< 0.001	0.43	< 0.001
Fatigue	0.67	< 0.001	0.45	< 0.001
TJC	0.44	< 0.001	0.48	< 0.001
SJC	0.28	< 0.001	0.39	< 0.001
Physician global	0.48	< 0.001	0.50	< 0.001
ESR	0.13	0.03	0.12	0.05
C-Reactive protein	0.16	0.03	0.07	0.39
DAS28-ESR	0.43	< 0.001	0.48	< 0.001

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The Relationship Between Disease Activity, Sleep, Psychiatric Distress and Pain Sensitivity in Rheumatoid Arthritis. Yvonne C. Lee[1], Lori B. Chibnik[1], Bing Lu[2], Ajay D. Wasan[1], Robert R. Edwards[1], Anne H. Fossel[1], Simon M. Helfgott[1], Daniel H. Solomon[2], Daniel Clauw[3] and Elizabeth W. Karlson[4], [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham & Women's Hospital, Boston, MA, [3]University of Michigan, Ann Arbor, MI, [4]Brigham & Women's Hosp, Boston, MA

Purpose: To examine the association between disease activity, sleep, psychiatric distress and experimental pain sensitivity in rheumatoid arthritis (RA) patients.

Method: Fifty-nine female RA patients completed questionnaires and underwent physical examination, blood work and pressure pain threshold testing for hyperalgesia/allodynia at joint and non-joint sites. The association between disease activity, sleep problems, psychiatric distress and pain threshold was assessed using Pearson/Spearman correlations and multivariable linear regression.

Results: In unadjusted analyses, CRP was not correlated with pain threshold at any site, whereas tender joint count was inversely correlated with pain threshold at all sites (wrist: r = -0.49, p = 0.0001; thumbnail: r = -0.37, p = 0.004; trapezius: r = -0.36, p = 0.004). Sleep problems were inversely associated with pain threshold at all sites (wrist: r = -0.51, p < 0.0001; thumbnail: r = -0.44, p = 0.0005; trapezius: r = -0.43, p = 0.0008). Psychiatric distress was associated with low pain threshold at the wrist (r = -0.42, p = 0.0009) and thumbnail (r = -0.35, p = 0.006). In multivariable analyses, adjusting for age and biologic disease modifying anti-rheumatic drug use, CRP was inversely associated with wrist pain threshold (β = -0.15, p = 0.003). Sleep problems were inversely associated with pain threshold at all sites (wrist: β = -0.04, p = 0.007; thumbnail: β = -0.06, p = 0.002; trapezius: β = -0.04, p = 0.01), but psychiatric distress was not.

Conclusion: Multivariable models are essential in analyses of complex outcomes such as pain. Among RA patients, high CRP levels were associated with low pain thresholds at the wrist (the only joint commonly affected by RA that was evaluated in this study), suggesting that local inflammation may heighten pain sensitivity at joints. In contrast, sleep problems were associated with low pain threshold at all sites, indicating that poor sleep may increase widespread pain sensitivity, as in central pain conditions such as fibromyalgia. Future studies examining hyperalgesia at joint and non-joint sites may identify subsets of patients with differing underlying mechanisms of pain.

Table. The association between CRP, Medical Outcomes Study Sleep Score, Hospital Anxiety and Depression Scale Total Score, and pain threshold at the wrists, thumbnails and trapezius, adjusted for age and biologic DMARD use.

Variables	**Wrist Pain Threshold**		**Thumbnail Pain Threshold**		**Trapezius Pain Threshold**	
	β [1]	**p-value**	**β[1]**	**p-value**	**β[1]**	**p-value**
CRP	-0.15	0.003	-0.13	0.05	-0.03	0.55
Medical Outcomes Study Sleep Score	-0.04	0.007	-0.06	0.002	-0.04	0.01
Hospital Anxiety and Depression Scale Total Score	-0.03	0.48	0.01	0.80	-0.009	0.85

[1] The β-coefficient represents the change in outcome given a one unit change in the predictor, holding all other variables constant.

Disclosure: Y. C. Lee, None; **L. B. Chibnik**, None; **B. Lu**, None; **A. D. Wasan**, None; **R. R. Edwards**, None; **A. H. Fossel**, None; **S. M. Helfgott**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 ; **D. Clauw**, None; **E. W. Karlson**, None.

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A State of Sustained DAS Remission Is Determined by Time to Achieve Remission. Lydia G. Schipper[1], Jaap Fransen[1], Alfons A. Den Broeder[2] and Piet L.C.M. van Riel[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands

Purpose: Reaching remission is an important goal in current treatment of early RA. However, the number of patients who achieve and sustain remission in daily practice is still small, and determinants for achieving sustained remission are largely unknown. Therefore, this study analysed the association between time to achieve first remission and sustainability of remission in a cohort of early RA patients, treated according to daily practice.

Method: For this study, three-year follow-up data were used from the Nijmegen Inception RA Cohort of 1985 to 2005. Patients were included upon diagnosis (ACR criteria), were systematically evaluated at three-monthly visits and were treated according to daily practice routine. Remission was defined according to the Disease Activity Score (DAS) < 1.6 and according to the ACR remission criteria. Six months duration of remission or more (three consecutive visits) was defined as sustained remission. Univariate predictors for achieving and sustaining remission were identified using Cox-regression and logistic regression, respectively. The relation between time to achieve first remission and sustained remission was analyzed using longitudinal binary regression, including correction for potential confounders.

Results: There were 753 patients included, with a mean age of 67 years, 63% was female, 77% had a positive rheumatoid factor, and mean baseline DAS was 4.0. Within three years, 398 (53%) patients achieved remission at least one visit. The median time to remission was 12 months. Male patients and younger patients reached remission significantly sooner than female patients or older patients ($P<0.01$). Also, patients with a lower baseline DAS or HAQ achieved remission more rapidly than those with a higher value at baseline ($P<0.0001$). There were 142 (36%) patients who experienced sustained remission (mean 78 weeks). Sustained remission was determined by a shorter time to achieve first remission ($P<0.0001$), besides low DAS and HAQ at baseline ($P<0.05$). There was a significant relation between time to achieve remission and sustained remission (odds ratio 1.11, 95% CI 1.10-1.12, $P<0.0001$, adjusted for baseline DAS), which was constant over the whole period of 1985 to 2005. Results with the ACR remission criteria were similar.

Conclusion: Remission was more often sustained in patients who achieved their first remission rapidly. These results support the use of aggressive treatment to aim for early remission in RA.

Disclosure: L. G. Schipper, None; **J. Fransen**, None; **A. A. Den Broeder**, None; **P. L. C. M. van Riel**, None.

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Autonomic Nervous System Activity Upon Mental Stress in Patients with Rheumatoid Arthritis with Various Disease Activities. Olga Malysheva, Petra Baum, Anke Voitzsch and Christoph G. Baerwald, University Hospital, Leipzig, Germany

Purpose: To characterize the pattern of the autonomic response to mental stress in patients with rheumatoid arthritis (RA) and healthy controls. Stress is recognized as an important risk factor in the pathogenesis of RA. However, it is still incompletely understood how the autonomic nervous system and the immune system interact in patients with RA.

Method: Heart rate variability (HRV) test was performed in 70 RA patients with various disease activity and 100 matched healthy controls (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany). Standard tests of autonomic nervous system function involving mental arithmetic tasks to induce mental stress were performed. HRV measures including frequency domain analysis (employing rapid processing of a 5 minute ECG rhythm strip) yielding measures of parasympathetic and sympathetic activity as well as total power (high frequency (HF), low frequency (LF), and very low frequency (VLF)) heart rate variability, variation coefficient, and square root of the mean of the squares of successive R-R interval differences (RMSSD).

Results: Patients with RA had an impaired response to mental stress with a paradox increase of VLF HRV ($2.1 \pm 0.1 \times 10^{-4}$ Hz at rest vs. $2.7 \pm 0.2 \times 10^{-4}$ Hz after stress, $p < 0.05$). In particular in patients with higher disease activity ($DAS > 3.2 \leq 5.1$) VLF HRV significantly increased upon stress ($1.7 \pm 0.1 \times 10^{-4}$ Hz at rest vs. $2.9 \pm 0.1 \times 10^{-4}$ Hz after stress, $p < 0.01$). Moreover, LF HRV, HF HRV as well as sympathetic/parasympathetic ratio did not differ significantly. However, in RA patients in remission ($DAS \leq 2.3$) mental stress led to a significant increase of LF HRV ($1.0 \pm 0.1 \times 10^{-4}$ Hz at rest vs. $1.5 \pm 0.04 \times 10^{-4}$ Hz after stress) and a tendency to an increase of LF/HF ratio. Interestingly, RA patients receiving a combination therapy of anti-TNF agents with MTX exhibited a decreased level of LF HRV at baseline compared to MTX monotherapy ($1.1 \pm 0.02 \times 10^{-4}$ Hz vs. $1.6 \pm 0.04 \times 10^{-4}$ Hz, $p<0,05$) as well as a decreased LF/HF ratio ($0.7 \pm 0.02 \times 10^{-4}$ Hz vs. $1.17 \pm 0.14 \times 10^{-4}$ Hz, $p<0,001$). In patients with anti-TNF combination therapy HF HRV response to mental stress was significantly increased compared to MTX monotherapy ($1.4 \pm 0.1 \times 10^{-4}$ Hz vs. $1.9 \pm 0.1 \times 10^{-4}$ Hz after stress, $p<0.05$).

Conclusion: Our findings demonstrate that in RA patients the autonomic response to minor psychological stress is characterized by a reduced sympathetic activity which is associated with disease activity. Anti-TNF therapy can actively modify stress reactivity towards predominance of the parasympathetic system. Further studies are under way to determine the role of the autonomic nervous system in the disease process of RA and the modulation of neuro-immune interactions by various medications.

Disclosure: O. Malysheva, None; **P. Baum**, None; **A. Voitzsch**, None; **C. G. Baerwald**, None.

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Disease Activity of Rheumatoid Arthritis After Total Knee Arthroplasty : Results of 3-Year Followup. Koichiro Yano, Katsunori Ikari, Atsuo Taniguchi, Hisashi Yamanaka and Shigeki Momohara, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Though excellent clinical results have been reported for total knee arthroplasty (TKA) in rheumatoid arthritis (RA) patients, the medium-term efficacy of TKA on disease activity of RA remains unknown. This analysis aimed to assess the systemic effect of TKA on RA disease activity 3 years after intervention.

Method: The study was part of an observational cohort project that included over 4000 Japanese RA patients, established in the year 2000 by the Institute of Rheumatology, Tokyo Women's Medical University (IORRA: Institute of Rheumatology RA cohort). Out of the registered RA patients, a total of 130 total knee arthroplasty (TKA) patients could be followed for 3 years after the operation. The patients who underwent bilateral TKA were excluded. Disease activity of RA was measured using Disease Activity Score 28 (DAS28). Patients were divided into three groups according to pre-operative baseline DAS28 for sub-analysis: low (DAS28 less than or equal to 3.2, n=8), moderate (DAS28 more than 3.2, but less than or equal to 5.1, n=68), and high (DAS28 more than 5.1, n=54) disease activity. Post-operative DAS28 (a few months [DAS1] and 3 years [DAS3] after operation) of the patients were compared with their baseline DAS28 (DAS0) using paired t-test.

Results: For all patients who underwent TKA, the mean DAS28 decreased from 4.85 (DAS0) to 4.14 (DAS1, P=1.1e-12), and a similar result was still seen at 3 years (DAS3=3.97, P=4.7e-15). Sub-analysis results revealed that a systemic effect of TKA on disease activity was found in patients with moderate or high disease activity (DAS0=4.33 , DAS1=3.72, P=5.9e-6 and DAS3=3.81, P=7.9e-6, and DAS0=5.79,

DAS1=4.86, P=1.1e-8 and DAS3=4.37, P=1.0e-11, respectively), while no effect was found in patients with low disease activity (DAS0=2.86, DAS1=2.75, P=0.26, DAS3=2.6, P=0.14). Moreover, among patients whose DAS28 had been recorded 1 year before surgery, the mean DAS28 remain unchanged prior to surgery (DAS0, 4.71; DAS-1, 4.62 [P=0.22]), but decreased after surgery (DAS1, 4.01 [P=1.70E-08]; DAS3=3.94 [P=4.54E-09]). While no significant changes in medication were noted, the average dose of prednisolone tended to decrease over time.

Conclusion: We conclude that TKA, which is known to result in good clinical outcomes on damaged knees, has a secondary systemic effect on disease activity of RA, especially in patients with moderate to high disease activity at their pre-operative baseline.

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Utilizing Electronic Medical Records for Discovery Research in Rheumatoid Arthritis. Katherine P. Liao[1], Tianxi Cai[2], Vivian Gainer[3], Sergey Goryachev[1], Qing Zeng[1], Soumya Raychaudhuri[1], Pete Szolovits[4], Susanne Churchill[5], Shawn Murphy[3], Isaac Kohane[5], Elizabeth W. Karlson[1] and Robert M. Plenge[1], [1]Brigham & Women's Hosp, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Partners HealthCare, Charlestown, MA, [4]MIT, Cambridge, [5]Harvard Medical School, Boston, MA

Purpose: Electronic medical records (EMRs) are a rich resource of clinical data for research, but are underutilized due to the inability to extract data from narrative text and to analyze codified data in conjunction with narrative text. We tested the hypothesis that EMR data can more accurately identify patients with rheumatoid arthritis (RA) than codified data alone, and that EMR data can effectively subset RA patients into relevant phenotypes.

Methods: Our study utilized the EMR of two large academic centers caring for ~4 million patients. We extracted RA clinical features from narrative notes using natural language processing (NLP) and codified EMR data (ICD9 codes, laboratory values, prescriptions). We performed chart reviews on 500 patients with at least one ICD9 code for RA to establish a training set with gold-standard RA status based on rheumatologists' diagnosis of RA. Penalized logistic regression was used to establish an algorithm to classify RA cases using NLP and codified data (goal 97% specificity). Two rheumatologists validated the algorithm by reviewing the medical records of 400 patients classified with RA by the algorithm to confirm RA diagnosis. We performed a case-only analysis to demonstrate the association between RF and anti-CCP positivity and higher risk of erosions in RA patients. To calculate the odds ratio (OR), we constructed contingency tables comparing prevalence of erosions defined by NLP, among individuals with anti-CCP and/or RF laboratory values in the codified EMR.

Results: Our algorithm utilizing both codified and NLP data from the EMR accurately classified 3585 patients with RA (63% sensitivity, 93% positive predictive value (PPV) on validation). In comparison, an algorithm using codified data or NLP only data had lower sensitivity (51%, 56%) and PPV (88%, 89%). The clinical characteristics of our RA patients were comparable to published data from a large cohort study at another center (**Table 1**).

In our case-only analysis the risk of erosions was higher in anti-CCP+ patients (OR 1.5 95% CI 1.2-1.9) than RF+ patients (OR 1.3, 95% CI 1.1-1.6). This elevated risk of erosions in anti-CCP+ patients is established in the literature.

Conclusion: We demonstrate the ability to use codified and narrative data to classify RA patients from the EMR with a PPV of 93%. Furthermore, EMR data can be used to study clinical phenotypes such as the association between anti-CCP and radiographic erosions.

Table 1. Comparison of characteristics of our RA patients and a traditional prospective cohort.

Characteristics (%)	EMR RA, n=3585	CORRONA*, n=7971
Mean age, yrs	57.5	58.9
Female	79.9	74.5
Anti-CCP	63	N/A
RF	74.4	72.1
Erosions	59.2	59.7

MTX	59.5	52.8
Anti-TNF	32.6	22.6

*Consortium of Rheumatology Researchers of North America (Greenberg, et al., Ann Rheum Dis 2009)

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Mortality Risk in RA: Simple Tools for Mortality Assessment in the Clinic and Research Setting. Frederick Wolfe[1], KD Michaud[2], Montserrat Vera-Llonch[3] and Gerry Oster[3], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]U Neb Med Cntr and NDB, Omaha, NE, [3]Brookline, MA

Purpose: Mortality risk in RA is about 1.5 to 2 times higher than in the general population. Relative risk may vary in relation to age and health status. In this study, we examined two commonly used measures of health status, the Health Assessment Questionnaire (HAQ) and the Short Form-36 (SF-36) Physical and Mental Component Summary scales (PCS, MCS) as potential clinically useful predictors of mortality risk.

Methods: As part of a longitudinal study of RA outcomes, we identified all persons with RA who completed at least 2 semiannual questionnaires between 1999 and 2006. HAQ, PCS, and MCS scores were available for up to 4 years. Deaths were documented using the National Death Index. Changes of >=5 units in the PCS or MCS, or >=0.25 units in the HAQ, were designated as clinically important. Cox multivariate regression was used to estimate mortality risk in relation to age, sex, baseline HAQ, PCS, and MCS, and changes in these measures; alternative model specifications were compared with Harrell's concordance coefficient (C).

Results: We identified 10,319 subjects with RA who had completed at least two semiannual questionnaires. Among these persons, there were 1,317 deaths over 64,888 person-years of follow-up. Age and sex-adjusted mortality risk was strongly associated with baseline PCS, MCS, and HAQ (Table 1), with risk increasing at higher levels of disability. After adjusting for age, sex, and baseline PCS and MCS, declines in PCS also were found to be associated with increased mortality risk; however, improvements in PCS of 5-14 or 15-30 units were not associated with a reduction in mortality. Changes in the HAQ >=0.25 units were associated with small changes in mortality risk while changes in the MCS were not associated with mortality. When change scores were added to baseline PCS, MCS, and HAQ, there was minimal or no improvement in the prediction of mortality. Harrell's C for the final models was 0.778.

Conclusion: Health status as measured by the SF-36 (PCS, MCS) and the HAQ is strongly associated with mortality risk in RA. Age and sex-adjusted mortality risk is significantly higher at lower levels of health status. The SF-36 PCS and the HAQ are approximately equal in their predictive ability.

Table 1. SF-36 (PCS, MCS), HAQ and mortality risk among patients with RA

Variable	*Category*	*% in Category*	*H.R. (95% CI)*
PCS	>=50	14.5	1.0
	41-50	22.6	1.6 (1.2, 2.1)
	31-40	30.6	2.0 (1.6, 2.6)
	21-30	27.3	3.1 (2.5, 4.0)
	<=20	5.1	4.9 (3.6, 6.4)
MCS	>=50	57.2	1.0
	41-50	21.4	1.4 (1.2, 1.6)
	31-40	15.2	1.7 (1.5, 2.0)

	21-30	5.5	2.0 (1.5, 2.5)
	<=20	0.7	1.6 (0.7, 3.8)
HAQ	0.00	12.3	1.0
	0.125-0.375	14.8	1.4 (1.1, 1.8)
	0.500-0.875	25.7	1.5 (1.2, 1.9)
	1.000-1.375	22.3	1.8 (1.4, 2.2)
	1.500-1.875	17.2	2.7 (2.2, 3.5)
	2.000-2.375	6.4	4.0 (3.1, 5.2)
	2.500-3.000	1.3	5.5 (3.9, 7.7)

Disclosure: F. Wolfe, None; **K. Michaud**, None; **M. Vera-Llonch**, None; **G. Oster**, None.

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Utility of An Interferon-Gamma-Release Assay to Detect Latent Tuberculosis in Patients Evaluated for Immunosuppressive Therapy with Biologic Agents – a Retrospective Analysis of Routine Clinical Practice in a Low-Prevalence Population. Boris Ehrenstein[1], Felix Nessyt[1], Wolfgang Hartung[2], Rotraud Meyringer[2] and Martin Fleck[2], [1]University Medical Center Regensburg, Regensburg, Germany, [2]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany

Purpose: Screening for latent tuberculosis infection (LTBI) utilizing tuberculin skin test (TST) and chest x-ray (CXR) is mandatory prior to initiating TNF-alpha inhibitors and recommended before initiating other immunosuppressive therapies. Pilot studies suggested better sensitivity and specificity for detecting LTBI of interferon-gamma-release assays (IGRA) compared with TST and CXR in this setting. We aimed to evaluate the diagnostic gain of performing an IGRA in addition to standard screening with TST and CXR in routine clinical practice.

Method: Evaluation for LTBI by TST, CXR and additionally by a commercially available IGRA was introduced in routine clinical practice from April 2008 for all inpatients of a referral tertiary-care facility specializing in rheumatic diseases. A retrospective chart review was performed for all patients receiving IGRA testing as part of diagnostic workup prior to commencing biologic immunosuppressive therapy from April to December 2008.

Results: 205 patients with rheumatic diseases (rheumatoid arthritis n=125; spondyloarthritis n=46; psoriatic arthritis n=19; other n=15) received IGRA testing as part of evaluation for LTBI before initiating biologic immunosuppression. Of the 205 IGRA, 19 (9%) were positive, 168 (82%) negative and 18 (9%) indeterminate. Among the 19 patients with LTBI detected by IGRA, only 3 had a positive TST result (of 16 evaluated), 1 had signs suggestive of LTBI in the CXR (of 16 evaluated), and 5 patients reported risk factors for LTBI (of 17 with sufficient information). Utilizing only results of TST and CXR, 14 (74%) of the 19 patients with LTBI diagnosed by IGRA would have been missed. Only 7 of 158 (4%) performed TST were positive: 4 of those had also a positive IGRA; 2 had no other evidence of LTBI, including a negative IGRA; 1 had classical signs of LTBI by CXR, reported a direct exposure to active tuberculosis, but had a negative IGRA. Indeterminate IGRA results occurred more frequently among patients pre-treated with corticosteroids at doses above 10 mg/d prednisolone-equivalent (8/33, 24%) than among patients who were untreated or pre-treated with lower doses (10/172, 6%), $p<0.001$ by Chi^2 test.

Conclusion: Performing only TST and CXR would have failed to detect nearly three quarters of patients with LTBI diagnosed by IGRA. The rates of false-negative IGRA- (0.5%) and false-positive TST-results (1.0%) were both low. Despite IGRA outperforming TST, it remains unclear whether outright replacement of TST with IGRA is justified. However, our data strongly support augmentation of TST with IGRA to detect LTBI.

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Health Literacy Predicts the Discrepancy Between Patient and Physician Global Assessments of Rheumatoid Arthritis Activity at a Public Urban Rheumatology Clinic. Joel M. Hirsh[1], Dennis J. Boyle[1], David H. Collier[1], Abbey Oxenfeld[1], Alison Collier[1], Alyssa Cohen[1] and Liron Caplan[2], [1]Denver Health, Denver, CO, [2]Univ of CO Denver School of Med, Aurora, CO

Purpose: Numerous studies report that significant discordance exists between patient and physician measures of disease activity for patients with rheumatoid arthritis (RA). We undertook a study to determine whether health literacy explains the discordance between patient and physician global measures.

Method: We recruited English-speaking adult RA patients at Denver Health for this cross-sectional study. Subjects completed two versions of patient global assessments of disease activity (PTGA), using standard terminology from the Multi-Dimensional Health Assessment Questionnaire (MDHAQ) and Disease Activity Score 28 (DAS 28). The Physician global assessment (MDGA) was also obtained. The discrepancy between PTGA and MDGA was calculated as the absolute difference between these assessments. We utilized a validated instrument to assess health literacy: The Short Test of Functional Health Literacy in Adults (s-TOFHLA). We employed the unpaired t-test and linear regression, where appropriate.

Results: 110 subjects participated in the study. Patient demographics, results of global assessments and health literacy testing appear in Table 1. PTGA and MDGA showed fair to good correlation (r=0.66-0.68), though both versions of the PTGA were significantly higher than MDGA by the t-test ($p<0.001$). The s-TOFHLA correlated with the absolute difference between the MDGA and PTGA by linear regression, i.e., for each point the s-TOFHLA improves, the difference in PTGA and MGA narrows by one half a point. The relationship between the s-TOFHLA and absolute difference of PTGA and MDGA remained statistically significant in multivariate analysis (Table 2).

Table 1. Patient Demographics, Results of Global Assessments and Health Literacy Testing

Variable	N	Mean	SD
Age	110	53.21	12.39
Sex	110	0.21	0.41
Education (per year)	110	12.35	3.09
Current smoker	110	0.3	0.46
Caucasian	110	0.27	0.45
Married	110	0.24	0.43
Currently employed	110	0.19	0.39
Disabled	110	0.65	0.48
Retired	110	0.07	0.26
Duration of RA, years	110	12.51	10.2
Positive RF	110	0.88	0.32
Positive aCCP	74	0.85	0.36
MD-HAQ	110	1	0.61
DAS 28	110	4.37	1.53
ESR	105	29.39	23.94

CRP	106	15.83	23.29
PTGA (MDHAQ version)	108	44.51	27.38
PTGA2 (DAS version)	110	49.12	25.51
MDGA	110	32.5	25.51
s-TOFHLA	110	27.55	9.2

Table 2. Results of Multivariate Analysis Regarding Relationship Between s-TOFHLA and Absolute Difference of PTGA and MDGA.

Variable	**Coefficient**	**P value**	**95% Confidence Interval**	
			Lower Bound	Upper Bound
s-TOFHLA	-0.39706	0.031	-0.75795	-0.03618
Current biologic use	5.64341	0.059	-.211152	11.49796
Education (per year)	-.450206	0.413	-1.53566	.6352489
Sex (male)	3.690053	0.082	-3.436316	10.81642
Age (per year)	.0503813	0.690	-.199284	.300046

Conclusion: Health literacy was independently associated with the extent of discrepancy between PTGA and MDGA in English-speaking RA patients at an urban safety-net clinic. This finding is relevant to both rheumatology practice and research.

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People with Rheumatoid Arthritis Who Smoke or Do Not Smoke Have Similar Clinical Status: Data From the QUEST-RA Multinational Database. Tuulikki Sokka[1], Theodore Pincus[2], H. Makinen[3], A. Naranjo[4] and QUEST-RA Investigators, [1]Central Hospital, Jyvaskyla, Finland, [2]NYU Hospital for Joint Diseases, New York, NY, [3]Tampere University Hospital, Tampere, Finland, [4]Hospital Doctor Negrin, Las Palmas GC, Spain

Purpose: Smoking has been implicated in the pathogenesis and severity of rheumatoid arthritis (RA), particularly according to rheumatoid factor (RF) positivity and nodules. However, conflicting data are reported concerning clinical measures in people with RA according to whether patients never smoked, discontinued smoking, or continue to smoke. The QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis) multinational database, with 8,040 patients from 86 sites in 33 countries, provided a resource to analyze clinical severity according to smoking status in 6,870 patients.

Method: QUEST-RA was established in 2005 to promote quantitative assessment in usual rheumatology care and develop a baseline cross-sectional database of consecutive RA patients seen in usual care in many countries. Three or more rheumatologists were asked to assess 100 consecutive unselected patients in each country with a standard protocol to evaluate RA (SPERA), which includes a clinical assessment and 4-page patient self-report questionnaire. Smoking status was assessed by self-report as “never smoked,” “smoked in the past but stopped” and “currently smoking.” Analyses of patients who never vs ever smoked, and stopped vs continued to smoke, were performed for demographic and RA Core Data Set measures, rheumatoid factor, nodules and cardiovascular comorbidity, compared by t tests and chi square tests; Core Data Set measures were adjusted for age, sex, and disease duration.

Results: Among the 6,870 QUEST-RA patients, status as “never smoked,” “current smoker” and “stopped smoking” was reported by 70.8%, 12.8% and 16.3% of women, and 37.3%, 25.9% and 36.8% of men, respectively (Table). Patients who smoked were more likely to be RF-positive, have nodules and/or coronary artery disease (CAD) ($p < 0.001$). By contrast, patients who never smoked had slightly poorer status compared to those who ever smoked according to all 7 Core Data Set measures – 28 swollen and tender joint count, physician global

estimate, erythrocyte sedimentation rate (ESR), HAQ-function, pain, and patient global estimate – as well as DAS28; some differences were statistically significant, although none appears clinically important. No meaningful differences were seen between current smokers vs ex-smokers, although ex-smokers were older and had a higher proportion of CAD.

TABLE

	Never smoked	Ever smoked		P never vs ever	P current vs ex-smoker
		Current smoker	Ex-smoker		
Number of patients	4,406	1,059	1,405	-	-
% of all patients	64.1%	15.4%	20.5%	-	-
Age (years)	54.9	53.1	58.4	<0.001	<0.001
Women (n=5,436)	70.8%	12.8%	16.3%	-	-
Men (n=1,374)	37.3%	25.9%	36.8%	-	-
Rheumatoid factor	71.9%	77.8%	76.3%	<0.001	0.37
Erosions	63.4%	58.7%	61.6%	0.021	0.16
Nodules	17.7%	25.5%	20.9%	<0.001	0.010
Coronary artery disease	6.8%	4.8%	12.1%	<0.001	<0.001
*DAS28 (0-10)	4.4	4.0	4.0	<0.001	0.87
*HAQ-function (0-3)	1.1	0.90	0.93	0.010	0.54
*Swollen joint count (0-28)	4.5	4.1	4.1	0.062	0.76
*Tender joint count (0-28)	7.3	6.0	5.7	<0.001	0.80
*Physician global (0-10)	3.1	2.7	2.6	0.001	0.97
*ESR (mm/h)	32	26	28	<0.001	0.11
*Pain (0-10)	4.2	4.0	3.9	0.28	0.062
*Patient global (0-10)	4.1	4.0	3.8	0.16	0.079

*For Core Data Set variables, analyses adjusted for age, sex and disease duration.

Conclusion: RA patients who had ever smoked were more likely to have rheumatoid factor, nodules, and/or coronary artery disease, but values for other clinical status measures were similar for smokers, ex-smokers and never-smokers – the never-smokers were a little worse. Most RA patients are non-smokers. Potential limitations of these cross-sectional data include patient selection, a probable higher mortality rate among smokers prior to acquisition of these data in a rheumatology clinic, i.e., left-censoring, and lack of data on pack-years.

Disclosure: T. Sokka, None; **T. Pincus**, None; **H. Makinen**, None; **A. Naranjo**, None.

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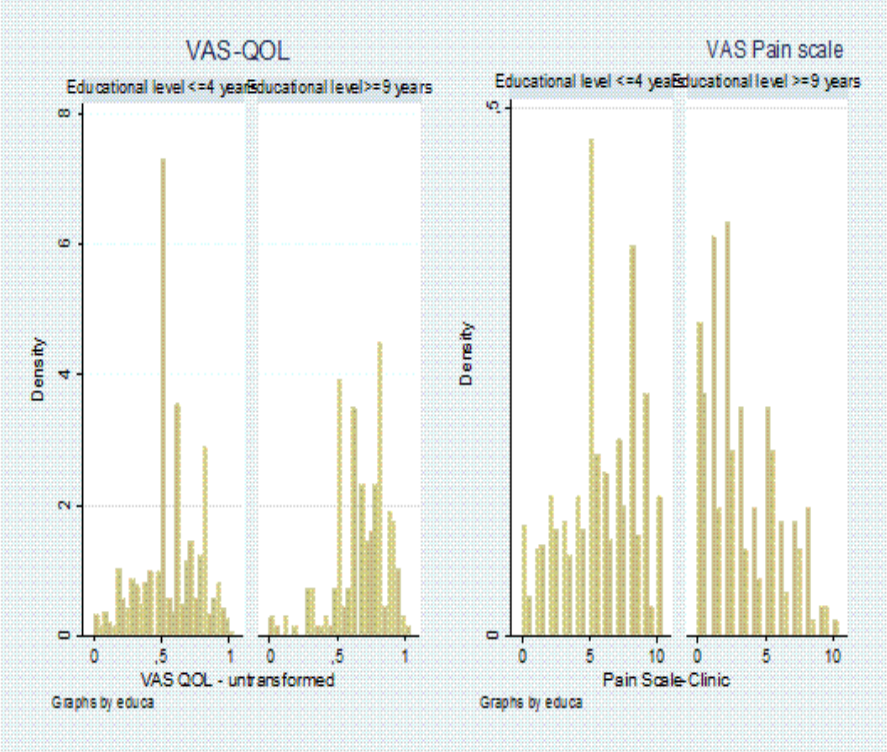
VAS Scales Might Not Be Appropriate to Measure RA Outcomes Among Patients with Low Education Levels. Joana Vasconcelos[1], Sofia Pedro[1], Ana Rita Marques[2], Irina Chaves[2], Andreia Rodrigues[1], Kaleb D. Michaud[3], Fred Wolfe[4] and Elizabeth Benito Garcia[2], [1]Bioepi, Oeiras, Portugal, [2]Bioepi Clinical and Translational Research Center, Oeiras, Portugal, [3]University of Nebraska Medical Center and NDB, Omaha, NE, [4]National Data Bank, Wichita, KS

Purpose: Visual analogue scales (VAS) are universally and widely accepted to evaluate outcome measures in Rheumatoid Arthritis (RA). In clinical practice, there is some discomfort in relying on these scales to measure RA outcome such as pain and quality of life (QoL). We hypothesized that educational level might influence the performance of these scales.

Methods: 1151 patients from an ongoing biannual cohort of Portuguese RA patients since 2003 (NDB-Portugal) were analyzed. Educational level, dichomotized into groups of 4th grade or lower, and 9 years or higher was used to assess differences in VAS responses to pain (VAS-pain, 0-10) and quality of life (VAS-QOL, 0-1). Patients' responses, stratified by educational level, were compared to higher or lower function (HAQ) and regional pain scores (RPS), that are important RA outcomes and reflect disease severity.

Results: Patients with the lower educational levels' responses to the VAS-pain and VAS-QOL, stratified or not by HAQ or RPS seemed be more concentrated in the middle of the scale (5). Patients in the higher educational level did respond with a wider variation throughout the scales and but also tended to not value pain as much as patients with lower educational levels (See figures).

Conclusion: VAS-scales might not measure pain and quality of life accurately, especially among patients with lower educational levels. For patients with higher educational levels, their perception to pain and quality of life captured by the VAS are much lower than patients in the lower educational level.



Disclosure: J. Vasconcelos, None; **S. Pedro**, None; **A. R. Marques**, None; **I. Chaves**, None; **A. Rodrigues**, None; **K. D. Michaud**, None; **F. Wolfe**, None; **E. Benito Garcia**, None.

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The Impact of Comorbidity On Physical Function. Helga Radner[1], Josef S. Smolen[2] and Daniel Aletaha[1], [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria

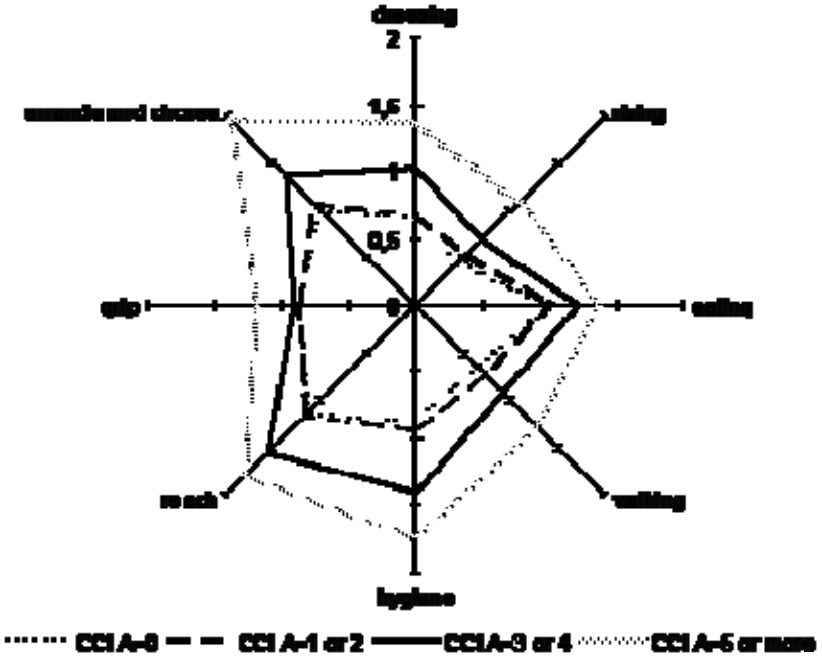
Background: Physical function and activity of daily living are in the center of interest when evaluating chronic diseases like Rheumatoid Arthritis (RA). Disability is not only related to disease activity and joint damage, but also to other factors not primarily associated with the disease process. Comorbid conditions are of particular importance in this context, given their high prevalence in patients with chronic rheumatic disease.

Purpose: To quantify the contribution of comorbidity to physical disability and to activities of daily living in patients with RA.

Method: We ascertained comorbidities in 380 patients with established RA seen at our outpatient clinic over one year, using age adjusted version of the Charlson Comorbidity Index (CCI_A (1)) which ranges from 0-9. Furthermore we collected time integrated clinical disease activity by Clinical Disease Activity Index ($CDAI_T$) as well as physical function using the Health Assessment Questionnaire (HAQ_T). After dividing patients into 4 subgroups by CCI_A (0; 1-2; 3-4; 5-9) we calculated estimated marginal means (EMM) by general linear model (GLM) to explore whether HAQ_T and values of each HAQ-domain (dressing 1, rising 2, eating 3, walking 4, hygiene 5, reach 6, grip 7, errands and chores 8) increase depended on the level of comorbidity (groups of CCI_A). The GLM was adjusted for disease duration, gender and disease activity (based on the CDAI). Furthermore we stratified our patients into different levels of disease activity by $CDAI_T$ (remission: CDAI≤2.8, low disease activity: 2.8<CDAI≤10; and moderate to high disease activity: CDAI>10) and recalculated GLM.

Results: The adjusted GLM showed significant ($p<0.01$) differences of estimated marginal mean (EMM) HAQ_T scores across the 4 subgroups of CCI_A (0.67 (n=67); 0.80 (n=184); 1.24 (n=89); 1.40 (n=40). Results were similar for every single domain of HAQ (Figure 1), showing significant differences of EMM of HAQ-domains within groups of CCI_A. In subgroup analyses stratified by disease activity state, there was a similar increase in mean HAQ_T values across the four levels of CCI_A (Remission: 0.26 vs. 0.31 vs. 0.47 vs. 0.88; Low disease activity: 0.83 vs. 0.78 vs. 0.98 vs. 1.36; moderate and high disease activity: 1.22 vs. 1.33 vs. 1.70 vs. 1.91, respectively; $p<0.01$).

Figure 1. Plot depicts estimated marginal mean of 8 HAQ-domains of respective groups of age adjusted Charlson Comorbidity Index (0; 1-2; 3-4; 5-9)



Conclusion: In patients with RA, all domains of daily living activities represented in the HAQ are increasingly impaired with rising levels of comorbidity. This effect is independent of disease activity with a relatively constant increase of HAQ scores across all disease activity states.

Reference:
(1) Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of A Combined Comorbidity Index. *Journal of Clinical Epidemiology* 1994; 47(11):1245-1251.

Disclosure: H. Radner, None; **J. S. Smolen**, None; **D. Aletaha**, None.

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Attaining Public Health Physical Activity Guidelines for Persons with Rheumatoid Arthritis (RA): Does It Improve Their Health Utility? Jae Chul Lee, L. M. Manheim, Jing Song, R. W. Chang and D. D. Dunlop, Northwestern University, Chicago, IL

Purpose: Health utility (HU) is a standard economic measure of effectiveness in clinical trials. Although physical activity can improve the health of persons with RA, it is an open question whether or not attaining public physical activity guidelines improves their HU. This study examines if persons with RA who meet U.S. Surgeon General (USSG) guidelines have improved HU over one year.

Methods: Participants with RA were recruited from the Increasing Motivation for Physical Activity in Arthritis Clinical Trial (IMPAACT), an ongoing randomized clinical trial that evaluates a behavioral intervention to increase physical activity in persons with arthritis. We focused on IMPACCT participants with RA whose data were available at a baseline, a 6-month visit, and a 12-month visit. USSG guidelines attainment was objectively assessed every 6 month using accelerometer monitoring. If persons had ≥150 minutes of moderate or vigorous (MV) physical activity) per week, they were identified as meeting the guidelines. The IMPACCT data included n=77 who have RA and valid physical activity data (aged 23-78) during baseline with a 6 month HU followup; n=42 also had valid physical activity data (aged 24-78) at 6 months with a 12 month HU followup. Regression analysis examined the baseline relationship of guideline attainment with HU. Longitudinal analyses using GEE examined the relationship between USSG attainment and subsequent HU.

Results: Only 18% (n=14) of this RA cohort met USSG guidelines at baseline. Attaining USSG guidelines was not related to HU at baseline or longitudinally. Further analyses examined the relationship between MV physical activity quartiles and HU. This RA cohort had very low activity levels (Q1: 0; Q2: 1-15; Q3:16-90; Q4:>90 min MVPA a week); persons below the median had almost no MV physical activity (<15 min/week). Baseline HU is almost identical for persons with RA below the median (Q1:HU=0.67, Q2: HU=0.69). Those with RA above the median had higher baseline HU (Q3: HU=0.74, Q4: HU=0.74), which suggests attaining even low amount of MV activity is beneficial for those with RA. At baseline having MV activity above the median was associated with significantly higher utility compared to persons below the median (0.72 vs 0.67, p=0.004). Longitudinally, persons with MV activity above the median had better subsequent utility than those below the median (0.72 vs 0.68, p=.012).

Conclusion: Few persons with RA attained USSG guidelines. USSG attainment was not associated with HU at baseline or longitudinally. In contrast, persons who attained even low levels of MV physical activity had significantly better utility at baseline and better subsequent utility compared to persons attaining little or no MV activity. These findings suggest that moving persons with RA from none to some MV physical activity may be a more effective strategy than working to attain USSG guidelines. Separate public health physical activity guidelines should be investigated for persons with RA.

Disclosure: J. C. Lee, NIH, 2 ; **L. M. Manheim**, NIH, 2, Arthritis Foundation, 2 ; **J. Song**, NIH, 2, Arthritis Foundation, 2 ; **R. W. Chang**, NIH, 2, Arthritis Foundation, 2 ; **D. D. Dunlop**, Arthritis Foundation, 2, NIH, 2 .

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In Rheumatoid Arthritis Females Display Higher Disease Activity and Functional Disability, but Have Similar Degree of Joint Destruction Compared to Males. Isabel Castrejón[1], Karen Visser[2], Naomi B. Klarenbeek[2], Isidoro González-Álvaro[1] and Tom WJ Huizinga[2], [1]Rheumatology Department. Hospital Universitario de La Princesa, Madrid, Spain, [2]Leiden University Medical Center, Leiden, Netherlands

Purpose: To evaluate whether disease activity, functional disability and radiographic progression differ between males and females in two cohorts of patients with rheumatoid arthritis (RA) from two different countries.

Method: 217 patients with RA from the Leiden Early Arthritis Clinic (L-EAC) (73.7% women), The Netherlands and 195 patients from the Madrid Early Arthritis Clinic (M-EAC) (76.9% women), Spain were included. At baseline, 1, 2, 3, 4 and 5 year the following data were

collected: the Disease Activity Score (DAS) (including tender and swollen joint counts, erythrocyte sedimentation rate, and VAS general health), C-reactive protein (CRP), health assessment questionnaire (HAQ), patient reported pain (VAS pain 0-100 mm) and radiographs of hands and feet. The radiographs were scored according to the Sharp van der Heijde (SHS) method. At baseline, differences in disease activity measures, function and joint damage were compared between males and females using student t-test or the Mann-Whitney U-test. The pattern of DAS, HAQ and the SHS for males and females over time were compared using linear mixed models, correcting for confounding factors.

Results: Females were significantly younger than males in both cohorts, mean (SD) age 56 (15) and 61 (13) years respectively in the L-EAC and mean (SD) age 51 (16) and 58 (15) in the M-EAC. At baseline, females had higher scores for VAS general health (44.6 vs 35.1, p=0.023), VAS pain (52.7 vs 44.9, p=0.032) and HAQ (1.18 vs 0.99, p=0.014) whereas males had higher CRP (30.2 vs 24.4, p=0.04) in the L-EAC. We found similar results in the M-EAC with higher scores for VAS pain (49.2 vs 35.8, p=0.003), HAQ (1.17 vs 0.75, p=0.001) and DAS28 (4.71 vs 3.76, p<0.001) in females versus males. In contrast swollen joint counts and ESR were not significantly different in both cohorts. In the L-EAC, the females had on average 0.36 units higher DAS44 during 5 years follow up than males (p=0.01), adjusted for the DAS44 at baseline, RF and age. Similarly, the HAQ was 0.21 units higher in females than in males (p=0.04) over time, adjusted for HAQ at baseline, RF and age. The M-EAC showed similar results (data not shown). The radiographic scores (total sharp score, erosion score and joint space narrowing) at baseline were similar for males and females in both cohorts and the radiographic progression over 5 years time was not significantly different.

Conclusion: Female RA patients have higher disease activity and functional disability, but similar degree of radiographic joint destruction, compared with male RA patients, not only at baseline but sustained over 5 years time. This might be due to females perceiving the disease differently, or due to a gender difference in the link between activity and joint damage.

Disclosure: I. Castrejón, None; **K. Visser**, None; **N. B. Klarenbeek**, None; **I. González-Álvaro**, None; **T. W. Huizinga**, None.

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Patient Reported Outcomes in Inflammatory Arthritis: Development and Validation of a Combined Questionnaire for Functional Impairment and Quality of Life Assessment. Yasser El Miedany[1], Maha El Gaafary[2], Deborah Palmer[1] and Sally Youssef[3], [1]Darent Valley Hospital, Dartford, United Kingdom, [2]Ain Shams University, Abbassia, Egypt, [3]Ain Shams University, Cairo, Egypt

Purpose: to develop, assess validity, reliability and sensitivity to change of a new questionnaire for assessment of functional disability as well as quality of life in patients with inflammatory arthritis.

Method: Using Rasch analysis and item pools of 34 questions for functional disability and 29 questions for quality of life; content analysis and semi structured group discussion, the combined inflammatory arthritis questionnaire (CIAQ) was developed including: 10-items scale to assess functional impairment (CIAQ-FI), and 10-items to assess quality of life (CIAQ-QoL). We studied the CIAQ in 534 RA patients, 246 psoriatic arthritis and 241 patients with inflammatory bowel disease associated arthritis. Construct validity was assessed by correlating the score of the questionnaire to parameters of disease activity namely, the joint count (both tender and swollen), Pain score, Patient and Physician Global assessment, Fatigue score, HAQ, psychological score, grip strength, duration of morning stiffness, DAS score, ESR and CRP as well as the occupational status. Sensitivity to change of the developed CIAQ was also assessed. Each patient completed also both Stanford HAQ and HAQ-II questionnaires.

Results: The CIAQ questionnaires showed accepted validity as it correlated significantly with clinical parameters of disease activity, DAS-28 score, as well as CRP (p< 0.01). CIAQ-FI was as well as HAQ II or better correlated to clinical disease outcomes. The CIAQ was also reliable (Cronbach's alpha for CIAQ-FI was 0.90), compared to 0.83 for HAQ and 0.88 for HAQII, and had no misfitting items. Cronbach's alpha for CIAQ-QoL was 0.92. In addition, both the CIAQ-FI and CIAQ-QoL were sensitive to change. A significant correlation (p< 0.01) was observed in percentage change and effect size of both CIAQ-FI and CASQ-QoL with those of disease activity parameters and DAS-28 score.

Conclusion: the CIAQ is a valuable tool which is reliable and valid for assessment of functional impairment and quality of life in inflammatory arthritis patients. The CIAQ is well accepted by patients, sensitive to change, easy to administer and score, and more feasible to monitor the impact of management.

Disclosure: Y. El Miedany, None; **M. El Gaafary**, None; **D. Palmer**, None; **S. Youssef**, None.

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Differences in Inflammatory Arthritis Activity Across Mexican Mestizos, Canadian Native American Indians and Canadian Caucasians: HLA Associations. Carol A. Hitchon[1], Christine A. Peschken[1], Jose Luis Montiel[2], Peter Nickerson[3], David B. Robinson[1], Hani S. El-Gabalawy[1] and Daniel X. Xibille[4], [1]University of Manitoba, Winnipeg, MB, [2]Universidad Autonoma del Estado de Morelos, Mexico, [3]University of Manitoba, MB, [4]Hospital General de Cuernavaca, Cuernavaca Morelos, Mexico

Purpose: Mexican Mestizos (MM) and Canadian Native American Indians (NAI) with inflammatory arthritis are younger at presentation, have higher disease activity and are less likely to achieve remission than Canadian Caucasians (CC). We sought to determine whether these differences in phenotype severity and clinical outcome were associated with HLA DRB1 alleles or anti-CCP status.

Method: Patients with early inflammatory arthritis (EIA< 12 months symptom duration; rheumatoid arthritis (RA) or undifferentiated arthritis (UA)) were followed in outpatient clinics in Central Canada and Mexico and were treated at the discretion of their rheumatologist. Clinical outcomes of remission (DAS28-3ESR<2.6) and EULAR treatment response were determined at one year. Antibodies to citrullinated peptides (anti-CCP2) were measured by ELISA. Rheumatoid factor (RF) was measured by nephlometry. HLADRB1 typing was determined by DNA sequencing (SE alleles: 0101, 0102, 0401, 0404, 0405, 0408, 0410, 1001, 1402; "protective epitope" alleles (PA): 0103, 0402, 1103, 1301, 1302). Statistical associations were tested by Chi2 and non-parametric tests. Values are reported as percentages or mean (SD).

Results: At their baseline visit, MM (n=52; RA 92%) and NAI (n=51; RA 53%) with EIA were younger than CC (n=202; RA 42%) (39(12) and 40(14) vs 48(14) years $p<0.001$), had higher DAS28-3ESR scores (5.6(1.1) and 4.3(1.4) vs 3.8(1.5) $p<0.001$), and were more likely to be anti-CCP2 +ve (89%, 69%, 42% $p<0.001$) or RF+ve (71%, 70%, 54% ($p<0.01$). At one year, MM (1/19), NAI (3/26) and CC (64/108) achieved remission ($p<0.001$). HLA sequencing was available for 176 patients (MM n=72, 22 EIA, 49 Late rheumatoid arthritis (symptoms >12 months at baseline); NAI n=34 all EIA; CC n=127 all EIA). More NAI had at least one SE copy (FN 27/34(79%) vs MM (37/72(51%) (11/22 MM with EIA) and CC 79/127(62%) $p<0.05$). The proportion of NAI, CC and MM with two SE copies was 7/34(15%), 4/72(22%), and 19/127(6%) $p<0.06$). NAI were less likely than MM or CC to have at least one PA 1/34(3%) vs 9/72(13%) (2/22 MM with EIA) vs and 24/125(19%) $p<0.01$). Early UA were more likely than early RA to have at least one PA (26% vs 8% $p<0.001$). In addition EIA subjects with at least one PA (14 REM/18 +ve PA (78%) were more likely to achieve remission than those without PA (29 REM/79 -ve PA (36%) $p<0.01$). EULAR treatment response was not associated with SE or PA. Consistent with previous studies, SE was associated with anti-CCP2 (OR 4 (2-8) $p<0.001$).

Conclusion: The increased severity of EIA seen in Mexican Mestizos and Canadian Native American Indians compared to Caucasians is only partially explained by increased shared epitope, reduced protective alleles and anti-CCP. Further study on environmental factors is required.

Disclosure: C. A. Hitchon, None; **C. A. Peschken**, None; **J. L. Montiel**, None; **P. Nickerson**, None; **D. B. Robinson**, None; **H. S. El-Gabalawy**, None; **D. X. Xibille**, None.

ACR/ARHP Poster Session B

Rheumatoid Arthritis Treatment: Strategies and Outcomes

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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A Faster Clinical Response to Certolizumab Pegol (CZP) Treatment Is Associated with Better 52-Week Outcomes in Patients with Rheumatoid Arthritis (RA). Edward C. Keystone[1], Jeffrey R. Curtis[2], Roy Fleischmann[3], P. Mease[4], D. Khanna[5], J. S. Smolen[6], D. E. Furst[7], G. Coteur[8] and B. Combe[9], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Univ of Alabama at Birmingham, Birmingham, AL, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Seattle Rheumatology Associates, Seattle, WA, [5]UCLA, Los Angeles, CA, [6]Medical Univ Vienna, Vienna, Austria, [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, [8]UCB, Brussels, Belgium, [9]Immuno-Rheumatology, Montpellier, France

Purpose: CZP, the only PEGylated anti-TNF approved for the treatment of RA, provides rapid improvements in the signs and symptoms of RA, physical function and relief of pain and fatigue when added to methotrexate (MTX). The objective of our analysis was to determine if a more rapid response to CZP treatment was associated with better long-term outcomes in patients with active RA.

Methods: In the RAPID1 clinical trial, patients treated with CZP 200 mg + MTX who had an ACR20 response or DAS28 change of ≥1.2 points from baseline (BL) at Wk 12 were divided into 2 subgroups depending on response at Wk 6: Wk 6 responders and WK 6 non-responders (who responded at Wk 12). ACR20/50/70 response rates at Wk 52 were compared between responder subgroups using logistic regression; HAQ-DI, Pain-VAS and Fatigue Assessment Scale (FAS) at Wk 52 were compared using ANCOVA, adjusted for BL.

Results: BL characteristics were similar between the 2 subgroups in both analyses. Overall, response to CZP treatment was rapid with the majority of Wk 52 responders achieving a DAS28 or ACR20 responses by Wk 6 (Table). Wk 6 DAS28 and ACR20 responders had higher ACR20/50/70 response rates at Wk 52 than Wk 12 responders (Table). At Wk 52, Wk 6 DAS28 responders also had a significantly greater improvement in Pain VAS than Wk 12 responders, but not in HAQ-DI or FAS. Wk 6 ACR20 responders also reported significantly greater improvements in HAQ-DI and Pain VAS, but not FAS, than Wk 12 responders.

Table. Wk 52 Outcomes in Wk 6 versus Wk 12 responders

Responder definition	**ACR20**	**ACR50**	**ACR70**	**HAQ (0–3)**	**Pain VAS (0–100)**	**FAS (0–100)**
Change in DAS28 ≥1.2						
Wk 6 responder (n=200)	81.5[a]	61.0[a]	37.0[a]	–0.84	–42.8[b]	–3.7
Wk 12 responder (n=57)	56.1	36.8	12.3	–0.71	–34.3	–3.3
ACR 20						
Wk 6 responder (n=178)	83.1[a]	66.7[a]	39.0[a]	–0.87[c]	–44.8 [a]	–3.8
Wk 12 responder (n=87)	66.7	34.5	16.1	–0.69	–34.3	–3.2

[a]$p<0.001$; [b]$p\leq0.01$; [c]$p\leq0.05$ vs Wk 12 responders (adjusted mean difference in change from BL).

Conclusion: A faster response to treatment is associated with improved long-term outcomes at 52 wks in active RA patients treated with CZP + MTX. Rapid (Wk 6) responders demonstrated significantly greater ACR responder rates and greater improvements in physical function and pain relief than later (Wk 12) responders. Largely independent of whether ACR20 or DAS28 change ≥1.2 is used to assess response, these observations highlight the importance of a rapid, 6-wk response in RA outcomes over 1 year.

Disclosure: E. C. Keystone, Abbott, Amgen, AstraZeneca, BMS, Centocor, Hoffmann-Roche, Novartis, Schering-Plough, UCB, Wyeth, 2, Abbott, Amgen, BMS, Centocor, Genentech, GlaxoSmithKline, Hoffmann-Roche, Schering-Plough, UCB, Wyeth, 5, Abbott, Amgen, BMS, Centocor, Genentech,Hoffmann-Roche, Schering-Plough, UCB, Wyeth, 8 ; **J. R. Curtis**, Amgen, Merck, CORRONA, 2, Roche, UCB, 5, Roche Pharmaceuticals, 8 ; **R. Fleischmann**, Amgen, Wyeth, Centocor, Abbott, Genentech, BiogenIdec, UCB, Regeneron, Lilly, Pfizer, 2, Amgen, Wyeth, Centocor, Abbott, Genentech, Biogen Idec, UCB, AstraZeneca, Pfizer, Lilly, 5, Amgen, Wyeth, Abbott, 8 ; **P. Mease**, UCB, 5, UCB, 9 ; **D. Khanna**, Actelion, Gilead, Takeda, Savient, ,NIH, 2, Actelion, Takeda, Savient, UCB, Wyeth, 5, Actelion, Abbott, Gilead, Takeda , 8 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **D. E. Furst**, Abbott, Actelion, Amgen, BMS, Genentech, Gilead, GSK, Nitec, Norvartis, Roche, UCB, Wyeth, Xoma, 2, Abbott, Actelion, Amgen, Biogen Idec, BMS, Centocor, Genentech, Gilead, Merck,

Nitec, Norvartis, UCB, Wyeth, Xoma, 5, Abbott, Actelion, Amgen, Biogen Idec, BMS, Centocor, Genentech, Gilead, GSK, Nitec, 9, Abbott, Actelion, UCB, 8 ; **G. Coteur**, UCB, 3 ; **B. Combe**, UCB, MSD, Roche, Schering, Wyeth, 2, UCB, Abbott, GSK, MSD, Roche, Schering, Wyeth, 5 .

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The Relationship Between Different Isotypes (IgM, IgG and IgA) of Rheumatoid Factor and IgG Anti-Cyclic Citrullinated Peptide Antibody and the Clinical Response to Infliximab in Rheumatoid Arthritis. Ruth Klaasen, Tineke Cantaert, Carla A. Wijbrandts, Danielle M. Gerlag, Theo A. Out, Monique J. de Nooijer, Dominique L. Baeten and Paul P. Tak, Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: It is unclear whether IgM rheumatoid factor (RF) and IgG anti-citrullinated peptide antibodies (ACPA) can predict response to tumor necrosis factor (TNF) blockade in patients with rheumatoid arthritis (RA). We investigated if different isotypes of RF and IgG ACPA (by anti-CCP test) can predict response to infliximab.

Methods: Serum of 104 RA patients with active disease (DAS28 □ 3.2) despite stable methotrexate treatment was collected before and 16 weeks after start of infliximab. IgM, IgG, IgA RF and IgG anti-CCP2 were measured by ELISA. Presence of RF was defined as a level □ 20 U/ml and of anti-CCP □ 25 U/ml. Clinical response was defined as a decrease in DAS28 □ 1.2 at week 16.

Results: Clinical response to treatment was observed in 70% of the patients. At baseline, the level of all RF, but not anti-CCP IgG, was positively correlated to CRP levels, ESR and DAS28. Responders were more frequently IgM RF positive than non-responders (table 1), also when controlling for DAS28 at baseline in a logistic regression analysis. The level of all RF isotypes, but not anti-CCP IgG, at baseline was positively correlated to the absolute decrease in DAS28 after 16 weeks (r between 0.223 and 0.304; P<0.02). This association persisted after adjustment for DAS28 at baseline (multiregression analysis). Patients with IgA or IgG RF levels of □ 100 U/ml all responded to therapy, but numbers were small (5 and 4 patients, respectively). The simultaneous presence of all three isotypes of RF at baseline did not further contribute to prediction of response. During treatment, the level of all RF isotypes (all P < 0.001) as well as the level of IgG anti-CCP (P = 0.041) decreased significantly.

Conclusion: High baseline levels of IgM, IgG and IgA RF are associated with a better response to infliximab treatment in RA patients.

Table 1. Percentage of patients positive for autoantibodies in responders versus non-responders as well as positive predictive value (PPV) and negative predictive value (NPV) for the prediction of clinical response to infliximab treatment in RA.

	All patients	**Responders**	**Non-responders**	**PPV**	**NPV**	**P-value**
IgM RF+ (%)	62%	70%	44%	78%	46%	***P = 0.010***
IgG RF+ (%)	24%	30%	13%	83%	37%	P = 0.06
IgA RF+(%)	34%	37%	26%	76%	34%	P = 0.29
All isotypes RF+(%)	19%	24%	10%	84%	32%	P = 0.09
IgM RF >100 u/ml	28%	35%	13%	86%	38%	***P = 0.018***
IgG RF > 100 u/ml	4%	6%	0%	100%	33%	P = 0.16
IgA RF > 100 u/ml	5%	7%	0%	100%	32%	P = 0.32
IgG CCP+(%)	76%	81%	66%	73%	44%	P = 0.10

Disclosure: R. Klaasen, None; **T. Cantaert**, None; **C. A. Wijbrandts**, None; **D. M. Gerlag**, None; **T. A. Out**, None; **M. J. de Nooijer**, None; **D. L. Baeten**, None; **P. P. Tak**, None.

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Evidence That the Response to Rituximab in RA Depends On B Cell Depletion, as Determined by Highly Sensitive Flow Cytometry, Rather Than Dose of Drug Administered. Edward M. Vital[1], Andrew C. Rawstron[2], Shouvik Dass[1], Karen Henshaw[1], Julie Madden[3], Paul Emery[1] and Dennis McGonagle[1], [1]University of Leeds, Leeds, United Kingdom, [2]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Calderdale and Huddersfield NHS Foundation Trust, Halifax, United Kingdom

Purpose: Published clinical trials showed that responses with rituximab (RTX) 2 x 500mg are similar to 2 x 1000mgs for ACR20, but worse for ACR70 and EULAR Good. All patients in these studies appeared to deplete completely, regardless of dose. Highly sensitivite flow cytometry demonstrates that depletion is more variable than earlier studies indicated. Using 2 x 1000mg RTX, many patients still have incomplete depletion, which is predictive of worse clinical responses(1). Incomplete depletion is predicted by higher circulating preplasma cells, which may correlate with higher synovial or lymphoid B cell activity(2). The relationship between dose of RTX, B cell depletion and clinical response has not previously been investigated.

Method: 21 patients who received 2 x 500mg RTX (RTX500) were compared to 82 receiving 2 x 1000mg RTX (RTX1000, previously reported, 1). All had baseline DAS28 > 5.1 despite 2 or more DMARDs. B cell subsets were measured using highly sensitive flow cytometry as previously described(1). Briefly, 500 000 events were analysed by 6 colour flow cytometry in two tests, using an extensive sequential gating strategy with multiple exclusion markers to allow reproducible enumeration of B cells at 0.002% (equivalent to absolute B cell count 0.0001 cells x109/L) . Complete depletion was defined as B cell count < 0.0001 x109/L after both the 1st and 2nd infusions. Clinical response was assessed using EULAR criteria after 6 months. Categorical variables were compared using Fisher's exact test and B cell levels using Mann Whitney U test.

Results:

Depletion

There was a trend to greater depletion in RTX1000. Rates of complete depletion were 4/16 (25%) and 34/82 (42%) for RTX500 and RTX1000 respectively (p = 0.22). In each group, complete depletion was related to baseline preplasma cell count. For RTX500 median baseline preplasma cells 0.0010 vs. 0.0031 for complete vs. incomplete (p = 0.079). For RTX1000 preplasma cells 0.0013 vs. 0.0021 (p = 0.05).

Clinical Response

For RTX500: mean DAS28 was 5.93 (±0.80) at baseline and 4.01 (±1.78) at 6 months. Overall EULAR Non/Moderate/Good response rates were 33/27/40%.

15/21 RTX500 patients had complete B cell and clinical data. EULAR responses were better in patients with complete depletion and similar to the RTX1000 group with complete depletion. 5 patients failed to respond: all had incomplete depletion (p=0.099). All 4 patients with complete depletion had a Good EULAR response, compared to 2/11 of patients with incomplete depletion (p = 0.01).

Conclusion: In this pilot study there was a trend to less complete B cell depletion using RTX500. Some patients still achieved complete depletion at lower dose, and this was predicted by lower numbers of circulating preplasma cells at baseline. Regardless of dose of RTX, complete B cell depletion is associated with better clinical response, which could have implications for dosing schedules in RA.

(1) Dass S et al. Arthritis Rheum. 2008 Oct;58(10):2993-9. (2) Vital EM et al. EULAR 2009.

Disclosure: E. M. Vital, Roche, 9 ; **A. C. Rawstron**, None; **S. Dass**, Roche Pharmaceuticals, 9 ; **K. Henshaw**, None; **J. Madden**, None; **P. Emery**, Roche Pharmaceuticals, 8, Wyeth Pharmaceuticals, 8, Abbott Laboratories, 8, Schering, 8 ; **D. McGonagle**, None.

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Probability to Achieve Low Disease Activity at 52 Weeks in Rheumatoid Arthritis (RA) Patients Treated with Certolizumab Pegol (CZP) Depends On Time to and Level of Initial Response. Désirée M.F.M. van der Heijde[1], M. Schiff[2], Edward C. Keystone[3], R. Landewé[4], T.K. Kvien[5], J. R. Curtis[6], D. Khanna[7], K. Luijtens[8], D.E. Furst[9] and John J. Cush[10], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Univ of Colorado School of Medicine, Denver, CO, [3]Professor of Medicine/University of Toronto, Toronto, ON, [4]Maastricht Univ Medical Ctr, Maastricht, Netherlands, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Univ of Alabama at Birmingham, Birmingham, AL, [7]UCLA, Los Angeles, CA, [8]UCB, Brussels, Belgium, [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, [10]Baylor Research Institute, Dallas, TX

Purpose: The relationship between an early response to biologic therapy and longer-term clinical outcomes has not been well characterized. We conducted a posthoc analysis to determine the relationship between initial improvement in DAS28(ESR) score within 12 weeks (wks) and probability to achieve low disease activity (LDA; DAS28 ≤3.2) at Wk 52 in RA patients (pts) treated with CZP.

Methods: The proportion of pts treated with CZP (200 or 400 mg) + MTX who had LDA at Wk 52 was assessed among pts who achieved or failed to achieve various DAS28 responses (ie, DAS28 decrease from baseline [BL] <0.3, 0.6, 0.9, 1.2, 1.5 and 1.8 units) by Wks 1, 2, 4, 6, 8, 10 or 12. **Results:** were analyzed for the ITT (LOCF) population. Pts with non-imputable missing data during the first 12 wks of treatment were excluded from the analysis.

Results: Of the 783 pts randomized to CZP + MTX, 98% had DAS28 >5.1 at BL; 30% achieved LDA by Wk 52. By Wk 12, 98%, 87% and 74% of CZP-treated pts had DAS28 decreases from BL ≥0.3, ≥1.2, and ≥1.8, respectively. CZP-treated pts who improved their DAS from BL by <0.3 up to Wk 6 (N=41) had 0% probability of achieving LDA at Wk 52 (Table). Similarly, pts who improved their DAS from BL by <0.6 or 0.9 up to Wk 10 (N=45 and N=76, respectively) had 0% chance to achieve LDA at Wk 52. Pts who had a change of <0.3 at Wk 4, <0.6 and 0.9 at Wk 6, <1.2 at Wk 8, or <1.5 and 1.8 at Wk 12 had a <5% probability of achieving LDA at Wk 52 (bolded rows of Table).

Conclusion: : Long-term response to CZP can be estimated early in the course of treatment. The majority of RA pts respond within the first 12 wks of CZP treatment. Furthermore, the probability of not achieving LDA at Wk 52 can be predicted by a combination of the change in DAS28 from BL and the time at which DAS28 was assessed after starting CZP treatment.

Table. Percentage* of CZP-treated pts with LDA at Wk 52 out of those who failed to achieve DAS decreases up to wk of follow-up for the first 12 wks

	Wk						
DAS28 Change	**1**	**2**	**4**	**6**	**8**	**10**	**12**
<0.3	19.5 (N=220)	11.6 (N=112)	**3.2 (N=63)**	**0 (N=41)**	**0 (N=27)**	**0 (N=19)**	**0 (N=14)**
<0.6	21.0 (N=352)	14.8 (N=209)	7.1 (N=126)	**2.5 (N=79)**	**3.2 (N=63)**	**0 (N=45)**	**0 (N=34)**
<0.9	22.8 (N=457)	17.0 (N=317)	8.9 (N=202)	**4.2 (N=144)**	**2.8 (N=106)**	**0 (N=76)**	**0 (N=67)**
<1.2	24.7 (N=546)	19.1 (N=418)	12.8 (N=288)	7.5 (N=214)	**4.5 (N=157)**	**3.1 (N=129)**	**1.0 (N=103)**
<1.5	26.1 (N=605)	21.5 (N=492)	16.5 (N=369)	11.7 (N=281)	7.2 (N=221)	**5.5 (N=182)**	**2.1 (N=145)**
<1.8	27.9 (N=656)	24.4 (N=573)	17.4 (N=448)	12.3 (N=357)	9.5 (N=294)	7.3 (N=245)	**4.9 (N=206)**

*N numbers are denominators for % calculations and are the number of pts not achieving the DAS28 change threshold at the wk presented.

Disclosure: D. M. F. M. van der Heijde, UCB, 2, UCB, 5, UCB, 9 ; **M. Schiff**, UCB, 2, UCB, 5 ; **E. C. Keystone**, Abbott, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb; Centocor, Inc., F. Hoffmann-LaRoche Inc., Novartis Pharmaceuticals' Schering-Plough Corporation, UCB, Wyeth Pharmaceuticals , 2, Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, Centocor, Inc, F. Hoffmann-La Roche Inc., Genentech, Inc., GlaxoSmithKline, Schering-Plough Corporation, UCB, Wyeth Pharmaceuticals, 5, Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, Centocor, Inc., F. Hoffmann-La Roche Inc., Genentech, Inc., Schering-Plough Corporation, Wyeth, 8 ; **R. Landewé**, Abbott, Amgen, BMS, Centocor, Schering-Plough, UCB and Wyeth, 5 ; **T. K. Kvien**, UCB, Abbott, BMS, Roche, Schering-Plough, Wyeth, MSD, 2, UCB, Abbott, BMS, Roche, Schering-Plough, Wyeth, MSD, Pfizer, 5, Abbott, Roche, Wyeth, MSD, Pfizer, 8 ; **J. R. Curtis**, Amgen, Merck, CORRONA, 2, Roche, UCB, 5, Roche Pharmaceuticals, 8 ; **D. Khanna**, Actelion, Gilead, Takeda, Savient, NIH, 2, Actelion, Takeda, Savient, UCB, Wyeth, 5, Actelion, Abbott, Gilead, Takeda, 8 ; **K. Luijtens**,

UCB, 3 ; **D. E. Furst**, Abbott, Actelion, Amgen, BMS, Genentech, Gilead, GSK, Nitec, Novartis, Roche, UCB, Wyeth, Xoma, 2, Abbott, Actelion, Amgen, BMS, BiogenIdec, Centocor, Genentech, Gilead, Merck, Nitec, Novartis, UCB, Wyeth, Xoma, 5, Abbott, Actelion, Amgen, BMS, BiogenIdec, Centocor, Genentech, Gilead, Merck, Nitec, 9, Abbott, Actelion, UCB, 9 ; **J. J. Cush**, Celegene, 2, Roche, 2, Centocor, Inc., 2, Genentech, 5, Pfizer Inc, 2, UCB, 5, Abbott Laboratories, 2, Centocor, 5, Amgen, 5, UCB, 2, Genentech , 2 .

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The Belgian MIRA (MabThera in Rheumatoid Arthritis) Registry: Clues for the Optimization of Rituximab Treatment Strategies.

Bert Vander Cruyssen[1], Rene Westhovens[2], Patrick Durez[3], Filip De Keyser[4] and MIRA study group, [1]University Hospital Ghent, Ghent, Belgium, [2]University Hosp KU Leuven, Leuven, [3]Univ Catholique de Louvain, Brussels, Belgium, [4]Ghent University Hospital, Ghent, Belgium

Purpose: In Belgium, RA patients are eligible for treatment with rituximab if they failed at least 1 anti-TNF and have a baseline DAS28 > 3.7. From month 6 on, patients can be retreated if they had a moderate or good EULAR response at week 16, and a current DAS28 score of at least 3.2. The Belgian MIRA registry aims to record safety and efficacy data, and to evaluate the retreatment conditions.

Method: All Belgian rheumatologists could participate in the study. Patients entered the registry as from November 2006 and the entry is still open. All patients were treated with 2 infusions per course of rituximab (2 x 1000 mg) in combination with 100 mg of methylprednisolone and MTX. Baseline patient's characteristics, and DAS28-variables were recorded every 2 months

Results: By March 2009, 332 patients had entered the registry with a mean follow-up time of 54 (range 0-122) weeks. Patients (mean age of 57 years, 78 % female) had a mean disease duration of 12 years.

Rituximab therapy decreased the overall mean disease activity from DAS28-ESR 6.1 (SE = 0.1) at baseline to 4.2 (SE = 0.1) at week 16. 82% of patients obtained a good or moderate EULAR response. Further decrease of DAS was observed at the end of year 1 and year 2 with a mean DAS28-ESR of 3.8 (SE = 0.2) and 3.7 (SE = 0.5) at these respective time points. 191 and 75 patients received a 2nd and 3rd course of rituximab respectively. The median time to retreatment was 34 weeks for the first course and 39 weeks for the second course.

At baseline, 83% of the patients had a high disease activity. This percentage dropped to 24% at 16 weeks, with 23% of patients reaching remission or low disease activity status. At the start of the second course, 60% of patients had a high disease activity. With retreatment, this percentage dropped to 19% at 16 weeks, with 31% reaching remission or low disease activity status.

34 patients (10.2%) stopped treatment at a median follow-up time of 21 weeks; 19 due to inefficacy and 15 stopped due to safety issues (allergic infusion reactions in 6 patients, 2 infections and other safety reasons were reported in the remaining 7 patients). 1 patient died after a pneumonia in relation to a hip fracture. 4 patients were lost to follow-up.

Conclusion: This study describes the current follow-up of a daily clinical practice cohort of 332 RA patients with longstanding refractory disease treated with rituximab. Continued decrease of DAS28 scores at each treatment course was obtained with rituximab therapy with a favourable safety profile. Relatively high DAS28 values at the start of each retreatment, compared to values at week 16 of each treatment course, suggest that treatment of RA patients with rituximab could be optimized by earlier retreatment.

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TNFα-Inhibitors in Established Rheumatoid Arthritis: The Effect of Age On Treatment Response and Predictors of Remission.

Ludvig L. Dahl, P. Geborek, Martin Englund, Tor Olofsson and Ingemar F. Petersson, Lund University, Department of Clinical Sciences, Lund, Sweden

Purpose: To study the impact of age at treatment start on response and remission in patients with rheumatoid arthritis (RA) receiving anti-TNFα-treatment for the first time.

Methods: Patients with RA receiving their first course of TNFα-inhibitor were enrolled from the South Swedish Arthritis Treatment Group register. Maximum follow-up length was 60 months. The effect of age was examined by comparing patients in the 1st quartile of age with

the rest of the patients. Fulfillment of the EULAR remission criteria at least once during the follow-up was used as the main response measure. Predictors of remission were analyzed using logistic regression.

Results: 2346 patients were included. The 1st quartile of age corresponded to 48 years. At treatment initiation the older group had significantly longer disease duration, a lower proportion of men, worse DAS28- and HAQ-scores and more often used concomitant DMARDs and steroids.

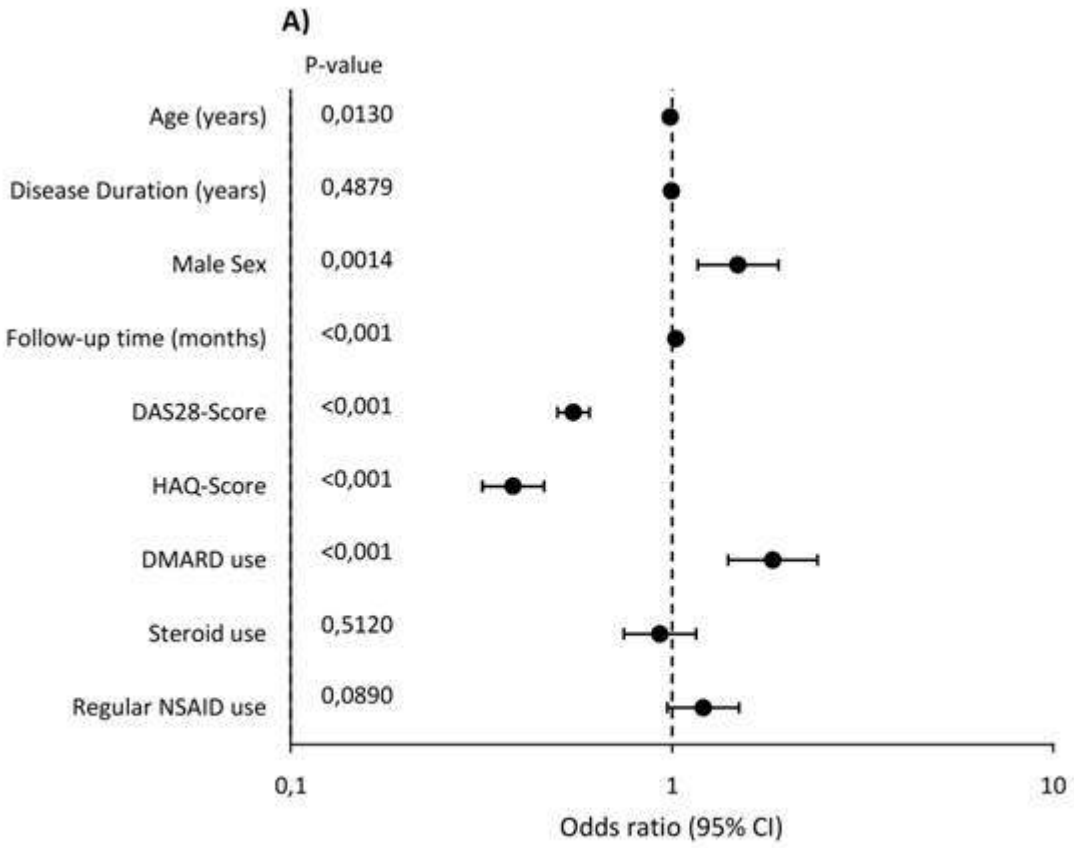
Rapid decreases in DAS28-scores and HAQ-scores were seen within the first 3 months. DAS28- and HAQ-score remained significantly lower in the younger group at all times.

The frequency of patients in remission rose rapidly during the first 3 months and continued to increase during the follow-up period. At all times the frequency was significantly higher in the younger group. After 3 years 31% (95% CI 26-35%) of the older group and 45% (95% CI 37-53%) of the younger group were in remission. The younger group tended to reach remission sooner (8.7 vs. 10.1 months (ns). The older group had significantly worse ACR and EULAR response at 6 and 12 months, and significantly worse mean drug survival time, 54 vs. 66 months.

Multivariate predictors of remission (Figure 1) were: Age ≤ 48 years (OR 1.4 95% CI 1.1-1.7), male gender (OR 1.5 95% CI 1.2-1.9), concurrent DMARD use (OR 1.8 95% CI 1.4-2.4), baseline HAQ-score (OR 0.38 95% CI 0.32-0.46) and baseline DAS28-score (OR 0.55 95% CI 0.50-0.61). In the younger group gender and DMARD use were not significant predictors, but there was a trend for regular NSAID use (OR 1.5, p=0.08) and steroid use (OR 0.7, p=0.11).

Conclusion: Age had a significant impact on treatment outcome in RA patients receiving anti-TNFα-treatment for the first time. DMARD treatment and male gender were positive predictors, while higher age, higher DAS28-scores and higher HAQ-scores were negative predictors of remission. The impact of some predictors was dependent on age.

Figure 1. Baseline predictors of remission: on at least one assessment, not including baseline. Multivariate binary logistic regression, ORs, 95% CI and significance levels. **A)** Whole study population **B)** Predictors in the 2 age groups: < 48 years (black squares) and ≤ 48 years (grey diamonds).


A)
P-value
Age (years)
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Disease Duration (years)
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Male Sex
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Follow-up time (months)
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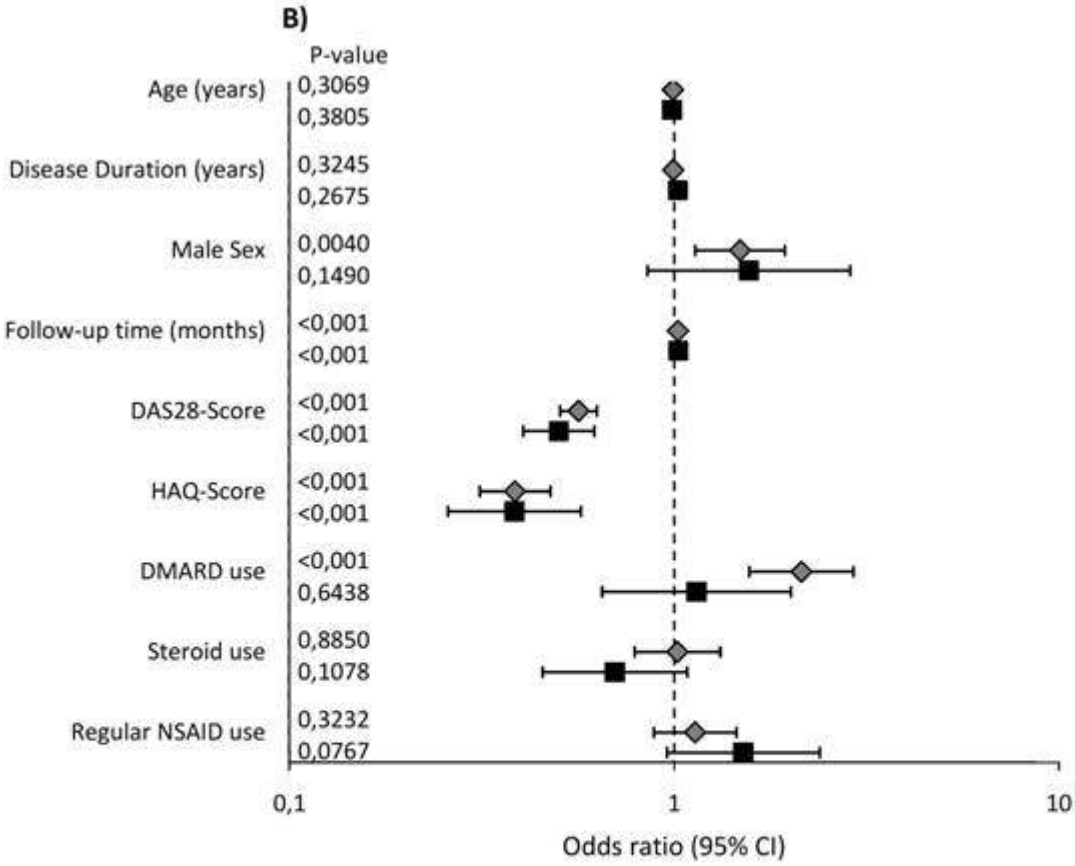
DAS28-Score
<0,001
HAQ-Score
<0,001
DMARD use
<0,001
Steroid use
0,5120
Regular NSAID use
0,0890
0,1
1
10
Odds ratio (95% CI)


B)
P-value
Age (years)
0,3069
0,3805
Disease Duration (years)
0,3245
0,2675
Male Sex
0,0040
0,1490
Follow-up time (months)
<0,001
<0,001
DAS28-Score
<0,001
<0,001
HAQ-Score
<0,001
<0,001
DMARD use
<0,001
0,6438
Steroid use
0,8850
0,1078
Regular NSAID use
0,3232
0,0767
0,1
1
10
Odds ratio (95% CI)

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The Time for 6—Month Placebo Trials in Rheumatoid Arthritis Has Passed: A Systematic Comparison of 3— and 6—Month Response Rates in Trials of Biologic Agents. Maarten Boers, VU Univ Medical Center PK6Z165, Amsterdam, Netherlands

Purpose: Most trials in rheumatoid arthritis (RA) are registration trials. These trials traditionally compare an experimental agent with placebo in the setting of an incomplete response to disease-modifying treatment (DMARD-IR) that is continued during the trial. The standard duration of such trials continues to be 6 months or longer in the face of serious methodological and ethical shortcomings. This study compares the contrast in response between the treatment groups at 3 and 6 months.

Method: Secondary use of dataset for meta-analysis of randomized trials of biologic agents in RA. Eligible trials enrolled DMARD-IR patients, and reported data of ACR20, -50, and -70 responses at 3 and 6 months. Trial contrasts were categorized as placebo control or active control (e.g. methotrexate in methotrexate-naive control patients). The ratio of each ACR (20,50,70) response rate between control and experimental groups was summarized separately for the placebo and active control contrasts, by weighted Mantel-Haenzsel random effect risk ratios (i.e. 'risk' of response in the experimental group given the response in the control group).

Risk ratios of responses at 3 and 6 months were compared in a stratified analysis, applying the same weights as in the first step. Finally, for the placebo trials sample size calculations were performed for a range of plausible response rates.

Results: Twenty trials (10 multiple arm) yielded 15 placebo and 18 active control contrasts in 10,514 patients. Most included patients had severe, longstanding RA. Responses were higher at 6 than at 3 months in both control and experimental groups. In placebo trials contrasts were all highly significant for ACR20 and -50 levels at all time points, and the mean contrast did not change significantly between 3 and 6 months (Table). For ACR70 at 3 months the contrast between placebo and experimental groups was not significant in 4 out of 15 trials, decreasing to 1 out of 15 at 6 months, and the 'risk' of a response on experimental compared to placebo treatment increased significantly (3 months: 4.1; 6 months 5.8; p=0,02). This was mainly due to an increase of patients meeting ACR70 only in the experimental groups.

As expected, in active control groups responses were much higher than in placebo groups, and contrasts with the experimental groups correspondingly smaller. For ACR20 contrasts did not change significantly between 3 and 6 months. For ACR50 and-70 contrasts decreased somewhat (significant for ACR50), corresponding with a 'catch-up' response in the control group.

Suggested sample sizes at 3 and 6 months were similar for ACR20 and 50 and well below the 100 patients per group for a range of plausible response rates (power 90%; two-sided alpha 5%). For ACR70 placebo trials of only 3 months duration are likely to be at a disadvantage (i.e., need about twice the number of patients) to show a significant difference between treatment groups.

Conclusion: To detect efficacy for signs and symptoms of RA, the placebo phase of registration trials can be safely limited to a duration of 3 months.

Table		event rate		risk ratio*	P
		control	experimental	(mean, 95%CI)	
placebo control					
ACR20	3 months	0,26	0,55	2,1 (1,9-2,3)	<0.001
	6 months	0,28	0,59	2,3 (1,9-2,8)	<0.001
	6 y 3			1,1 (1,0-1,2)	0,10
ACR50	3 months	0,07	0,28	3,8 (3,3-4,4)	<0.001
	6 months	0,10	0,36	3,6 (3,1-4,3)	<0.001
	6 y 3			0,9 (0,8-1,1)	0,42
ACR70	3 months	0,02	0,11	4,1 (3,1-5,3)	<0.001
	6 months	0,03	0,18	5,8 (4,5-7,4)	<0.001
	6 y 3			1,4 (1,1-2,0)	0,02
active control					
ACR20	3 months	0,53	0,59	1,1 (1,1-1,2)	<0.001
	6 months	0,56	0,62	1,1 (1,0-1,2)	0,003
	6 y 3			1,0 (1,0-1,0)	0,30
ACR50	3 months	0,24	0,31	1,3 (1,1-1,4)	<0.001
	6 months	0,32	0,39	1,2 (1,1-1,3)	<0.001
	6 y 3			0,9 (0,9-1,0)	0,02
ACR70	3 months	0,08	0,12	1,5 (1,1-1,8)	0,002
	6 months	0,15	0,21	1,4 (1,3-1,6)	<0.001
	6 y 3			1,0 (0,9-1,0)	0,40

* risk ratio: the risk of a response in the experimental group v the control group

Disclosure: M. Boers, Roche, 9 .

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Usefulness of in Vitro Interferon-γ Release Assays (IGRAS) for Diagnosis of Latent Tuberculosis Infection in Rheumatic Patients Scheduled for Anti-TNF-α Treatment. Lourdes Mateo[1], Sonia Mínguez[2], Irene Latorre[1], José Domínguez[1], Anna Moltó[3], Emma García[2], Dolors Grados[1], Susana Holgado[1], Alejandro Olivé[1], Jerónima Cañellas[1] and Xavier Tena[1], [1]Hospital Germans Trias i Pujol, Badalona, Spain, [2]Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [3]M.D., Resident., Badalona, Spain

Purpose: Detection of latent tuberculosis infection (LTBI) is mandatory in rheumatic patients candidates for treatment with anti-TNF-a agents. Although there is not a "gold standard" for diagnosis of LTBI, tuberculin skin test (TST) is the standardized method worldwide. Spanish Society of Rheumatology recommends the performance of a second-step TST, 1-2 weeks after the first one, and a chest radiograph. However, the existence of false-positive (BCG vaccination, nontuberculous mycobacterias) and false-negative (anergy, immunosuppression) TST results, has led to the development of new *in vitro* techniques in order to improve the sensitivity and specificity in LTBI detection.

Our aim is determining the usefulness of blood interferon-g release assays (IGRAS) and to compare them with TST in patients with different inflammatory rheumathic diseases scheduled for anti-TNF treatment.

Method: The study included individuals with inflammatory rheumatism staring an anti-TNF-a agent. All patients underwent 2 TST, a chest radiograph and 2 IGRAS: One assay, (QuantiFERON GOLD *in tube*) measures IFN-g concentration in supernatant by enzyme-linked immunosorbent assay in response to specific antigens (ESAT-6, CFP-10 and TB7.7); the other enumerates IFN-g-secreting T cells by enzyme-linked immunospot (T-SPOT.TB). We performed a descriptive statistical study and calculated concordance between TST/T-SPOT.TB, TST/QFT and T-SPOT.TB/QFT by Cohen´s kappa test, with k value > 0.75 representing excellent agreement, 0.4-0.75 good-moderate and <0.40 poor agreement.

Results: We included 23 patients (10 males/13 females) with a mean age of 52.4 ± 13.2 years and different rheumatic diseases: 7 rheumatoid arthritis (RA), 4 ankylosing spondylitis, 5 psoriatic arthritis, 3 seronegative arthritis, 2 systemic lupus erythematous, 1 undifferentiated spondyloarthropaty and 1 SAPHO. Average time of disease evolution was 9.6 ± 9 years. All patients with RA had seropositive and erosive forms. Prior to anti-TNF-a treatment, 16 patients had received 2 DMARD (range 0-5) and 10 (43.5%) systemic glucocorticoids. 3/23 (13%) patients displayed positive TST. Only one had positive second-step TST after being negative the first one. T-SPOT.TB was positive in 7 / 23 (30.4%) and QFT in 5 / 23 (21.7%). QFT was undetermined in 3 cases (13%), while none for T-SPOT.TB. Level of agreement (kappa test) between TST/T-SPOT.TB was 0.51; between TST/QFT 0.46 and between T-SPOT.TB/QFT 0.79. Five patients (21.7%) received secondary prophylaxis for tuberculosis, 2 of them with negative TST and positive IGRAS.

Conclusion: 1) IFN-g release assays are more accurate methods for diagnosis of latent tuberculosis infection than tuberculin skin test in rheumatic patients, even using a second-step TST. 2) Correlation between IGRAS and TST is moderate in immunocompromised individuals. 3) T-SPOT.TB seems to have greater sensitivity and lower rate of indeterminate results than QFT.

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Direct Comparison of 4 Years' Drug Survival of Adalimumab, Etanercept and Infliximab in Rheumatoid Arthritis Patients. An Observational Study From the DANBIO Registry. M.L. Hetland[1], I.J. Christensen[2], U. Tarp[3], L. Dreyer[1], A. Hansen[1], I.T. Hansen[1], G. Kollerup[1], L. Linde[1], H.M. Lindegaard[1], U.E. Poulsen[1], A. Schlemmer[1], D.V. Jensen[1], S. Jensen[1] and M. Østergaard[1], [1]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Sealand and Capital Region, Copenhagen, Denmark, [2]Copenhagen, Denmark, [3]DANBIO, Copenhagen, Denmark

Purpose: Data on the withdrawal rates of different TNF-inhibitors (TNF-I) in clinical practice are scarce. The aim was to determine 4-year drug survival of the different TNF-I and calculate Hazard Ratios (HRs) of their withdrawal based on the DANBIO registry.

Methods: 2935 RA patients (832 (28%) adalimumab, 703 (24%) etanercept, 1400 (48%) infliximab) were followed from start of first TNF-I treatment to withdrawal of treatment or Oct 1st 2008 (whichever came first). HRs were calculated correcting for baseline disease activity, age, disease duration, concomitant methotrexate and prednisolone, number of previous DMARDs, HAQ score and hospital department. Propensity scores and various subanalyses gave similar results, not shown.

Results: Figure shows 4 years' (unadjusted) drug survival: adalimumab:56%(95%CI:51-61%); etanercept:63%(58-68%); infliximab:44%(41-47%), p<0.0001, log rank test.

Below the figure, numbers of events and numbers of patients at risk at different time points for each drug are shown.

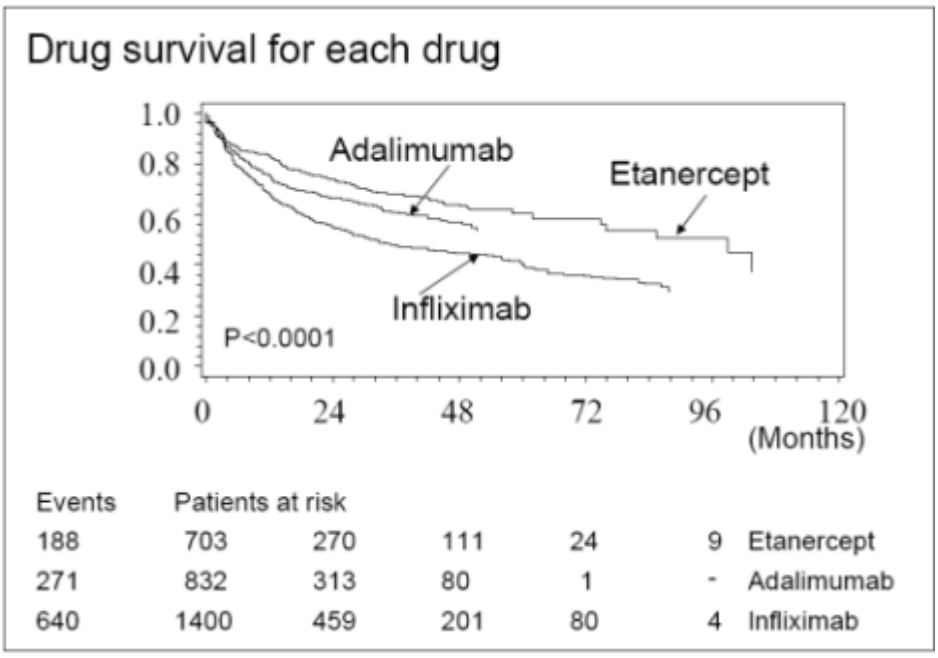
HRs for drug withdrawal, incl. subanalyses by reason for withdrawal, are shown in table.

Table:

Hazard Ratios (95% CI) for drug withdrawal

	Adalimumab vs. etanercept	**Infliximab vs. etanercept**	**Infliximab vs. adalimumab**
All pts (1099 events)	1.56 (1.26-1.94)	2.10 (1.70-2.59	1.35 (1.13-1.61)
LOE (727 events)	1.51 (1.17-1.96)	1.73 (1.35-2.23)	1.15 (0.92-1.42)
AE (327 events)	1.73 (1.14-2.62)	3.19 (2.15-4.72)	1.85 (1.35-2.52)

LOE: lack of efficacy; AE: adverse event



Conclusion: In this nationwide follow-up study of 2935 RA patients, 4 years' drug survival was highest for etanercept. After correcting for differences in baseline characteristics, the hazard ratio for withdrawal was overall highest for infliximab and lowest for etanercept regardless of reason for withdrawal.

Conflict of Interest: The DANBIO registry received unrestricted grants from Abbott, BMS, Roche, Schering-Plough, UCB Nordic and Wyeth.

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Focus On Persistent Disease Activity: Experiences From the BARFOT Early RA Cohort After 8 Years. Björn Svensson[1], Kristina Albertsson[2], Sidona Valentina Bala[3], Kristina Forslind[3] and Ingiäld Hafström[2], [1]University of Lund, Villands Vånga, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]Helsingborgs Hospital, Helsingborg, Sweden

Purpose: Remission is reported in an increasing proportion of patients and is ascribed to novel treatment options and strategies. However, a substantial number of patients suffer from ongoing active disease. This study focuses on these patients and describes the consequences on clinical symptoms, function and joint destruction.

Method: 628 patients (66% women) from the BARFOT early (duration less than a year) RA cohort have been followed for 8 years. Mean age at baseline was 54 years and disease duration 6.3 months. 60% were anti-CCP positive and 65% RF positive. Disease activity (DA) was defined as low or no (*low*) - DAS28 <3.2 and as medium or high (*high*) - DAS28 ≥3.2. *Persistent DA* was defined as DAS28 3.2 or more on all the three follow-ups at 2, 5 and 8 years. DAS28, HAQ and SOFI (Signals Of Functional Impairment) and radiographs of hands and feet were assessed. The radiographs were scored by the van der Heijde modification of the Sharp score (SHS).

Results: After 8 years almost 40% were in remission while 55% had low and 45% high DA. Patients with high DA had more pain and poorer function as measured by HAQ and SOFI (a performance index) compared with the patients with low DA (p=0.001 for all variables).

27% of the patients had persistent DA, and these patients had remarkably more severe symptoms and worse daily life and physical function compared with the patients without. Thus, mean pain-VAS was 47 vs 24, general health 48 vs 24, swollen joints 5.2 vs 1.6, tender joints 6,0 vs 1,34, HAQ 1.1 vs 0.5 and SOFI 10 vs 5, respectively, all differences p=0.001.

These clinical differences between persistent and no persistent DA were reflected by a marked difference in joint destruction. Thus, the median change in SHS after 2, 5 and 8 years was considerably greater in patients with persistent DA compared with patients without: 4 vs 2, p=0.011, 12 vs 6, p=0.003 and 14.2 vs 5, p=0.001, respectively.

DMARD and biologic treatment was overall statistically different between patients with and without persistent DA at 2, 5 and 8 years of follow-up. At these time points patients with persistent DA got more DMARD combination therapy (16% vs 6%, 19% vs 7% and 13% vs 9%) and at 5 and 8 years also more biologics (9% vs 5% and 19% vs 13%) than patients with persistently low DA. The proportion of patients treated with prednisolone was higher in the persistent DA group at 5 and 8 years (39% vs 23%, p=0.001 and 36% vs 20%, p=0.001, respectively).

In a logistic regression model, including 85% of the patients, female gender independently predicted persistent DA, OR(95%CI) 0,41(0.25-0.66), p=0.001, as well as baseline DAS28, OR(95%CI) 1.35(1.11-1.64), p=0.002, and disease duration 1.09(1.02-1.16), p=0.003.

Conclusion: This study shows that although half of the patients from an early RA cohort did well after 8 years, more than one quarter suffered from persistently active disease with pain, restricted daily life functions, impaired physical function and progressive joint destruction. Obviously increased focus on this particular group of patients is necessary.

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Identifying Clinical Features of Disseminated Histoplasmosis in Patients Receiving TNF Inhibitors. P. A. McCroskery[1], A. Verma[2] and C. Blosch[3], [1]Amgen, Thousand Oaks, CA, [2]Amgen, So San Francisco, [3]Amgen, Seattle, WA

Purpose: To identify clinical features of disseminated histoplasmosis in patients receiving TNF inhibitors. Recently the FDA reviewed 240 reports of disseminated histoplasmosis associated with TNF inhibitors and reported that a delay in diagnosis and treatment was possibly associated with fatal outcomes in 12 patients. Methods: All serious adverse events in histoplasmosis cases from the Amgen ARISg safety database were identified and reviewed. Results: Sixteen cases of new disseminated histoplasmosis were identified in patients receiving etanercept (n=12) and/or other immunosuppressants (n=4), including 3 cases with fatal outcomes (2 from multi-organ failure, 1 from splenic rupture) in patients receiving etanercept. All etanercept cases were from post-marketing spontaneous reports in the US and in 15 of 16 cases, patients were from endemic areas. Malaise, non-productive cough, and pulmonary infiltrates were the most frequently reported symptoms in patients with mild disease. In 9 of the 16 cases of severe disease, thrombocytopenia or pancytopenia and abnormal liver function tests (LFTs) or hepatosplenomegaly were present. Three patients underwent cholecystectomy before the subsequent diagnosis of histoplasmosis.

Age (yrs), Gender (M/F)	**Clinical Presentation**	**Exposure* (months)**	**Platelet count**	**LFTs**	**Comments**	**Outcome**
38, M	Pneumonitis, severe pancytopenia	11	Pancytopenia	NA	NA	Recovered
70, M	Weakness, jaundice	36	40,000	Markedly increased	Ascending cholangitis	Fatal
61, F	Pneumonitis and hypoxemia	2	NA	NA	NA	Recovered
60,	Nausea, weakness, fever	6	61,000	NA	Bone marrow asp	Recovered

Age (yrs), Gender (M/F)	**Clinical Presentation**	**Exposure* (months)**	**Platelet count**	**LFTs**	**Comments**	**Outcome**
F					positive for histo	
40, M	Fever, abdominal pain	21	NA	Abnormal	Cholecystectomy	Not recovered
55, M	Dyspnea, fever	2	NA	NA	NA	Recovering
46, M	Dyspnea productive cough	12	Pancytopenia	NA	NA	NA
43, F	Fever, fatigue, dypnea	10	NA	Markedly increased	Jaundice	NA
45, M	Dyspnea, dry cough, fever	31	Pancytopenia	Increased jaundice	Cholecystectomy	Recovered
40, F	Dyspnea, fever, sharp chest pain	NA	Decreased	NA	Nodules in liver	Not recovered
NA, F	Abdominal pain, symptomatic cholelithiasis	84	NA	Abnormal	Cholecystectomy	Recovered
33, F	Diffuse interstitial infiltrate, small pleural effusion	7	Decreased	Increased	Required ventilator	Recovered
64, M	Pancytopenia, fever, hepatosplenomegaly	53	Markedly decreased	Abnormal	Splenic rupture	Fatal
47, M	Abnormal liver function tests, fever	16	NA	Markedly increased	Ascending cholangitis	NA
60, M	Cough, dyspnea, chest pain	36	NA	Increased	Multisystem organ failure	Fatal
Child, NA	Malaise, fever	NA	Pancytopenia	NA	NA	NA

***Exposure to etanercept or another drug;**

NA = insufficient information available

Conclusion: Disseminated histoplasmosis was "very rare" according to CIOMS criteria with etanercept use (0.9 cases reported in 100,000 pt-yrs) in this database, but 3 fatal cases were reported. Thrombocytopenia/ pancytopenia and abnormal LFTs may identify patients with more severe disease and, in endemic areas, should be recognized as possible signs of disseminated histoplasmosis.

Disclosure: P. A. McCroskery, Amgen Inc, 3 ; **A. Verma**, Amgen Inc., 3 ; **C. Blosch**, Amgen Inc., 3 .

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Predictors of Radiographic Joint Destruction in Rheumatoid Arthritis Patients During TNF-Inhibitor Treatment in Clinical Practice. L. M. Ørnbjerg[1], M. Østergaard[1], P. Bøyesen[2], A. Thormann[1], U. Tarp[1], H. Røgind[1], W. Böhme[1], H. Lindegård[1], U. Poulsen[1], A. Hansen[1], V. Ringsdal[1], N. Graudal[1], A. R. Andersen[1], J. Espesen[1], G. Kollerup[1], T. G. Christensen[1], R. Pelck[1], O.R. Madsen[1], D.V. Jensen[1], O. Majgård[1] and M. L. Hetland[1], [1]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

Purpose: Tumour necrosis factor inhibitor (TNF-I) treatment of rheumatoid arthritis (RA) patients in clinical practice reduces radiographic progression(1). This report investigates predictors of radiographic progression in RA patients in the Danish nationwide DANBIO registry during 2 years of TNF-I treatment.

Method: X-rays of hands and wrists obtained at the start of TNF-I (baseline) and approximately 2 years after start of TNF-I treatment (follow-up) were collected from 18 departments in Denmark, and combined with clinical data in the DANBIO registry. The X-rays were scored according to the Sharp/van der Heijde score by an experienced reader blinded to chronology.

Multiple regression analysis with stepwise backward selection with change in Total Sharp Score (ΔTSS) as the dependent variable, and logistic regression analysis with +/- radiographic progression as dependent variable were performed. Explanatory variables were potential predictive baseline variables (28-joint Disease Activity Score (DAS28), TSS, age, gender, IgM Rheumatoid Factor (IgM-RF), disease duration, number of previous Disease-Modifying Anti-Rheumatic Drugs (DMARDs), concomitant methotrexate (MTX), concomitant prednisolone) and follow-up variables (duration of TNF-I treatment and number of TNF-I switches in follow-up period).

Results: 283 patients (78% women, 76% IgM-RF positive, age 54 (23-81) years (median(range)); disease duration 4.5 (0-67), years), TSS 23 (29) (mean(SD)) 11.5 (2-32) (median (inter-quartile range (IQR))) had X-rays. At baseline 66% started treatment with infliximab, 17% with etanercept and 17% with adalimumab. 16% received TNF-I monotherapy, 78% combination therapy with MTX and 6% with other DMARDs. At follow-up (median 561, IQR 389-762days), 62% were treated with the initial TNF-I, 24% had switched to another TNF-I and 14% had withdrawn from TNF-I.

Mean (SD) ΔTSS was 1.0 units/yr (2.9), median 0 (IQR 0-1). 36% of patients progressed radiographically (ΔTSS >0) during TNF-I treatment. Independent predictors of ΔTSS during TNF-I treatment ($p < 0.05$) were IgM-RF and age, while the other variables did not reach statistical significance. Independent predictors of progression were IgM-RF, concomitant prednisolone, age and TSS at baseline (Table).

Table: Final models of multiple(a) and logistic(b) regression analyses

(a) Predictors of ΔTSS	**Regression coefficient**	**P value**
TSS	0.011	0.06
Age	0.029	0.04
IgM-RF	0.84	0.04
(b) Predictors of X-ray progression	**Odds Ratio**	**P value**
TSS	1.02	0.0009
Age	1.03	0.03
IgM-RF	2.56	0.03
Concomitant prednisolone	1.99	0.02

Conclusion: Positive IgM-RF and high age were consistently predictors of radiographic progression in RA patients during 2 years of TNF-I treatment in clinical practice.

Ref: (1) Ann Rheum Dis 2009; 68 (S3): 121-2.

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The Effect of Smoking History, Gender and Age On Risk of Pneumonia While On Biologic Agents. Margaret E. Fisher[1], Ivan Y. Lim[2], Jackie Blank[3] and Daniel Rourke[4], [1]Mid-Atlantic Permanente Medical Group, Springfield, VA, [2]Mid-Atlantic Permanente Medical Group, Rockville, MD, [3]Kaiser Permanente, Rockville, MD, [4]Ars Analytica, Rockville, MD

Purpose: It is known that the risk of pneumonia is approximately double in patients taking the biologic agents which are prescribed for rheumatic and other diseases. It would be helpful in clinical practice to be able to predict if certain subgroups are at particular risk when being given drugs that are often prescribed electively. Using a retrospective review of our electronic medical record, we undertook to determine whether that risk might be particularly high in smokers or former smokers.

Methods: The Mid Atlantic States region of Kaiser Permanente provides health care for approximately 500,000 people. All patients age 18 or older were identified who had received prescriptions for non-cancer indications through our pharmacies of etanercept, adalimumab or anakinra or who had received infusions in one of our centers of infliximab, abatacept or rituximab. The electronic data base provided us with smoking status, age, gender, co-morbidities (asthma, COPD, CAD, CHF, DM) and the diagnosis of pneumonia. Chart reviews were performed when necessary to clarify the smoking history and on all cases of pneumonia to confirm the diagnosis and recent use of biologic agents.

Results: 993 patients were prescribed one of the above medications from 2001–2008; 52 of those patients (5.2%) were treated for pneumonia. The rate of pneumonia is significantly higher in female former smokers (13.6%) compared to all nonsmokers (4.5%, $p<0.001$) and to all current smokers (4.2%, $p=0.004$) but not compared to male former smokers (7.5%, $p=0.208$). The pneumonia rate for all who ever (current and former) smoked (7.8%) is significantly larger than all nonsmokers (4.5%, $p=0.035$). In addition, the pneumonia rate was significantly higher with increasing age ($p=0.0014$). No relationship was found between co-morbidities and the risk of pneumonia.

Smoking	***Number of Patients and Percent by Sex***			***Mean Age***			***Number and Percent with Pneumonia***		
Status	*Males*	*Females*	***Total***	*Males*	*Females*	***Total***	*Males*	*Females*	***Total***
Current	65 (21%)	103 (15%)	168 (17%)	42.8	49.4	46.9	2 (3.1%)	5 (4.9%)	7 (4.2%)
Former	67 (21%)	110 (16%)	177 (18%)	57.4	56.4	56.8	5 (7.5%)	15 (13.6%)	20 (11.3%)
Never	149 (48%)	410 (60%)	559 (56%)	47.6	50.8	49.9	7 (4.7%)	18 (4.4%)	25 (4.5%)
Unknown	32 (10%)	57 (8%)	89 (9%)	46.0	46.5	46.3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	313 (100%)	680 (100%)	993(100%)	48.5	51.1	50.3	14 (4.5%)	38 (5.6%)	52 (5.2%)

Conclusion: Smoking status has an effect on the risk of pneumonia in patients given biologic agents, with female former smokers being at highest risk. In addition, the risk of pneumonia increases with age

Disclosure: M. E. Fisher, None; **I. Y. Lim**, None; **J. Blank**, None; **D. Rourke**, None.

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Effect of Adherence to the EULAR 2007 Guidelines On Early Arthritis Outcome. Data From the ESPOIR Cohort. Cécile Escalas[1], Marie Dalichampt[2], Bernard Combe[3], Bruno Fautrel[4], F. Guillemin[5], Maxime Dougados[1] and Philippe Ravaud[2], [1]University of Paris V, Cochin Hospital, Paris, France, [2]University of Paris VII, Bichat Hospital, Paris, France, [3]University I of Montpellier, Lapeyronie Hospital, Montpellier, France, [4]University of Paris VI, Pitie Salpetriere Hospital, Paris, France, [5]Nancy-University EA 4003, Nancy, France

Purpose: EULAR 2007 guidelines for management of early arthritis highlight the interest of early DMARD (*e.g*. Methotrexate) initiation and adjustment of therapy in cases of persistent active disease (1). The objective of the study was to assess whether adherence to such guidelines reduces radiographic progression and disability.

Method: *EULAR guidelines adherence* was defined by the 3 following recommendations: 1/ initiation of a DMARD in case of risk of developing persistent or erosive arthritis; 2/ Methotrexate as the DMARD of choice; 3/ remission as the only acceptable goal. *ESPOIR cohort*: Multicenter French prospective cohort of early arthritis, DMARD naïve, of less than 6 months duration, recruited from 2003 to 2005. Disease activity, functional impairment and treatment details were prospectively and systematically collected at baseline and after 6,12,18 and 24 months of follow up at each investigating centre. The reading of the baseline and one year X-rays was performed by one central reader. *Outcome measures*: Radiographic progression defined as the occurrence of at least one new erosion between baseline and year 1 and disability defined as a HAQ score ≥1 at year 2. *Statistical analysis*: Elaboration of a propensity score adjusted on baseline characteristics to model the probability of being treated in accordance with recommendations and analysis using multivariate regressions with the propensity score to assess the impact of guideline adherence on outcomes.

Results: Of the 813 enrolled patients, adherence to EULAR guidelines was observed in 178 (21%). After adjustment for propensity score, centre and confounding factors, risks of radiographic progression (one additional radiological erosion) at year 1 and of functional impairment (HAQ ≥1) at year 2 increased in patients not treated in accordance with the guidelines with OR: 2.04 [95% CI: 1.09 – 3.80] and OR: 2.12 [95% CI: 1.05 – 4.29], respectively.

Conclusion: This study demonstrates the clinical and radiological benefit for patients with early arthritis to be monitored and treated in accordance with the EULAR guidelines.

Reference:
1. Combe B, *et al*. Ann Rheum Dis 2007;66:34-45.

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Sequential Pharmacoeconomic Model of Biologic Strategies for Rheumatoid Arthritis in Sweden Based On Disease Activity. Carl Turesson[1], Annika Teleman[2], Ann Bengtsson[3], Karin Sennfält[4], Danielle Dupont[5] and Ariel Beresniak[6], [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Spenshult, Oskarshamn, Sweden, [3]Linköping University Hospital, Linköping, Sweden, [4]Bristol-Myers Squibb, Bromma, Sweden, [5]Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [6]Data Mining International, Geneva, Switzerland

Purpose: Treatment of moderate to severe Rheumatoid Arthritis (RA) in Sweden includes the use of biologic therapies such as etanercept (ETA), adalimumab (ADA), infliximab (INF), abatacept (ABA) or rituximab (RTX) in various sequences. In absence of clinical trials comparing the efficacy of one biologic treatment sequence over another, simulation models can assess various treatment strategies.

Method: Four simulation models were developed to assess the cost-effectiveness of treatment strategies composed of successive biologic agents over 2 years in patients with an insufficient response (IR) to 1 anti-TNF agent, namely: A) ETA-ABA-ADA, B) INF-ABA-ADA, C) ETA-RTX-ADA, D) INF-RTX-ADA. At the end of each 6-month period, the treatment was maintained in case of good response (LDAS or remission) or switched in case of an IR. The cost-effectiveness was reported as cost per day in Remission State (RS) (strategy A+C) or in Low Disease Activity State (LDAS) (strategy A-D). Data sources included published clinical efficacy data, expert opinion on medical practice and official reimbursement tariffs in Sweden. A probabilistic sensitivity analysis was performed computing all possibilities of distribution parameters.

Results: 6-month medical costs (excluding biologic costs) were estimated at 20’530 SEK (SD 5,773) for patients achieving RS, 22,978 SEK (SD 5,848) for patients achieving LDAS and 51,825 SEK (SD 12,621) for patients in moderate to high disease activity. Over 2 years, strategy A appeared significantly ($p<0.01$) more efficacious over 2 years (102 days in LDAS, 52 days in RS) compared to strategy C (82 days in LDAS, 32 days in RS). Cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS or RS in strategy A (4’271SEK/day in LDAS, 8,324 SEK/day in RS) compared to strategy C (4’977 SEK/day in LDAS, 12,541 SEK/day in RS). Strategy B appeared significantly ($p<0.01$) more efficacious over 2 years (102 days in LDAS) compared to strategy D (82 days in LDAS). Cost-

effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS in strategy B (4’289 SEK/day in LDAS) compared to strategy D (4’999 SEK/day in LDAS).

Conclusion: Medical costs for RA patients in LDAS or RS appear to be 50% lower than patients with moderate to high disease activity levels, suggesting that efficacious treatment strategies contribute to reducing medical costs and use of health care services. Considering both costs and effectiveness over 2 years, these results suggest that strategies including ABA after an insufficient response to one anti-TNF agent appear more efficacious and cost-effective than similar strategies with RTX.

Disclosure: C. Turesson, Bristol-Myers Squibb, 5 ; **A. Teleman**, Bristol-Myers Squibb, 5 ; **A. Bengtsson**, Bristol-Myers Squibb, 5 ; **K. Sennfält**, Bristol-Myers Squibb, 3 ; **D. Dupont**, Bristol-Myers Squibb, 3 ; **A. Beresniak**, Bristol-Myers Squibb, 5 .

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Determinants of TNF Switching in Patients with Rheumatoid Arthritis (RA). J. R. Curtis[1], A. John[2] and O. Baser[3], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Roche, Nutley, NJ, [3]University of Michigan Health Systems, Ann Arbor, MI

Purpose: Switching among tumor necrosis factor-α inhibitor (TNFi) agents or to another biologic is relatively common, but determinants of choice of drug and drug sequence are largely unknown. In a number of pts, switching from 1 TNFi to another TNFi is not always effective; thus, switching to a different mechanism of action may help optimize treatment for these pts. Among individuals switching from their first TNFi, we identified factors associated with the time to first switch and the choice of dose escalation or switching to a second TNFi or a non-TNFi biologic agent in a retrospective analysis of medical and pharmacy claims and eligibility data.

Method: Eligible pts were ≥18 y of age, were diagnosed with RA (2 diagnoses ≥2 mo apart) from Jan. 2003–March 2008, had initiated a new TNFi prescription after a 6-mo biologic-free period, and had at least 6 mo of continuous enrollment. Kaplan-Meier (KM) analysis and Cox regression were used to analyze time to first switch. Among RA pts who changed biologic therapy, pts were considered as (1) switching to another TNFi; (2) switching to a biologic other than TNFi; or (3) escalating dose (only for adalimumab [ADB] or infliximab [IFX]). Multinomial logistic regression was used to determine factors affecting switching and dose escalation.

Results: A total of 11,903 (6.9%) of 173,533 RA pts were identified as changing biologic therapy after a median (interquartile range [IQ]) treatment duration of 231 (161, 362) days. KM analysis showed time to change in therapy was shorter for pts initially started on IFX compared with etanercept (ETN) or ADB (log rank $p<0.001$). Even after adjustment for baseline differences, IFX and ADB users were more likely than ETN users to switch or escalate dose. Among pts who made a change, various patterns were to (1) a second TNFi (14%, n=1726) after a mean of 336 days; (2) a non-TNF biologic (2%, n=238) after a mean of 455 days; or (3) escalate dose (16%, n=1903) after a mean of 261 days. Comorbidity scores such as claims-based index for RA severity (CIRAS) and Elixhauser were higher for pts switching to another TNFi vs those switching to a non-TNFi, but individual comorbidities were similar across groups. Likelihood of switching to a biologic with a non-TNFi mechanism of action was increased by female sex and baseline use of cytotoxic agent (Table). Baseline use of methotrexate raised the likelihood of dose escalation (relative risk ratio, 1.58) while IV administration raised the likelihood of switching to a non-TNFi.

Conclusion: After initiating TNFi treatment, many RA pts failed to remain on therapy and escalated doses or switched to a second TNFi or another biologic within ~1 y. Factors influencing whether pts received a non-TNFi biologic included gender and use of certain agents at initiation of the TNFi. A limitation of this study was that pts with <6 mo of TNFi treatment were not included.

Table

Effect of first TNFi on time to switch or dose escalation (adjusted hazard ratio)	
Etanercept (referent)	1
Infliximab	6.29
Adalimumab	1.18
Risk of switching to another TNFi (relative risk ratio [IQ])	
Age	0.99 (0.984, 0.995)
Female sex	1.34 (1.184, 1.523)
Baseline use of corticosteroids	1.21 (1.06 , 1.365)
Baseline use of cytotoxic agent	1.40 (1.218, 1.613)
Risk of switching to a non-TNFi biologic (relative risk ratio [IQ])	
Age	1.00 (0.99, 1.02)
Female sex	1.40 (1.03, 1.919)
Baseline use of corticosteroids	1.46 (1.062, 2.00)
Baseline use of cytotoxic agent	1.22 (0.859, 1.73)

Disclosure: J. R. Curtis, Proctor & Gamble Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, 8, Centocor, Inc., 5, Amgen, 5, Proctor & Gamble Pharmaceuticals, 5, UCB, 5, Roche Pharmaceuticals, 5, Centocor, Inc., 2, Roche Pharmaceuticals, 2, Eli Lilly and Company, 2, Proctor & Gamble Pharmaceuticals, 2, Amgen, 2, Novartis, 2, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8, CORRONA, 2 ; **A. John**, Roche , 3 ; **O. Baser**, Roche Pharmaceuticals, 5, STATinMED Research, 9 .

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Differences in Biologic Patterns of Use Among Rheumatic Arthritis Patients Treated with or without Methotrexate. B. Tang[1], C.T. Carter[1], E. Buysman[2] and C.T. Piech[1], [1]Centocor Ortho Biotech Services, LLC, Horsham, PA, [2]i3 Innovus, Eden Prairie, MN

Purpose: To compare switching, discontinuation, and persistency among biologics used with and without methotrexate (MTX) in RA patients.

Methods: A retrospective claims data study between July 1, 2004 and December 30, 2008 was conducted. Adult patients (aged ≥ 18) with a diagnosis of RA (ICD-9=714.xx), with ≥ 1 claim for a biologic (abatacept, adalimumab, etanercept, or infliximab) were included. Due to the small sample size, rituximab was not included. Patients were required to have continuous enrollment for 24 months post-index and 6 months pre-index date, and patients who used any biologic in the 6 months prior to the index date were excluded. Switch was defined as a new biologic treatment identified during the post-index period. Discontinuation was defined as a gap of >60 days after the last date of supply of the index biologic agent. Patients with evidence of discontinuation prior to switching were defined as discontinuers. Persistence was defined as patients who continued to use their index biologic without discontinuation. Comparisons were made between 2 cohorts: patients with biologics combined with MTX (combination) or without MTX (monotherapy).

Results: Of 1,794 RA patients included in the study, the average age was 50.1 and 77.4% were female. Overall, 945 (52.7%) patients combined a biologic with MTX; 849 (47.3%) received monotherapy. Those receiving combination treatment had a higher switching rate (P= 0.031) compared with the monotherapy cohort, but patients in the combination group also had lower discontinuation and higher persistence rates, in addition to longer times to first switch and discontinuation (P<0.05).

	Monotherapy N=849	Combination N=945	p-value
1st Switch, N (%)	90 (10.6%)	132 (14.0%)	0.031
Time to medication switch	234.9	292.6	0.023
Discontinue, N (%)	549 (64.7%)	397 (42.0%)	<0.0001
Mean days to discontinuation	156.2	254.3	<0.0001
Persist, N (%)	210 (24.7%)	416 (44.0%)	<0.0001

Conclusion: RA patients who were treated with biologics combined with MTX had lower discontinuation rates and longer duration on therapy than patients who received monotherapy.

Disclosure: B. Tang, Centocor Ortho Biotech Services, LLC, 3 ; **C. T. Carter**, Centocor Ortho Biotech Services, LLC, 3 ; **E. Buysman**, Centocor Ortho Biotech Services, LLC, 5 ; **C. T. Piech**, Centocor Ortho Biotech Services, LLC, 3 .

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Efficacy of TNF Inhibitors in Rheumatoid Arthritis Patients with Anti-Ro/SS-A Antibody. Ran Matsudaira, Naoto Tamura, Fumio Sekiya, Michihiro Ogasawara and Yoshinari Takasaki, Juntendo University School of Medicine, Tokyo, Japan

Purpose: Anti-Ro/SS-A (Ro) antibody is frequently detected in rheumatoid arthritis (RA). The prevalence rate of anti-Ro antibody in RA is 3 to 15%, and patients with RA are often complicated with Sjögren's syndrome (SjS) that is thought to be one of clinical poor prognostic conditions of RA. To examine the relationship between anti-Ro antibody and the efficacy of tumor necrosis factor (TNF) inhibitors in patients with RA, we compared the clinical response to infliximab (IFX) or etanercept (ETN) between anti-Ro antibody positive and negative RA patients.

Method: Titers of anti-Ro antibody of sera from 156 patients with RA were measured using double immunodiffusion assay. Clinical response according to the disease activity score 28 (DAS28) EULAR response criteria at 12 to 14, 22 to 24 and 52 to 54 weeks was compared between anti-Ro antibody positive and negative groups. Factors for poor response to TNF inhibitors were estimated by univariate- and multivariate-logistic regression analysis.

Results: The patients treated with IFX and ETN (113 and 43, respectively) were examined. Anti-Ro antibody was detected in 26 of 156 patients (16.7%, IFX 16.8% and ETN 16.3%), and 17 patients were complicated with SjS. The percentage of moderate or more EULAR response at 12 to 14 weeks was not significantly different between anti-Ro antibody negative group and the positive group (86.6% and 73.7%, respectively, P =0.083). On the other hand, at 22 to 24 weeks, the moderate or more EULAR response was recognized in 104 of 127 patients (81.9%) in anti-Ro antibody negative group but only 16 of 26 patients (61.5%) in the positive group (P<0.03). The response rate at 52 to 54 weeks was also lower in anti-Ro positive group than that in negative group (53.8% and 77.7%, respectively, P<0.02). Moreover, TNF inhibitors were discontinued more frequently in anti-Ro antibody positive group compared with the negative group (46.2% and 26.6%, respectively, P<0.05) due to the lack of efficacy. When the response rate was compared between patients treated with IFX and ETN, it was significantly higher in IFX group than in ETN group regardless of the anti-Ro antibody (67.3% and 88.4%, respectively, p<0.008). The logistic regression analysis showed that anti-Ro antibody was an independent factor for poor response to the TNF inhibitors both in the univariate model (OR 3.18, 95%CI 1.32–7.66) and in the multivariate models (OR 5.50, 95%CI 1.39-21.75).

Conclusion: It was suggested that the presence of anti-Ro antibody might be related to the lack of clinical efficacy in patients with RA treated with TNF inhibitors, especially with IFX.

Disclosure: R. Matsudaira, None; **N. Tamura**, None; **F. Sekiya**, None; **M. Ogasawara**, None; **Y. Takasaki**, None.

1007

Real World Utilization of Nonbiologic and Biologic Disease Modifying Anti-Rheumatic Drugs in Rheumatoid Arthritis: A Systematic Review of the Literature. Zachary M. Pruhs and Leslie R. Harrold, Univ of Massachusetts Med Schl, Worcester, MA

Purpose: To date, no systematic review of the literature regarding real world use of disease modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis (RA) has been performed. Our goals in undertaking this review include 1) provide a comprehensive summary of published studies on real world utilization of DMARDs in patients with RA and 2) identify gaps in our current knowledge regarding medication use patterns.

Methods: Employing the Cochrane Collaboration systematic review guidelines, we conducted a MEDLINE search from January 1, 1989 through March 17, 2009 for English language articles evaluating real world utilization of biologic and non-biologic DMARDs in RA. Search terms included the key words: (rheumatoid arthritis) and (abatacept, or adalimumab, or etanercept, or hydroxychloroquine, or infliximab, or methotrexate, or minocycline, or leflunomide, or rituximab, or sulfasalazine). Articles were then limited to medical subject headings (MeSH) including pharmacoepidemiology or drug utilization or drug therapy.

Results: Our search strategy yielded 1,376 articles, of which 42 articles met inclusion criteria. The included articles were grouped by primary focus into those examining prescribing patterns, persistence, dosing, and adherence. Most articles evaluated prescribing patterns (n=23) and/or medication persistence (n=23). Most studies examining prescribing patterns showed a trend towards earlier and more frequent use of both biologic and non-biologic (particularly methotrexate) DMARDs. However, those studies that focused on patients cared for by primary care providers found lower rates of DMARDs use (range of 13 to 63%). Additionally, very few studies evaluated appropriateness of medication use or the factors influencing use of medications. Studies examining persistence found it was greatest among methotrexate users as compared to other nonbiologic DMARDs. There was conflicting data regarding persistence among the different biologic agents. There were only 6 studies evaluating dosing and all but one were focused on infliximab. Only 3 studies examined adherence, 2 of which found adherence to infliximab superior to methotrexate and etanercept respectively.

Conclusion: Most of the current literature on real world utilization of DMARDs in the management of RA finds earlier and more aggressive use of nonbiologic and biologic agents as well as greater persistence among methotrexate users. Very few studies have examined medication adherence or dosing of DMARDs other than infliximab. Of concern is possible DMARD underutilization based on studies of RA patients cared for by primary care providers. More investigation examining whether there is appropriate use of medications is needed in order to ensure optimal quality of care.

Disclosure: Z. M. Pruhs, None; **L. R. Harrold**, None.

1008

Bone Mineral Density in Patients with Recent Onset, Active Rheumatoid Arthritis: Two-Year Data of the NEO-RACo Study. Heikki Valleala[1], Hannu Kautiainen[2], Timo Möttönen[3], Pekka J. Hannonen[4], Markku Korpela[5], Oili Kaipiainen-Seppänen[6], Leena Paimela[7], Anna Karjalainen[8], Heikki Julkunen[1] and Marjatta Leirisalo-Repo[1], [1]Helsinki University Central Hospital, Helsinki, Finland, [2]Medcare Oy, Äänekoski, Finland, [3]Turku University Central Hospital, Turku, Finland, [4]Central Hospital, Jyvaskyla, [5]Tampere University Hospital, Tampere, Finland, [6]Kuopio University Hospital, Finland, [7]ORTON hospital, Helsinki, Finland, [8]Oulu University Central Hospital, Oulu, Finland

Purpose: We have previously reported that the intensive use of FIN-RACo strategy [initial combination of methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and prednisolone (PRED)] induced strict remission in 53% and sustained remission in 31% of patients with recent onset active rheumatoid arthritis (RA). Radiological progression was rare. Adding Infliximab (INFL) during the first 6 months reflected in higher frequencies of remissions over time and prevented radiological progression during 2 years. Here we report the effect of FIN-RACo strategy on bone mineral density (BMD) in the lumbar spine and the hip in the patients.

Method: In this multicenter (15 centres) trial, we enrolled 100 patients aged <65 y with early (symptoms ≤12 mo) active RA. FIN-RACo therapy targeted to remission was started in all patients. The patients were randomized in a double-blind way to receive INFL (3 mg/kg) or placebo (PLA) at weeks 4, 6, 10, 18 and 26. Doses of MTX (max 25 mg/week) and SSZ (max 2 g/day) were individually tailored, doses of HCQ (35 mg/kg/week) and PRED (7.5 mg/day) were constant. Local glucocorticoid injections were allowed. All patients received 1000 mg calcium and 800 IU vitamin D3 daily. BMD was measured by DEXA at entry and at two years.

Results:

Variable	FIN-RACo + PLA, n =31	FIN-RACo + INFL, n =32
Age (y)	45.8 ± 10.7	47.1± 7.8
Female / Male (n)	19 / 12	23 / 9
Symptom duration (mo)	3.8 ± 2.3	4.1 ± 2.7
DAS28	5.9 ± 1.2	5.5 ± 1.0
Lumbar spine T-score	-0.1 ± 1.6	-0.3 ± 1.2
Femoral neck T-score	-0.2 ± 1.0	-0.4 ± 0.8

Both baseline and 2 year BMD were available for 63 out of 100 patients. Baseline characteristics of these patients are presented above (Mean± SD). At baseline 3 patients in the FIN-RACo + PLA group and none in the FIN-RACo + INFL had T-score below - 2.5. During the 2 years BMD decreased significantly in both treatment groups. A mean (95% CI) change of lumbar spine T-score from 0 to 24 months was -0.2 (-0.4 to -0.1) in the FIN-RACo+PLA and -0.4 (-0.5 to -0.2) in FIN-RACo+INFL. For the femoral neck T-score the mean changes in the 2 groups were - 0.2 (-0.3 to -0.1) and -0.2 (-0.7 to - 0.1), respectively. At 2 years, 3 patients in the FIN-RAco + PLA group and 2 in the FIN-RACo + INFL had T-score below - 2.5. The BMD loss between the 2 groups was not significantly different.

Conclusion: 7.5 mg daily constant PRED led to significant BMD loss despite the marked decline in disease activity. Antiresorptive therapy with bisphosphonates for primary prevention of osteoporosis should be considered when starting long-term PRED ≥ 7.5 mg, daily in RA.

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Rheumatologists' Prescribing Patterns for Rheumatoid Arthritis Patients with Active Disease. Leslie R. Harrold[1], Jeffrey D. Greenberg[2], Jeffrey R. Curtis[3], Mary jane Bentley[1], George Reed[4] and J. Timothy Harrington[5], [1]Univ of Massachusetts Med Schl, Worcester, MA, [2]New York University School of Medicine, Millburn, NJ, [3]UAB, Birmingham, AL, [4]University of Massachusetts Medical School, Worcester, MA, [5]Univ of Wisconsin School of Medicine and Public Health, Madison, WI

Purpose: We examined the relationship between disease activity and provider prescribing practices prior to publication of the ACR treatment recommendations using a multi-centered observational registry within the United States (the Consortium of Rheumatology Researchers of North America: CORRONA).

Method: Patients with a diagnosis of rheumatoid arthritis (RA) who were biologic naïve, had a disease duration of <5 years and had ≥ 2 visits within 6 months prior to 6/15/08 were identified. Patients in remission and low disease activity based on the Clinical Disease Activity Index (CDAI) were excluded. Patients with a poor prognosis based on the ACR treatment recommendations (mHAQ >0.5, secondary Sjogren's syndrome, subcutaneous nodules, serologic positivity or bony erosions on radiographs) were identified. The population was divided into two cohorts. Cohort #1 comprised patients currently on methotrexate (MTX) monotherapy or who had used only MTX as a DMARD in the past. Cohort #2 was comprised of patients who were receiving or had received ≥ 2 nonbiologic DMARDs. Initiation of biologic DMARDs in response to disease activity (using the CDAI) was identified.

Results: There were 284 patients in Cohort #1 (Table 1). Among those with moderate disease activity with poor prognostic factors, only 9% received a biologic at the initial visit. In those with high disease activity, 8% received a biologic at the initial visit. Among those in cohort #1 (n=126) with no improvement in disease activity at a follow-up visit, at the conclusion of the 2nd visit a total of 12% were treated with biologics. There were 143 patients in cohort #2 (Table 1). Among those with moderate disease activity with poor prognostic factors, 5% were initiated on a biologic at the initial visit. In those with high disease activity with poor prognostic factors, 8% received a biologic at the

initial visit. Among those in Cohort #2 (n=61) with no improvement in disease activity at a follow-up visit, at the conclusion of the 2nd visit a total of 15% were treated with a biologic.

Table 1.

	Cohort #1 (Methotrexate Only)		**Cohort #2 (≥2 Nonbiologic DMARDs)**	
	Moderate disease activity* N=130	High disease activity N= 154	Moderate disease activity* N=81	High disease activity* N=62
Care consistent with ACR treatment recommendations				
Biologic initiated (N,%)	12 (9)	13(8)	4 (5)	5 (8)
Care not consistent with ACR treatment recommendations				
No DMARD therapy (N,%)	13 (10)	35 (23)	10 (12)	9 (15)
Nonbiologic DMARD therapy maintained (N,%)	99 (76)	105 (68)	67 (83)	47 (76)
A nonbiologic DMARD initiated (N,%)	6 (5)	1 (1)	0 (0)	3 (5)

*associated with poor prognostic factors

Conclusion: Prior to publication of the ACR treatment recommendations, most patients with active disease did not receive recommended therapy. Further exploration of the barriers to optimal medication use is necessary.

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In Early RA, Conventional DMARD or Anti-TNF Add-On to MTX Provides Stable Benefits From 12 to 24 Months of Follow-up: Two-Year Results of the SWEFOT Clinical Trial. Ronald F. van Vollenhoven[1], Sofia Ernestam[1], P. Geborek[2], Ingemar Petersson[3], Johan Bratt[4] and SWEFOT Study Group[5], [1]The Karolinska Institute, Stockholm, Sweden, [2]Lund University, Department of Clinical Sciences, Lund, Sweden, [3]Lund University, Department of Clinical Sciences, Lund, Lund, Sweden, [4]Karolinska Univ Hosp Huddinge, Stockholm, [5]Sweden

Purpose: To compare two therapeutic strategies in patients with early RA who after 3-4 months had failed to respond to MTX monotherapy.

Method: In an open, randomized, controlled trial, 487 patients with early RA (symptom duration <1 year) were started on MTX at up to 20 mg/week. After 3-4 months, the 258 patients who had not achieved DAS28≤3.2 (but who could tolerate MTX) were randomized. In arm A (n=130) sulfasalazine (SSZ) 1000 mg BID and hydroxychloroquine (HCQ) 400 mg qD were added. In arm B (n=128), infliximab (INF) was added at 3 mg/kg/infusion, rounded upward to the nearest 100 mg, given at 0, 2, 6 weeks and then q 8 weeks. DMARD dosages could be adjusted for intolerance, and INF infusion frequency but not dosage could be increased based on the response. Moreover, a single switch within each strategy was allowed for intolerance only: SSZ+HCQ could be replaced by cyclosporine A (2.5-5.0 mg/kg as BID dosing), and INF could be replaced by etanercept 50 mg weekly. The primary result, the Eular good response at 12 months based on intention-to-treat (ITT) for all randomized patients has been presented previously and showed arm B to be superior to arm A (39% vs. 25%, p<0.02).

Results: At 24 months of follow-up, 74/130 (57%) patients in arm A and 90/128 (70%) patients in arm B were still on treatment per protocol (p<0.05), the difference being accounted for by drop-outs due to loss of efficacy. In arm A, 43 patients (33%) achieved EULAR good response versus 55 (43%) in arm B (NS). EULAR good/moderate response percentages were 44% in arm A and 55% in arm B (p 0.08). In

arm A, 40 (31%) patients were in remission at 2 years, versus 43 (34%) in arm B (NS). The percentages of patients achieving good responses and favorable disease states were only marginally better at 24 compared to at 12 months.

Conclusion: In patients with early RA who after 3-4 months on MTX do not achieve a DAS28 ≤ 3.2, the addition of INF yields significantly better clinical results at 12 months, and has better survival-on-drug over 24 months than the addition of SSZ+HCQ. However, continuing either treatment from 12 to 24 months provides no meaningful additional benefit, supporting the view that frequent therapy changes are necessary to improve long-term outcomes.

Disclosure: R. F. van Vollenhoven, Schering-Plough, 2, Abbott Immunology Pharmaceuticals, 2, Wyeth Pharmaceuticals, 2, Roche, 2 ; **S. Ernestam**, Schering-Plough, 3 ; **P. Geborek**, None; **I. Petersson**, None; **J. Bratt**, None.

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Traditional Cardiovascular Risk Factors in Early Untreated Arthritis Patients From the ESPOIR Cohort: Prevalence and Impact of Inflammation. Jean Frederic Boyer[1], Vanina Bongard[2], Alain Cantagrel[3], Benedicte Jamard[3], Jean Pierre Daures[4], Xavier Mariette[5], Jean Ferrieres[2], Jean Bernard Ruidavets[2] and Arnaud Constantin[2], [1]JE2510, Toulouse, France, [2]INSERM U558, Toulouse, France, [3]Purpan Teaching Hospital, Toulouse, France, [4]Epidemiology unit, Montpellier, France, [5]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France

Purpose: The present study was conducted to assess the prevalence of traditional CV risk factors in an early arthritis cohort and to investigate the impact of early inflammatory state on lipid levels.

Method: Untreated early arthritis (EA) patients, aged 30 to 65 years, were selected from the French ESPOIR cohort study. Age- and sex-matched healthy controls from three different French regions were randomly selected in the framework of the MONICA population survey. Traditional CV risk factors (lipid levels, blood pressure [BP], fasting glycaemia and smoking) were recorded according to standard guidelines. Student's t-test or chi-square test was used for comparisons. Spearman's rho was used for measures of correlation.

Results: 609 EA patients (51.1 years, 76% females) and 1827 age- and sex-matched controls were studied (see Table). Total cholesterol was lower in EA patients than in controls (2.07 vs 2.28 g/l; P<0.0001), mainly resulting from a decrease in LDL cholesterol (1.23 vs 1.47 g/l; P<0.0001) and slightly from a non significant decrease in HDL cholesterol (0.59 vs 0.61; P=0.092). Total, LDL and HDL cholesterol were negatively correlated with CRP level in EA patients (-0.25; P<0.0001; -0.14; P=0.01 and -0.28; P<0.0001, respectively). Systolic BP slightly differed between EA patients and controls (129.2 vs 131.0 mmHg; P=0.042), while diastolic BP was lower in EA patients (77.3 vs 81.3 mmHg; P<0.0001). Fasting glycaemia was lower in EA patients than in controls (0.93 vs 0.99 g/l; P<0.0001). Current smoking was more prevalent in EA patients (21.0 vs 16.7 %; P=0.017). Similar results were observed when analysis was restricted to RA patients fulfilling the 1987 ACR criteria (see Table) and after adjustment on body mass index (data not shown).

Conclusion: This case-control study, focused on early untreated arthritis patients, emphasizes a specific lipid profile, which is associated with early inflammatory state and correlated with inflammation level, but not restricted to RA patients. Significant decreases in diastolic BP and fasting glycaemia appear as additional characteristics of early inflammatory state.

	EA patients	RA patients	Controls	P-value	P-value
	N=609 [1]	N=400 [2]	N=1827 [3]	[1] vs [3]	[2] vs [3]
Systolic BP [mmHg] mean (SD)	129.2 (16.1)	129.3 (16.9)	131.0 (19.6)	0.042	0.111
Diastolic BP [mmHg]	77.3 (11.0)	77.0 (10.6)	81.3 (11.6)	<0.0001	<0.0001
Total cholesterol [g/L]	2.07 (0.40)	2.08 (0.41)	2.28 (0.42)	<0.0001	<0.0001
HDL cholesterol [g/L]	0.59 (0.19)	0.60 (0.20)	0.61 (0.18)	0.092	0.481
LDL cholesterol [g/L]	1.23 (0.34)	1.22 (0.34)	1.47 (0.39)	<0.0001	<0.0001
Glycaemia [g/L]	0.93 (0.28)	0.93 (0.28)	0.99 (0.26)	<0.0001	<0.0001
Current smoking n (%)	128 (21.0%)	80 (20.0%)	306 (16.7%)	0.017	0.120

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Historical Trends of Patient Characteristics in Anti-TNF Clinical Trials for Rheumatoid Arthritis: An Analysis of the Literature Over the Past 16 Years. J. Buchanan[1], M. U. Rahman[2], M. K. Doyle[2], E. C. Hsia[2], T. Gathany[3], S. Parasuraman, D. Aletaha[4], E. L. Matteson[5], Désirée M.F.M. van der Heijde[6] and J. S. Smolen[4], [1]Malvern, PA, [2]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [3]Johnson and Johnson Pharmaceutical Services, LLC, Malvern, PA, [4]Medical University Vienna and Hietzing Hospital, Vienna, Austria, [5]Mayo Clinic, Rochester, MN, [6]Leiden University Medical Center, Leiden, Netherlands

Purpose: To evaluate how the clinical characteristics of patients enrolled in (anti-TNF) trials for rheumatoid arthritis (RA) have changed since the development of the first anti-TNF compound.

Methods: A systematic literature review was performed using predefined inclusion criteria to identify randomized, double-blind, controlled trials that compared etanercept, adalimumab, golimumab, infliximab, or certolizumab with any other agent in adult RA patients. Study entry criteria and baseline clinical characteristics were evaluated over time for disease modifying antirheumatic drug (DMARD)-experienced (including MTX) and MTX-naïve study populations. Enrollment start date for each trial was used as the time metric. The anchor time was the study with the earliest identifiable enrollment start date.

Results: 88 studies met the inclusion criteria. Of these, 44 primary publications (those reporting the primary study endpoint) were identified for certolizumab (4); etanercept (17); adalimumab (8); infliximab (10) and golimumab (5). Enrollment start dates for Elliott 1994 (Aug-1993) and Bathon 2000 (May-1997) were identified as the time anchors for the 37 studies in DMARD-experienced patients and the 7 studies for MTX-naïve patients, respectively. Not all publications reported all clinical variables. For DMARD-experienced trials, the inclusion criteria for swollen joint count (SJC) and tender joint count (TJC) ranged from a high of ≥10 and ≥12 to a low of ≥4 and ≥4, respectively, over the past 16 years; although, the slope of this decline was not statistically significant (SJC, p = 0.442; TJC, p=0.392). Trials with SJC inclusion criteria of ≥10, ≥6 and ≥4 enrolled patients with mean baseline SJCs of 21.7, 18.2 and 16.2 respectively. The mean number of swollen joints at baseline decreased over time (p=0.059). Sixteen DMARD-experienced trials and 5 DMARD-naive trials included minimum CRP levels in the inclusion criteria. These criteria have not changed over time, with trials using ≥2 mg/dl or ≥1.5 mg/dl (p=0.346). Despite this, baseline CRP values have declined significantly over time (p=0.027). For MTX-naïve trials, SJC and TJC inclusion criteria ranged from ≥10 and ≥12, respectively, in the earliest trials to ≥4 and ≥4, respectively, in the most recent trial (SJC, p=0.0187; TJC, p=0.023). Over time, mean number of swollen joints decreased (p=0.055, R^2=0.6436).

Conclusion: Over the past 16 years, inclusion criteria and baseline characteristics of RA patients in studies of anti-TNF agents have changed, with more recent trials enrolling cohorts with lower disease activity as assessed by joint examination and inflammatory markers.

Disclosure: J. Buchanan, JJPS, LLC, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 ; **M. K. Doyle**, Centocor Research and Development, Inc, 3 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **T. Gathany**, Johnson & Johnson, 3 ; **S. Parasuraman**, JJPS, LLC, 3 ; **D. Aletaha**, Centocor Research and Development, Inc, 9 ; **E. L. Matteson**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, Centocor Research and Development, Inc ; **D. M. F. M. van der Heijde**, Centocor Research and Development, Inc, 9 ; **J. S. Smolen**, Centocor Research and Development, Inc .

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Ability to Regain Normal Function in Moderate Vs. Severe Rheumatoid Arthritis: Analysis From Long-Standing and Early RA Patient Populations. Ronald van Vollenhoven[1], Mary Cifaldi[2], Sanjoy Roy[2], Naijun Chen[2], L. Gotlieb[3] and Michel Malaise[4], [1]Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden, [2]Abbott Laboratories, Abbott Park, IL, [3]Abbott Immunology, Louvain-la-Neuve, Belgium, [4]University Hospital Liège, Liège, Belgium

Purpose: Some studies suggest a window of opportunity for the treatment of rheumatoid arthritis (RA) to regain normal physical functioning.[1] The relationship between RA disease severity and ability to regain normal function during treatment has not yet been studied. We evaluated the effect of combination therapy with adalimumab and methotrexate (ADA+MTX) on physical function of patients who have moderate or severe disease and either early or long-standing disease.

Methods: Observed data were analyzed from patients who received combination treatment with ADA+MTX in 2 long-term clinical trials: DE019 (5 years of treatment for long-standing RA) and PREMIER (2 years of treatment for early RA). Patients were categorized by baseline disease activity as either moderate (3.2<28-joint Disease Activity Score [DAS28]≤5.1) or severe (DAS28>5.1). Mean Health Assessment Questionnaire (HAQ) scores for each group of patients were calculated at baseline, 6 months, 1 year, and 2–5 years. Improvements in physical function were evaluated through 2 different standards: HAQ≤0.49 for the normal population and HAQ≤1.2 for the RA population.

Results: In the long-standing RA population (DE019), patients with moderate disease achieved a 59% reduction of HAQ to a mean of 0.45, which was within the range for the normal population; this improvement was maintained over the 5-year study period. Patients with severe disease improved 43% to a mean of 0.88, which was within the range of normal functioning for RA patients but not for the normal population. By 1 year, >60% of patients with moderate disease but only 34% of patients with severe disease achieved normal population HAQ scores; this difference was maintained over 5 years. In the early RA population (PREMIER), patients with both moderate and severe disease at baseline regained physical functioning to within the range of the normal population at 1 year; patients with moderate disease had a 73% reduction in HAQ to a mean of 0.25, and patients with severe disease had a 71% reduction in HAQ to a mean of 0.44. At 1 year, 70% of patients in the moderate group and 61% of patients in the severe group reached normal functioning.

Conclusion: In both early and long-standing RA, patients with moderate disease who receive combination therapy have a great likelihood of achieving normal physical function. In contrast, for patients with severe disease, the efficacy of combination therapy is greater in the early RA group, suggesting that a window of opportunity for preventing irreversible functional loss exists in patients with highly active disease.

Reference: [1]Aletaha D, et al. *Ann Rheum Dis.* 2008;67;238–243.

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Regained Remission Following Restart of Treatment After Loss of Drug-Free Remission in Patients with Recent Onset Rheumatoid Arthritis. N.B. Klarenbeek[1], S.M. van der Kooij[1], M. Güler-Yüksel[1], J.H.L.M. van Groenendael[2], K.H. Han[3], P.J.S.M. Kerstens[4], T.W.J. Huizinga[1], B. A. C. Dijkmans[5] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]Franciscus Hospital, Roosendaal, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]JBI, Amsterdam, Netherlands, [5]VUMC, Amsterdam, Netherlands

Purpose: To determine the severity and duration of an increase in disease activity in patients who have to restart treatment following a period of drug-free remission.

Methods: In the BeSt study, 508 recent onset RA-patients were randomized into 4 treatment strategies: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Treatment adjustments were made based on threemonthly DAS measurements aiming at low disease activity (DAS ≤2.4). If DAS was ≤2.4 for ≥6 months medication was tapered to a maintenance dose. After 2 years, when DAS was <1.6 for ≥6 months on a maintenance dose the last DMARD was tapered and discontinued. If DAS increased to ≥1.6 the last DMARD was immediately reintroduced.

Results: During 5 years follow-up, 115 / 508 patients (23%) achieved drug-free remission. Of those 115 patients, 53 (46%) restarted treatment because of a DAS ≥1.6, after a median period of 5 months, 59 (51%) remained in drug-free remission (median duration 23 months), and 3 (3%) were lost to follow-up. Sixty percent of restarters were positive for both ACPA and RF, which was found to be a risk factor for loss of drug-free remission (OR 6.0, $p<0.001$). At restart of the DMARD monotherapy, mean DAS was 2.2 (increased from mean DAS 1.1). Mean increase in ESR was 9 mm/hour. Swollen joint count, tender joint count and VAS general health increased (medians) 2, 2, and 15 mm respectively. Of the 53 restarters, 25 (47%) again achieved clinical remission 3 months later and another 14 (26%) 6 months later. Eleven patients (21%) achieved a DAS ≤2.4, one patient (2%) did not achieve a DAS ≤2.4, and 2 patients (4%) were lost to follow-up. The median (mean) damage progression in the restarters during the year of DAS increase was 0 (0.61) units using the Sharp-van der Heijde score.

Conclusion: During 5 years DAS steered treatment, nearly ¼ of patients achieved drug-free remission. Forty-six percent of them had to restart DMARD monotherapy after an increase in disease activity ≥1.6. The majority of those patients again achieve clinical remission within 3 to 6 months and show no radiological progression.

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Real or Perceived Conflicts of Interest in Comparative Effectiveness Research. Gabriela Schmajuk[1] and Eswar Krishnan[2], [1]Stanford University, San Francisco, CA, [2]Stanford University School of Medicine, Palo Alto, CA

Purpose: Comparative effectiveness research (CER) is at the center of early healthcare reform proposed by the Obama administration. Most CER, and specifically cost-effectiveness (CE) research, is based on systematic reviews of existing literature. Consequently, the value of CER depends on the quality and objectivity of the individual studies included in such systematic reviews. This is an especially important issue in the evaluation of high-cost treatments such as the disease modifying anti-rheumatic drugs (DMARDs) used in rheumatoid arthritis, psoriasis, or inflammatory bowel diseases. In this study, we tested the hypothesis that there exists no relationship between study sponsorship and study conclusion among studies of CE of DMARDs.

Methods: We performed a systematic review of CE studies of proprietary DMARDs in English from January 1998 to December 2008. Terms used were: cost-benefit analysis AND (infliximab OR adalimumab OR etanercept OR leflunomide OR rituximab OR abatacept) AND (rheumatoid arthritis OR psoriasis OR inflammatory bowel disease). A study was included if its title or abstract described it as an analysis of CE for at least one of the drugs listed above and it contained a statement of the estimated CE of that drug within the abstract or discussion. Reviews, commentaries, letters, editorials, abstracts, and case studies were excluded. Favorable CE was defined as a value of less than 50,000 USD per quality-adjusted life year, if this was provided.

Results: Eighty five citations were retrieved from the MEDLINE search. Of these, 31 met both inclusion and exclusion criteria. Two additional articles were identified from review articles and references lists, so 33 studies were included in the analysis (see Table 1). CE studies commonly relied on pivotal regulatory trials which were designed to show the drug in best possible light. Pharmaceutical sponsorship was disclosed in 18 (55%) out of 33 included studies. Three studies had authors who were found to have undeclared affiliations with pharmaceutical companies. Studies sponsored by the manufacturers of the studied drug were more than twice as likely to report a favorable CE ratio compared with unsponsored studies (71% vs. 33%, Fisher's exact p=0.06).

Conclusion: Health policy decisions informed by CER that is based on published health-economics studies may be flawed.

Table 1.

	All studies n=33	Affiliated studies n=21	Non-affiliated studies n=12
Disease of interest			
Rheumatoid arthritis	21 (64)	14 (67)	7 (58)
Crohn's disease	5 (15)	2 (9)	3 (25)
Psoriatic arthritis	4 (12)	3 (14)	1 (8)
Psoriasis	3 (9)	2 (9)	1 (8)
Drug of interest			
Infliximab only	7 (21)	4 (19)	3 (25)
Etanercept only	5 (15)	2 (10)	3 (25)
Anakinra only	1 (3)	0 (0)	1 (8)
Abatacept only	1 (3)	1 (5)	0 (0)
Leflunomide only	4 (12)	4 (19)	0 (0)
Multiple drugs	15 (45)	10 (48)	5 (42)
Trial as data source	25 (76)	16 (76)	9 (75)
US study	10 (30)	6 (28)	4 (33)
Exclusive academic authorship	26 (79)	15 (71)	11 (92)
Pharmaceutical affiliation			
Declared	18 (54)	18 (86)	0 (0)
Not declared	3 (9)	3 (14)	0 (0)
Favorable CE conclusion	21 (64)	15 (71)	4 (33)

Disclosure: G. Schmajuk, None; **E. Krishnan**, None.

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Physician-Patient Communication about Rheumatoid Arthritis and Biologic Therapy: Results of An in-Office Linguistic Study. Meaghan Onofrey[1], Atul A. Deodhar[2], J. Eugene Huffstutter[3], Richard W. Martin[4] and Corey Eagan[1], [1]MBS/Vox, CommonHealth, Parsippany, NJ, [2]Oregon Health & Science University, Portland, OR, [3]Arthritis Associates PLLC, Hixson, TN, [4]Michigan State University College of Human Medicine, Grand Rapids, MI

Purpose: Effective rheumatoid arthritis (RA) management is multifactorial, depending on accurate physical examination, laboratory studies, and provider-patient communication. To evaluate current discussions of RA and its treatment, an observational study was conducted using accepted sociolinguistic methodologies.

Method: 696 community-based rheumatologists were sent invitation letters; the first 16 to respond and meet screening criteria were enrolled in the sample. Regularly scheduled visits with patients likely to discuss biologic therapy were recorded without a researcher present. Separate patient and physician post-visit interviews were recorded and demographic questionnaires completed. Recordings were transcribed and analyzed. Analyses included: quantification of topics discussed and time spent on each; quantification and qualification of questions asked and answered; identification of requests for information or making of recommendations; classification of linguistic markers demonstrating level of knowledge.

Results: 45 physician-patient interactions were analyzed. Physicians were 81% male; patients were 71% female, had a mean age 58 (13.7 SD) and a mean duration of RA 11 (10.6 SD). Mean duration of visits was 11.4 minutes (range 2.6-49.0). 87% of patients report using "outside sources" for information about RA, most often "the internet." However, physicians controlled visits, speaking about 1.5 times as many words as patients and driving the majority of treatment decisions. Patients used a variety of linguistic techniques to downplay their symptoms, including hedging, diminutives, negation, and depersonalization. Post-visit, about a third of patients admitted minimizing symptoms; some reported not wanting to be perceived as "complainers." Post-visit, 75% of physicians and patients disagreed about disease severity, possibly due in part to the minimization of symptoms in visits. Benchmarking of progress was idiosyncratic. Validated tools to assess patient progress were not used in any visits. Discussions of progress most often focused on activities and pain relief. 95% of visits contained confirmation of medication inventory; potential barriers to adherence were discussed in 75% of visits. The most often discussed barrier was side effects. Problem-solving took place in 60% of visits in which barriers were discussed.

Conclusion: In-office dialogue is marked by physician-directed discussions of RA and patient minimization of symptoms, which may lead to post-visit disagreement about disease severity. Expanded use of health status instruments as advocated by ACR quality standards may reduce this. Attempts to allow the patient to set the dialogue agenda may increase accurate reporting and lead to more effective partnership in decision making.

Disclosure: M. Onofrey, Centocor, 5 ; **A. A. Deodhar**, Centocor, Inc., 8 ; **J. E. Huffstutter**, Centocor, Inc., 8, Bristol-Myers Squibb, 8, Centocor, Inc., 9, Roche Pharmaceuticals, 2 ; **R. W. Martin**, None; **C. Eagan**, Centocor, Inc., 5 .

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Safety of ANTI-Tnfα Blockers In HBcAb-Positive Patients. Francesca Bobbio-Pallavicini[1], Marta Caprioli[1], Roberto Caporali[1], Fabiola Atzeni[2], Donatella Ventura[2], Piercarlo Sarzi-Puttini[2] and C. Montecucco[1], [1]Chair and Division of Rheumatology, Policlinico San Matteo, Pavia, Italy, [2]L. Sacco University Hospital, Milano, Italy

Purpose: It is well known that therapy with anti tumor necrosis factor α(TNF α) blockers can be associated with an increased rate of serious infections. In oncology, reactivation of hepatitis B virus (HBV) replication during immunosuppressive therapy can occur in up to 50% of hepatitis B surface antigen (HBsAg) positive patients with a mortality of 5%-12% . Recently, cases of HBV reactivation have been described in infliximab-treated Chron's disease both in HBsAg positive patients and in HBsAg negative/ hepatitis B core antibody (HBcAb) positive patients. The safety of anti TNF α therapy in rheumatic diseases with chronic HBV infection is still a matter of debate. The aim of this study is to assess the safety of anti TNF α therapy on the course of HBV infection in HBcAb positive patients with inflammatory arthropathies.

Method: From January 2001 to December 2008, serological HBV-markers were done before the first administration of anti TNFα agents in 306 consecutive patients affected by inflammatory arthropathies treated with anti TNF α at two outpatient rheumatologic clinics in Northern Italy. Patients were prospectively evaluated and HBV markers and HBV DNA were done in case of transaminases elevation or at the end of the study. HBV-markers were identified using the following techniques: HBsAg, antibodies to hepatitis B surface antigen (anti-HBs), antibodies to hepatitis B core protein (anti-HBc), hepatitis B e antigen (HBeAg), antibodies to HBeAg (anti-HBe), were detected by the Axsym Abbott, and HBV-DNA by real time PCR technique (<100 copies/ml). Liver function tests and disease activity scores were determined every eight weeks.

Results: At the time of recruitment 69 patients were HBcAb positive; 2 were HBsAg positive and were treated with lamivudine (not included in the study); 2 had HCV co-infection. The male/female ratio of the 67 patients was 26:41, 59 patients were affected by rheumatoid arthritis (RA), 4 psoriatic arthritis (PsA) and 4 ankylosing spondylitis (AS). The mean follow-up was 42.55 months (SD ±21.33). The mean Disease Activity Score 28 was 5.65 (SD ± 0.96) in RA, while the mean BASDAI was 4.31 (SD ± 2.45), in PsA and AS. Out of 67 patients, 25 were treated with infliximab, 23 with etanercept and 19 with adalimumab. 51/67 patients were also treated with methotrexate, 52 with NSAIDs, and 43 with low-dose oral prednisone, 3 of them with a dose >7.5 mg/day. All HBcAb positive patients were HBV-DNA negative at the first observation. During the follow-up 1 patient presented HCV reactivation while no patients presented HBV reactivation; no patients became HBsAg positive one patient died for myocardial infarction. In two patients HBcAb positivity was not confirmed at the end of follow-up.

Conclusion: In our study, anti TNF α therapy in HBcAb-positive patients, did not induce viral reactivation of HBV infection. These preliminary data require a confirmation in further studies on larger cohorts.

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Moderate Response to Biologic Treatment After 3 Months May Predict Good Response and Low Disease Activity State in Rheumatoid Arthritis After 6 Months. Till Uhlig[1], Elisabeth Lie[1], Marte S. Heiberg[1], Erik Rødevand[2], Cecilie Kaufmann[3], W. Koldingsnes[4], Knut Mikkelsen[5] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]St Olavs Hospital, Trondheim, Norway, [3]Buskerud Central Hospital, Norway, [4]University Hospital of Northern Norway, Tromsø, Norway, [5]Lillehammer Hospital for Rheumatic Diseases, Norway

Purpose: When prescribing biological medication for RA, rheumatologists are often advised to evaluate effectiveness of the biologic drug after 3 months treatment, in order to achieve rational use of these drugs. We determined in patients treated with a biologic for at least 6 months how response to drug treatment after 3 months could help to predict 6 month outcome as measured by response in disease activity (DAS28) and disease activity state.

Methods: Data were extracted from NOR-DMARD which is an observational study conducted in 5 Norwegian rheumatology departments. Adult patients with inflammatory arthropathies are consecutively included when they start a new DMARD regimen, and they are assessed after 3 and 6 months with core measures of disease activity and health status. In these particular analyses we focused on patients with RA starting with any biologic which who were evaluated at 3 and 6 months follow-up (n=876). Biologics included etanercept (41%), adalimumab (29%), infliximab (23%), rituximab (6%), abatacept (1%). Mean (SD) age was 52.4 (13.1) yrs, 74.9% were females, and mean disease duration was 11.1 (9.2) yrs. DAS28 was calculated based on ESR. We cross-tabulated low, moderate and good response (ΔDAS28 <0.6, 0.6-1.2, and ≥1.2) after 3 months against good response and achieved state of low disease activity (DAS28≤3.2) at 6 months and applied also logistic regression analyses. **Results:** were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Results: No response (ΔDAS28 <0.6) after 3 months of therapy was seen in 27%, moderate response (ΔDAS28 0.6-1.2) in 18%, and good response (ΔDAS28 >1.2) in 55%. Of the patients with no response at 3 months 18% had moderate and 24% good response at 6 months, and of those with moderate 3-months response 51% achieved good response at 6 months. 89% of patients with good response at 3 months had also maintained good response at 6 months.

At 6 months 38% of all patients were at a state of remission or low disease activity (DAS28≤3.2).

Adjusting for age, sex and baseline disease activity, patients with a good response at 3 months had a 9-fold increase in odds for achieving low disease activity state at 6 months vs. patients with no response (OR 9.4, CI 5.3 - 16.6), but also those with moderate response at 3 months had increased odds for achieving low disease activity state (OR 2.5, CI 1.3-4.6) at 6 months. In similar analyses good response at 6 months (ΔDAS28 >1.2) was predicted by good response at 3 months (OR 23.0, CI 13.5 - 39.1) but also by only moderate response at 3 months (OR 3.1 CI 1.8 - 5.4).

Conclusion: Patients with only moderate response during treatment with a biologic drug after 3 months may achieve good response or a state of low disease activity after 6 months. These data support that in real life treatment decisions for patients on biologic treatment should be individualized, and treatment should not be stopped if patients fail to have good response after three months.

Disclosure: T. Uhlig, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Schering-Plough, 5, BMS, 5 ; **E. Lie**, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5 ; **M. S. Heiberg**, None; **E. Rødevand**, None; **C. Kaufmann**, None; **W. Koldingsnes**, Wyeth Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5, Roche Pharmaceuticals, 5 ; **K. Mikkelsen**, Schering-Plough, 5, UCB, 5, Pierre-Fabre, 5, BMS, 5, Roche Pharmaceuticals, 5, Nycomed, 5 ; **T. K. Kvien**, Roche Pharmaceuticals, Abbot, Wyeth, Schering-Plough, BMS, UCB, 5 .

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Clinical and Radiological Outcomes of Four DAS Driven Treatment Strategies: Six-Year Results of the BeSt Study. N.B. Klarenbeek[1], L. Dirven[1], M. Güler-Yüksel[1], A.H. Gerards[2], P.J.S.M. Kerstens[3], T.H.E. Molenaar[4], T.W.J. Huizinga[1], B. A. C. Dijkmans[5] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]Vlietland Hospital, Schiedam, Netherlands, [3]JBI, Amsterdam, Netherlands, [4]Groene Hart Hospital, Gouda, Netherlands, [5]VUMC, Amsterdam, Netherlands

Purpose: To compare clinical and radiological outcomes of four treatment strategies after 6 years DAS-steered treatment in recent onset rheumatoid arthritis.

Method: 508 recent onset RA patients were randomized into four treatment strategies: 1. sequential monotherapy, 2. step up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Treatment adjustments were made based on threemonthly DAS measurements (if DAS >2.4: dose increase/switch next treatment step, if DAS ≤ 2.4 during ≥6 months: taper to maintenance dose, next if DAS <1.6 during ≥6 months: stop anti-rheumatic treatment). Functional ability (HAQ), measured threemonthly was analyzed with a linear mixed model (LMM) with time, treatment and time*treatment as independent variables. Joint damage progression (Sharp-van der Heijde Score (SHS) was assessed on X-rays of baseline and year 2, 3, 4, 5, 6, scored by two independent readers in random order, blinded for patient identity.

Results: During 6 years follow-up, 99 patients (19%) withdrew from the study. At t=6 year, 83% had a DAS ≤2.4 and 51% DAS <1.6 (remission), equally distributed among the four groups (table). The initial improvement of function, which occurred earlier in groups 3 and 4 than in groups 1 and 2 but was comparable between all groups from year 1 onwards, was maintained without deterioration of HAQ over 6 years time (LMM: HAQ yr6 – yr1 = +0.02, p=0.58). Radiological progression was higher in the first two years of treatment (median 0.5, mean 4.6), especially in groups 1 and 2**,** than in years 3-6 (medians 0, 0, 0, 0 for year 3-6, means 1.1, 1.2, 1.4, 1.1), reflecting the efficacy of DAS-steered therapy. After 6 years, 15, 16, 14 and 19% of patients in groups 1-4 were in drug free remission with a median (mean) duration of 32 (26) months. Mean SHS progression in patients in sustained drug free remission was 0.13 (median (IQR) 0 (0 - 0)) per person year drug-free.

Conclusion: After earlier improvement and less radiological damage progression with initial combination therapy, functional improvement was maintained and radiological progression stabilized with DAS steered treatment aiming at DAS ≤2.4 irrespective of initial treatment. After 6 years, 51% of patients are in clinical remission and 17% of patients in prolonged drug-free remission without radiological progression.

Table: 6-year results of the BeSt study, †completers analysis, ‡intention to treat, [*]1-2 vs 3-4 and 3 vs 4 p<0.01; [**]2 vs 4 <0.001, other comparisons n.s.; [#]LMM: 1 and 2 vs 4 p=0.02, other comparisons n.s.

	Group 1	**Group 2**	**Group 3**	**Group 4**	**p-value**
	n=126	**n=121**	**n=133**	**n=128**	

DAS ≤2.4, %†	84	80	84	84	0.90
DAS <1.6, %†	49	50	51	55	0.89
DAS <1.6 drug free, %†	15	16	14	19	0.76
Still on initial treatment, %‡	23	21	40	62	<0.001*
Current IFX users, %‡	14	6	11	20	0.01**
Mean HAQ during 6 years‡	0.70	0.70	0.63	0.56	<0.001#
SHS progression during 6 years, median / mean†	3.5 / 14.9	2.8 / 9.8	2.5 / 7.1	2.0 / 5.3	0.15
Drop outs n (%)‡	26 (21)	29 (24)	28 (21)	16 (13)	0.12

Disclosure: N. B. Klarenbeek, None; **L. Dirven**, None; **M. Güler-Yüksel**, None; **A. H. Gerards**, None; **P. J. S. M. Kerstens**, None; **T. H. E. Molenaar**, None; **T. W. J. Huizinga**, None; **B. A. C. Dijkmans**, None; **C. F. Allaart**, None.

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Predictors of Biologic Response Modifiers Discontinuation in 2,486 RA Patients. Sofia Ramiro[1], Fred Wolfe[2] and Kaleb D. Michaud[3], [1]Hospital Garcia de Orta, Lisbon, Portugal, [2]National Data Bank, Wichita, KS, [3]University of Nebraska Medical Center and NDB, Omaha, NE

Purpose: Biologic response modifiers (BRM) are recognized for enabling sustained improvement in Rheumatoid Arthritis (RA) while discontinuation of these drugs due to several reasons is an emerging problem. Our goal was to determine the discontinuation rate of the first BRM used in RA patients and identify predictors associated with this discontinuation.

Method: Using the National Data Bank for Rheumatic Diseases (NDB) longitudinal study, patients reporting use of a first BRM with at least 6 months of follow-up were followed, and their continuation or discontinuation status was assessed according to self-report. Interruptions longer than 6 months were considered as discontinuations. Patients participating in drug safety registries were excluded to reduce bias. To assess predictors of BRM discontinuation, we collected demographic, clinical and treatment data, comorbidity, VAS scales for pain, global and fatigue, HAQ, quality of life measures (SF-36 physical, PCS, and mental, MCS, scores), Rheumatoid Arthritis Disease Activity Index (RADAI) and calendar year. The influence of these on BRM discontinuation was analyzed using a Cox proportional hazards model and adjusted for potential confounders.

Results: With average (SD) age of 60 (13) years and 19% men, 2,486 patients met our inclusion criteria (mean length of follow-up 3.8 (3.7) years). 46% (1,137 patients) of these discontinued their first BRM with a median time on drug of 4.5 years and a discontinuation rate of 14.7% per year. The specific initial BRM used were etanercept (45%), infliximab (40%), and adalimumab (12%). From the discontinuations, 50.3% of the patients ceased all BRMs, while the other 49.7% started, throughout their follow-up in the registry, on at least a second BRM. As detailed in the table, age at BRM start, RADAI, current use of prednisone, female gender, HAQ, and comorbidity index were associated with discontinuation of the first BRM. Infliximab discontinuation predictors were similar to the predictors of discontinuation of BRM in general, while adalimumab discontinuation was inversely associated with NSAID use (HR 0.50, 95% CI 0.34, 0.75). Apart from the general factors, the number of DMARDs taken (HR 1.31, 95% CI 1.10, 1.55), duration of methotrexate (MTX) therapy at BRM start (HR 1.01, 95% CI 1.00, 1.02) and fatigue scale at BRM start (HR 1.06, 95% CI 1.02, 1.11) were associated with etanercept discontinuation, while the number of DMARDs taken at BRM start (HR 0.79, 95% CI 0.67, 0.94) and duration of MTX therapy (HR 0.99, 95% CI 0.99, 0.99) were inversely associated.

Conclusion: A significant number of RA patients do stay for a reasonably long period on their first BRM, similar to what happened to initial MTX therapy in the 90s and consistent with previous reports. RA severity described by high disease activity, worse function and prednisone intake predicts BRM discontinuation.

Table. Predictors of BRM discontinuation

Predictors	**HR (95% CI)**
Age	0.19 (0.13, 0.27)
Male gender	0.83 (0.70, 0.99)
Age at BRM start	5.35 (3.77, 7.58)
RADAI	1.27 (1.16, 1.39)
Current use of prednisone	1.24 (1.09, 1.41)
HAQ	1.20 (1.00, 1.43)
HAQ at BRM start	0.65 (0.56, 0.76)
Pain scale	0.93 (0.89, 0.98)
PCS	0.98 (0.97, 0.99)
MCS	0.99 (0.99, 0.99)
Comorbidity index	1.05 (1.00, 1.10)

Disclosure: S. Ramiro, None; **F. Wolfe**, None; **K. D. Michaud**, None.

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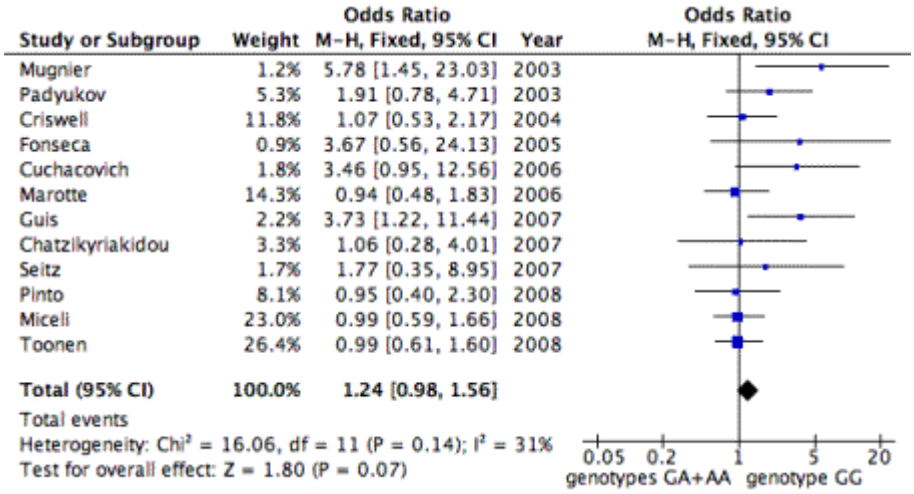
TNF Alpha –308 G>A Polymorphism Is Not Associated with Response to TNF-Alpha-Blockers in Patients with Rheumatoid Arthritis: a Systematic Review and Meta-Analysis. Stephan Pavy[1], Erik JM Toonen[2], Corinne Miceli-Richard[1], Pilar Barrera[2], Piet Van Riel[2], Marieke Coenen[2] and X. Mariette[1], [1]Hopital Universitaire de Bicêtre, Le Kremlin Bicêtre, France, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose: The tumour necrosis factor alpha (TNFA) -308G>A gene polymorphism has been reported as a potential predictor of the clinical response to anti-TNF treatment in rheumatoid arthritis (RA). Nevertheless, these results remain controversial. We performed a meta-analysis to determine whether the TNFA -308G>A polymorphism is associated with response to anti-TNF treatment in patients with RA .

Method: A bibliographic search was performed to identify studies in which the TNFA –308G>A gene polymorphism was investigated in RA patients treated with anti-TNF agents. Complementary data were requested when the DAS28 was not used as the primary outcome measure of clinical efficacy. Odds ratios (OR) for response based on DAS28 and standardized mean difference (SMD) for mean improvement of DAS28 were calculated in order to assess the potential association between TNFA -308 genotypes and response to anti-TNF agents. Studies were combined using fixed effect or random effect depending on the heterogeneity assessed by I2 statistic. Part of the sensitivity analysis was based on detailed patient data of a large unpublished Dutch cohort and a French clinical trial encompassing a total of 814 RA patients.

Results: Twelve studies met the inclusion criteria and were supplemented with the data from the Dutch cohort. The OR based on twelve studies including 1721 patients was 1.24 (95%CI 0.98-1.56) and the SMD based on eleven studies including 2576 patients was -0.15 (95%CI -0.38-+0.07). Sub-group analysis based on the two classes of anti-TNF agents did not demonstrate any association between TNFA -308 genotypes and anti-TNF treatment outcome. The sensitivity analysis based on individual patient data was consistent with the main results.

Conclusion: According to this meta-analysis, the TNFA -308 polymorphism is not a predictor of the clinical response to anti-TNF treatment in RA.



Disclosure: S. Pavy, None; **E. J. Toonen**, None; **C. Miceli-Richard**, None; **P. Barrera**, None; **P. Van Riel**, None; **M. Coenen**, None; **X. Mariette**, None.

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Biologics for Rheumatoid Arthritis: An Overview of Cochrane Reviews. Jasvinder A. Singh[1], R. Christensen[2], GA Wells[3], Marie E. Suarez-Almazor[4], Rachelle Buchbinder[5], Maria Lopez-Olivo[6], Elizabeth T. Ghogomu[7] and Peter Tugwell[8], [1]VA Medical Center, Minneapolis, MN, [2]RC, Copenhagen, Denmark, [3]University, Ottawa, [4]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [5]Cabrini Medical Center, Malvern, Australia, [6]MD Anderson Ctr Univ of TX, Houston, TX, [7]Cochrane Musculoskeletal Group, Ottawa, [8]Institute of Population Hlth, Ottawa

Background: There are no head-to-head comparisons of Biologic DMARD randomized controlled trials.

Purpose: To indirectly compare the efficacy and safety of abatacept (Aba), adalimumab (Ada), anakinra (Ana), etanercept (Eta), infliximab (Inf), and rituximab (Rit) in patients with rheumatoid arthritis (RA) by calculating the number needed to treat (NNT) for benefit and harm [1].

Methods: This ‘Overview of Reviews' was done on the basis of existing Cochrane reviews available in the Cochrane Library (CMSG). We included all Reviews on Biologics for RA; summarizing existing ‘Intervention reviews' rather than finding, summarizing or synthesizing original studies. We included only data on standard dosing regimens for these biologic DMARDs from placebo-controlled trials. The primary efficacy outcome was the ACR50 response; as clinical and statistical evidence shows that this is the preferred endpoint for contemporary RA clinical trials. The number of withdrawals due to adverse events was the primary ‘safety' outcome. Statistical analyses were based on Risk Ratios (RR) for efficacy, and the Peto Odds Ratio (POR) for safety. Using these combined estimates we calculated the NNT for each product by taking the empirical proportion of events across the placebo/control-groups as the Control Event Rate for each product.

Results: From the six available Cochrane reviews, we obtained data from 7 studies on Abatacept, 8 on Adalimumab, 5 on Anakinra, 5 on Etanercept, 4 on Infliximab, and 3 studies on Rituximab, respectively. As expected, all 6 drugs were significantly better than placebo/control: Aba, RR=2.21 (95% CI: 1.79 , 2.74); Ada, RR=2.44 (1.22 , 4.86); Ana, RR=2.13 (1.31 , 3.46); Eta, RR=1.87 (1.19 , 9.95); Inf, RR=1.70 (1.03 , 2.83); Rit, RR=3.54 (1.99 , 6.29). Converting these into NNT's for interpretation of clinical significance, we obtained 6, 4, 7, 3, 6, and 5 for each respective intervention. For safety, Abatacept, Infliximab and Etanercept were statistically not different from placebo with POR of 1.30, 1.58 and 1.56, respectively ($p \geq 0.05$). Adalimumab and Rituximab were significantly different from

placebo/control (*P*=0.005 and P=0.02), with a POR =1.58 (1.14 , 2.17) and 2.95 (1.15, 5.80), respectively; with a corresponding NNT in order to “harm” a patient of 39 for adalimumab and 70 for Rituximab. The primary safety-outcome was not available for Anakinra.

Conclusion: It was evident that all six biological therapies were efficacious. The expected number of patients who responded to therapy was most pronounced for etanercept and least pronounced for anakinra. Thus, we anticipate that in a group of 100 patients initiating biological therapy, between 14 and 33 patients will experience at least 50% disease reduction (i.e. ACR50 criterion).

[1] Osiri et al. Ann Rheum Dis. 2003 Apr;62(4):316-21.

Disclosure: J. A. Singh, TAP Pharmaceuticals Inc., 2, Allergan, 2, Savient, 2, Amgen, 2, Abbott Immunology Pharmaceuticals, 8 ; **R. Christensen**, None; **G. Wells**, None; **M. E. Suarez-Almazor**, None; **R. Buchbinder**, None; **M. Lopez-Olivo**, None; **E. T. Ghogomu**, None; **P. Tugwell**, None.

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Immunological Mechanisms Related to Clinical Responsiveness Differ Between Methotrexate Monotherapy and Methotrexate and Etanercept Co-Treatment in Rheumatoid Arthritis. Theo van den Broek, Nicole Schechter, Cathleen Cover, Norma Seaver, Farah Bughio, Nick Shen and Salvatore Albani, Arizona Arthritis Ctr, Tucson, AZ

Purpose: Methotrexate treatment is used as initial treatment for patients with rheumatoid arthritis. If unsuccesful, anti-TNFa therapy is added to methotrexate. The immunological mechanisms triggered in response to both therapies are still not fully understood and most certainly involve a cluster of immune response mechanisms beyond the ones typically purported. Understanding of these mechanisms may optimize current standard practice by discriminating a priori methotrexate responders from methotrexate failures.

Method: 6 rheumatoid arhtritis patients on either anti-TNFa (etanercept) and methotrexate (MTX, n=3) or MTX monotherapy (n=3) were analyzed based on clinical responsiveness., determined as a DAS-score of <3.2. CD4CD127+ (Teff), CD4CD25+CD127- (nTreg) were sorted by FACS. Immune response genes expression was measured by TaqMan real-time PCR after in vitro stimulation. CFSE suppression assay was used to determine the capability of Treg to suppress Teff proliferation.

Results: Table 1: changes in gene expression when clinical control is achieved with stated therapy compared with non responders).

	Methotrexate	Methotrexate and Etanercept
APCs	B7-H1, TNFa downregulation	B7-H1, TNFa downregulation
Teff	No significant changes	IL-10, PD-1
Treg	FoxP3, PD-1, CTLA-4, Granzym B	PD-1, CTLA-4 Granzym B, Perforin, TGF-b

Conclusion: These preliminary studies evidence substantial differences between ETN and MTX responders with respect to Teff, as ETN responses appear to be more related to immune deviation. Common traits can also be identified in both arms toward a functional restoration of Treg activity as a contributor to the mechanisms leading to clinical responsiveness

Disclosure: T. van den Broek, None; **N. Schechter**, None; **C. Cover**, None; **N. Seaver**, None; **F. Bughio**, None; **N. Shen**, None; **S. Albani**, None.

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Geriatric Rheumatoid Arthritis Patients Receive Anti-Tnfa Agents Later, Have Higher Disease Activity and Experience More Often Serious Adverse Events Compared to Younger Adults. Irini Flouri[1], Alexandros A. Drosos[2], Kyriaki A. Boki[3], Fotini N. Skopouli[4], Dimitrios Karras[5], Ioannis Papadopoulos[6], P. Geborek[7], Dimitrios Boumpas[1] and Prodromos Sidiropoulos[1], [1]University of Crete, Heraklion, Greece, [2]Ioannina Medical School, Ioannina, Greece, [3]Sismanogleion General Hospital, Athens, Greece, [4]Athens University Medical School, Athens, Greece, [5]NIMITS, Athens, Greece, [6]Kavala G Hospital, Kavala, Greece, [7]Lund University, Department of Clinical Sciences, Lund, Sweden

Purpose: Anti-TNFa agents are increasingly used to treat rheumatoid arthritis (RA) patients of all ages. There is still scarce data available concerning safety and efficacy of these agents in elderly patients. We aimed to explore the effectiveness and safety profile of anti-TNFa agents in geriatric patients (≥ 65 years old) with rheumatoid arthritis in clinical practice.

Method: The Hellenic Biologic Registry for Rheumatic Diseases collects efficacy and safety data from 7 Academic and State Rheumatology clinics in Greece. Demographics, disease characteristics and treatments are recorded according to a standardized evaluation protocol (South Swedish Arthritis Treatment Group protocol). This report is on behalf of the investigators of the "Hellenic Registry for Biologics in Rheumatic Diseases".

Results: Data were analyzed for 307 geriatric (mean age 71 (SD 7) yrs) and 771 non-geriatric (49 (11)) adults with RA. At baseline geriatric patients had longer disease duration (mean 13 (SD 10) yrs) vs 9 (SD 8), p<0.001), higher activity (DAS28 6,1(1.3) vs 5.8 (1.2), p=0.008) and higher disability (HAQ 1.1 (0.6) vs 1 (0.56), p=0.007). Improvements in disease activity following treatment by the EULAR criteria was comparable for the first 2 years of treatment; however a lower percentage of geriatrics were good responders at 24 months (p=0.05).

A total of 1335 events were recorded, 404 in the geriatrics and 931 in non-geriatrics. The time on therapy up-to the reported adverse event was shorter in geriatrics (515 (446) vs 634 (530) days, p<0.001). Infections were the most common AE reported in both groups accounting for almost half of the reports. As expected, cardiovascular events were more common in geriatrics (p=0.02) while infusion reactions were more common in non-geriatrics (p=0.01). Geriatric patients had higher incidence of a serious adverse event compared to non-geriatric adults (23% vs 11% , p<0.001).

Conclusion: Geriatric RA patients have a delayed treatment with anti-TNFa agents while disease activity is higher. Although response rates are comparable between the two age groups, geriatric patients experience a serious adverse event more often. Physicians treating geriatric patients with anti-TNF should carefully assess for predisposing factors for infections and vascular events.

Disclosure: I. Flouri, None; **A. A. Drosos**, None; **K. A. Boki**, None; **F. N. Skopouli**, None; **D. Karras**, None; **I. Papadopoulos**, None; **P. Geborek**, None; **D. Boumpas**, None; **P. Sidiropoulos**, None.

1025

Rituximab Versus Anti-TNF in Patients Who Previously Failed One or More Anti-TNFs in An Observational Cohort: The SARASTRA Study. K. Chatzidionysiou, C. C. Carli and R. F. van Vollenhoven, Karolinska Univ Hosp, Stockholm, Sweden

Purpose: Rituximab (RTX) is mostly used after the failure of at least one anti-TNF. Another option is to switch to another anti-TNF, and it is not yet clear which of these two options is the more successful strategy. The purpose of this study was to determine if patients who failed one or two anti-TNFs achieve better results when switching to another anti-TNF or when switching to RTX and find potential correlation between reason of discontinuation and efficacy of next treatment.

Method: The Stockholm registry "STURE" was used. Treatment results at 3 and 6 months were analyzed by: 1) biologic used; 2) whether as second or third biologic; 3) reason of discontinuation of the first or second agent (inefficacy or intolerance). Treatment segments with anakinra were disregarded for this analysis; of duplicate segments with the same anti-TNF only the first one was used.

Results: A total of 479 patients switched to a second biologic therapy. 229 of them (47.8%) discontinued their first agent because of inefficacy and 141 (29.4%) because of intolerance. The rest of the patients stopped for other reasons. When used as the 2nd biologic RTX achieved highly significant reductions from baseline in DAS28 at 3 and at 6 months (p<0.001); these changes were numerically but not significantly greater than the change that occurred in patients who switched to another anti-TNF. The subgroup of patients who switched to RTX because of intolerance to the first anti-TNF agent had better response and a higher percentage of them achieved EULAR good/moderate response compared to those who switched to a second anti-TNF after they had not tolerated a first one (table 1).

153 patients switched to a third biologic. The reductions in DAS28 are similar for patients on RTX and an anti-TNF, but numerically higher for those patients on RTX who showed intolerance to a previous TNF antagonist (table 1). Intolerance to the 2nd anti-TNF strongly predicts good response to therapy with RTX when used as third biologic (p=0.007). Higher disease activity at baseline was found to be associated with a higher risk of discontinuation of treatment (p<0.0001).

Conclusion: In patients who failed one anti-TNF, RTX yields results that are as good as, and in some comparisons numerically better than, switching to another anti-TNF. For patients who previously did not tolerate an anti-TNF agent RTX seems to be a better alternative.

Table 1. Improvement in DAS28 and EULAR good/moderate response for patients receiving RTX or an anti-TNF agent according to the reason of discontinuation of their previous biological treatment.

		2nd biologic			3rd biologic		
Biologic used	Reason of discontinuation of previous therapy	N of patients	ΔDAS28 0-6m (mean±SD)	EULAR good/moderate resp at 6 m	N of patients	ΔDAS28 0-6m (mean±SD)	EULAR good/moderate resp at 6 m
anti-TNF	Ineffectiveness	220	1.6±1.4	71.3%	56	1.1±1.3	51.9%
RTX	Ineffectiveness	9	1.9±1.7	50%	24	1.3±0.9	33.3%
anti-TNF	Intolerance	124	1.7±1.2	64.4%	40	1.8±1.3	78.6%
RTX	Intolerance	17	2.1±0.8	77.8%	10	2.5±1.1	83.3%

Disclosure: K. Chatzidionysiou, None; **C. C. Carli**, None; **R. F. van Vollenhoven**, Roche Pharmaceuticals, 2 .

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Non-Responders to Rituximab or Tocilizumab After TNF-Alpha Inhibitor Failure in the Treatment of Rheumatoid Arthritis in the United Kingdom. Maximillian Lebmeier[1], Jane Shaw[2], Volker Koscielny[2] and Maria Deeg[3], [1]Wyeth Pharmaceuticals, Maidenhead, United Kingdom, [2]Wyeth, United Kingdom, [3]Wyeth, Muenster, Germany

Purpose: Anti-TNF agents or rituximab (RTX) are routinely used in clinical practice after failure of a first or second anti-TNF agent in the treatment of rheumatoid arthritis (RA). Recently tocilizumab (TOC), an IL-6 antagonist, has been licensed for the treatment of RA, providing clinicians with potential further options for the treatment of patients failing anti-TNF therapy. In the absence of comparative data models may help to estimate the number of patients not responding to RTX and TOC after failure of a first anti TNF compared to a second anti-TNF. This may provide insights into the most appropriate treatment algorithms and highlight areas requiring further research.

Method: An explorative analysis was conducted using a decision tree model. The model is based on data from RTX, and TOC clinical trials, as well as the British Society for Rheumatology Biologics Registry (BSRBR), which provides the most meaningful datasets on sequential use of biologics to date. The model compares the failure rates for a second anti-TNF, RTX or TOC in patients that have not responded to a first anti-TNF. In the REFLEX trial patients receiving RTX after not responding to at least one anti-TNF 49% of patients did not respond to RTX treatment (defined as not achieving ACR20 response). The RADIATE trial was conducted in patients not responding to at least one TNF. In this trial 50% did not respond to TOC treatment. Failure rates for a second TNF were obtained from the UK BSR, reporting the proportion of patients failing a 2nd TNF to be 27%. These failure rates were applied in the model which also used UK prevalence data for RA to predict potentially anti TNF eligible patients. The prevalence of RA in the UK is reported to be 1.16% in women and 0.44% in men, resulting in potentially 385,266 RA patients.

Results: The base case analysis calculated that 23,116 patients receive TNF inhibitor treatment, of which 4,221 can be expected to fail a first TNF inhibitor. If patients would receive RTX after the failure of a first anti-TNF 2,068 can be expected to fail this regime. If they would receive TOC, 2,110 could be expected fail. If patients would receive a second anti-TNF 1,140 may fail this treatment.

We furthermore calculated failure rates for RTX and TOC after lack of response to a second anti-TNF using data from the same sources. No published data for anti TNF agents in this population is available. Using RTX after a second anti-TNF would result in 559 vs. 570 patients failing treatment.

Conclusion: This exploratory analysis suggests that using 2 anti-TNFs sequentially, rather than switching to RTX or TOC after failure of only one anti-TNF may lead to fewer patients failing treatments. The data also suggests that RTX and TOC are equally effective when used after failure of a second anti -TNF agent. The model is based on limited data and further clinical comparative studies are needed.

Disclosure: M. Lebmeier, Wyeth Pharmaceuticals, 3 ; **J. Shaw**, Wyeth Pharmaceuticals, 3 ; **V. Koscielny**, Wyeth Pharmaceuticals, 3 ; **M. Deeg**, Wyeth Pharmaceuticals, 3 .

ACR/ARHP Poster Session B

Systemic Lupus Erythematosus - Animal Models

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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TWEAK Stimuation of Kidney Resident Cells in the Pathogenesis of Lupus Nephritis. Alberto Molano[1], Payal Lakhani[1], Adi Aran[1], Linda C. Burkly[2], Jennifer S. Michaelson[2] and Chaim Putterman[3], [1]Albert Einstein College of Medicine, [2]Biogen Idec, Cambridge, MA, [3]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

Purpose: The cytokine TWEAK demonstrates potent kidney proinflammatory and proliferative effects. Recently, we have shown that interactions of TWEAK with its receptor Fn14 are instrumental in the pathogenesis of nephritis in the chronic graft-versus-host (cGVH) induced model of lupus. Fn14 is expressed by macrophages and resident kidney cells; we hypothesized that TWEAK binding to both cell types contributes to the pathogenesis of lupus nephritis.

Method: To address the relevant importance of TWEAK activation of macrophages versus resident cells in the pathogenesis of lupus nephritis, we generated bone marrow chimaeras and compared the progression of nephritis during cGVH induced lupus in mice expressing Fn14 only on bone marrow-derived cells, versus mice displaying Fn14 only on non bone marrow-derived cells.

Results: While Fn14 deficiency did not significantly affect autoantibody titers, Fn14 deficiency on bone marrow-derived cells did not inhibit nephritis initiation in mice with Fn14 sufficient non-hematopoeitic cells. Conversely, expression of Fn14 only on bone marrow-derived cells resulted in a delayed, milder disease course. To further explore the role of macrophages, we depleted macrophages during cGVH induction. Surprisingly, we found that macrophage depleted mice displayed significantly increased titers of anti-DNA and other anti-nuclear antibodies, and worse kidney disease.

Conclusion: While macrophage activation by TWEAK may be important later on in the pathogenesis of nephritis, the presence of Fn14 on resident kidney cells alone may be sufficient to initiate nephritis in this murine model of lupus.

Disclosure: A. Molano, None; **P. Lakhani**, None; **A. Aran**, None; **L. C. Burkly**, Biogen Idec, 3, Biogen Idec, 1 ; **J. S. Michaelson**, Biogen Idec, 1, Biogen Idec, 3 ; **C. Putterman**, Biogen Idec, 2 .

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Role of Interferon-Inducible Gene IFI202b in the Suppressive Capacity of CD8+ Regulatory T Cells Induced in (NZB x NZW) F1 (BWF1) Lupus Mice. Ram P. Singh, Ravi Dinesh and Bevra H. Hahn, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: The interferon-inducible Ifi 202 gene family has been implicated in the susceptibility of BWF1 mice to SLE, particularly as its increased expression may protect autoreactive B cells from apoptosis. CD8+ Tregs induced by a peptide tolerogen can suppress anti-DNA-producing B cells. We tested the potential role of Ifi202 in the suppressive capacity of CD8+T regulatory cells.

Method: We compared 45,000 murine genes between peripheral white blood cells (WBC), $CD4^+$ T cells, and $CD8^+$ T cells from pCons-tolerized vs. non-tolerized mice using Affymetrix Gene Chip array 430. 2.0. Validation of differentially expressed genes was performed by real-time PCR. Protein expression was determined by intracellular FACS staining and by Western blot analyses. Anti-DNA ab was measured by ELISA. Gene silencing studies were performed by incubation of CD8+T cells with the appropriate si RNA.

Results: 1- In CD8+T cells from BWF1 mice tolerized with pCons, the expression of interferon inducible gene IFI202b was increased more than two-fold beginning at one week following pCons administration and extending through four weeks after treatment, with a decrease at 6 weeks. **2-** *In vitro* re-stimulation with pCons or polyclonal activation significantly increased IFI202b mRNA expression in tolerized $CD8^+$T cells compared to cells from untolerized mice. **3-** Silencing of IFI202b abrogated the suppressive capacity of tolerized $CD8^+$T cells on

syngeneic CD4+CD25- T cells and on anti-DNA production. Silencing did not affect the susceptibility of CD8+Treg to apoptosis. In contrast, the silencing of IFNar1 (also upregulated in expression) did not affect the ability of $CD8^+$T cells to suppress autoantibody production. **4-** Lastly, the silencing of IFI202b decreased mRNA and protein expression of TGFb - a major mediator of suppression by $CD8^+$ T regulatory T cells.

Conclusion: In conclusion, increased expression of IFI202b in induced $CD8^+$ Treg cells contributes to their suppressive capacity, probably by decreasing the expression of TGFb.

Disclosure: R. P. Singh, None; **R. Dinesh**, None; **B. H. Hahn**, None.

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Induction of Collapsin Response Mediator Protein 2 Expression During Immune-Mediated Nephritis. Aislinn Kelly[1], Calum Sutherland[2], Salim Merali[1], Michael P. Madaio[3] and Tracy L. McGaha[3], [1]Temple University, Philadelphia, PA, [2]University of Dundee, Dundee, Scotland, [3]Medical College of Georgia, Augusta, GA

Purpose: Protenuria occurs in most forms of glomerular injury and serves as both a marker of altered permeability and a factor that contributes to progressive disease. While proteinuria is a common manifestation in SLE our understanding of the mechanisms by which inflammation manifest this particular pathology is minimal at best. Using the nephrotoxic serum (NTS) nephritis model of immune-mediated glomerular injury, we investigated early time points after disease induction examining the initial stromal response to antibody deposition to gain insight into pathological mechanisms.

Method: Glomeruli were purified from mice 1d post-NTS injection and the proteomic profile was compared to sham-injected mice via 2D electrophoresis and MALDI-TOF mass-spectrophotometeric analysis. Identified proteins of interest were confirmed for differential expression via histological and Western blot analysis. Finally we examined a kidney visceral epithelial cell (podocyte) line for in vitro confirmation.

Results: Proteomic analysis of inflamed glomeruli from NTS-administered mice revealed upregulation of a protein with no previously described function in renal biology, collapsin response mediator protein 2 (CRMP2), an actin binding protein which influences cytoskeletal structure and cell polarity. The proteomic analysis was confirmed by immunofluorescence of renal tissue from nephritic mice demonstrating CRMP2 expression in glomeruli. Furthermore, Western blotting revealed the induction of CRMP2 was rapid, occurring by 1d post-NTS administration in purified glomerular lysates. Similarly, podocytes significantly increased CRMP2 protein levels 6h post-NTS stimulation in vitro suggesting that NTS-mediated injury rapidly induces CRMP2 production, and that this effect may be due to direct action on podocytes. Interestingly, this induction seems to be specific to immune-mediated renal injury as other models of podocyte damage failed to induce CRMP2 expression.

Conclusion: CRMP2 expression is closely associated with protenuria and podocyte damage in immune-mediated nephritis and may represent a previously unknown pathologic mechanism by which antibody deposition in the kidney contributes to disease manifestation and progressive target tissue damage.

Disclosure: A. Kelly, None; **C. Sutherland**, None; **S. Merali**, None; **M. P. Madaio**, None; **T. L. McGaha**, None.

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Altered Programmed Death 1-Programmed Death Ligand 1 (PD-1-PD-L1) Pathway in T Cells of (New Zealand Black x New Zealand White) BWF_1 Mice with Anti-PD-1 Antibody. Maida Wong, Antonio La Cava, Ram P. Singh and Bevra H. Hahn, Division of Rheumatology, David Geffen School of Medicine, UCLA, Los Angeles, CA

Purpose: PD1-PD-L1 pathway is reportedly a costimulatory pathway that regulates self-tolerance by providing negative signals to T cells, resulting in anergy and decreased cytotoxicity. We have shown that induction of suppressive $CD8^+$ T cells ($CD8^+T_{reg}$) by administration of an artificial anti-DNA Ig-based synthetic peptide pConsensus (pCons), reduces PD-1 expression on the suppressor cells, which have increases in expression of Foxp3 and production of TGF-β. Also, untolerized mice treated with anti-PD-1 have delayed onset of proteinuria and increased survival compared to unmanipulated mice. We therefore studied the kinetics of PD-1 expression in $CD8^+T_{reg}$ *in vivo*, as they moved from permissive to suppressive following administration of pCons to BWF_1 lupus-prone mice.

Method: Antibody against PD-1 or control isotype-matched IgG were injected into naïve vs. tolerized BWF_1 mice intraperitoneally. TGF-b, IFN-γ, IL-6, IL-17A, anti-dsDNA and total IgG production were assessed by flow cytometry and/or ELISA.

Results: In anti-PD1-treated mice, serum anti-dsDNA, IgG and IFN-γ production were reduced compared to unmanipulated controls; the low production was comparable to the levels in tolerized mice. In contrast, anti-PD-1-treated mice had increased TGF-b expression in the serum; they failed to develop the elevations in serum IL-6 and IL-17A levels and proteinuria that are characteristic of the unmanipulated BWF_1 controls.

Conclusion: PD-1 is likely one of the core participants in inherent autoreactivity of T cells and in the mechanisms of immune tolerance in our model. Blocking PD-1 in otherwise unmanipulated mice delays autoantibody production, nephritis and mortality for many weeks; it prevents the increase in pro-inflammatory IL-6, IFN-γ and IL-17A while increasing secretion of anti-inflammatory TGF-b. Such a pattern could result from the ability of PD-1 to participate in suppression of Th17 cells, either directly or by activation of T_{reg}. Complete silencing of PD-1 with siRNA eliminates suppressive capacity of $CD8^+T_{reg}$. In functional suppressive $CD8^+T_{reg}$ from tolerized $mice_i$, PD-1 is down-regulated, but not to zero. We conclude that the interplay between Th1, Th17 and T_{reg} cells depends in part on fine tuning of the expression of PD-1.

Disclosure: M. Wong, None; **A. La Cava**, None; **R. P. Singh**, None; **B. H. Hahn**, None.

1031

IRF9 Influences Isotype Switching by Modulating B Cell Activation and Intracellular Signaling in the Pristane Mouse Model of Lupus. Alvina D. Chu, Jordan V. Price and Paul J. Utz, Stanford University School of Medicine, Stanford, CA

Purpose: Mice injected with pristane develop a lupus-like inflammatory response mediated by type I interferons (IFNs) and Toll-like receptor 7 (TLR7). A crucial component of the type I IFN signaling pathway, interferon regulatory factor 9 (IRF9), is required for B cell activation in response to TLR7 agonism. The mechanisms by which IRF9 enhances the B cell response to TLR7 remain to be elucidated. We aimed to define a role for IRF9 in influencing isotype switching events, testing the hypothesis that IRF9 modulates TLR7-mediated B cell cytokine production and intracellular signaling involved with immunoglobulin isotype switching.

Method: Age and sex-matched BALB/c wild-type (WT) and IRF9-/- mice were injected intraperitoneally with pristane. Sera were collected at 6 months after pristane injection and analyzed for isotype-specific autoantibodies directed against lupus autoantigens by ELISA. Secreted antibody isotypes and cytokines were also measured from WT and IRF9-/- B cells cultured *in vitro* with combinations of a TLR7 agonist, CD40 agonist, and IFN-alpha for 10 days. B cells isolated from pristane-treated mice were incubated with a TLR7 agonist over a 60-minute time course. Cell lysates were generated and analyzed by reverse phase protein microarrays for phosphorylated proteins and validated by Western blot.

Results: IgG antibodies specific for Sm/RNP and Ribo P antigens, particularly of the IgG2a subtype, were detected in pristane-treated WT mice but not in mice lacking IRF9. Isotype switching to IgG2a required IRF9 in the presence of TLR7, CD40, and type I IFN receptor agonism, correlating with IL-6 and IL-10 production. IgG1 production by B cells stimulated with anti-CD40 was not affected by the absence of IRF9. The presence of a TLR7 agonist induced protein phosphorylation within intracellular kinase pathways involving P38 MAPK, SAPK/JNK, and NFkB that was abrogated in IRF9-/- B cells.

Conclusion: Taken together, these results demonstrate that the adjuvant activity of type I IFNs on B cells requires IRF9 for isotype switching to IgG2a antibodies against RNA-containing antigens. Signaling studies suggest that IRF9 modulates intracellular kinase pathways that are activated by TLR7 signaling. P38 MAPK, SAPK/JNK, and NFkB are of special interest because they have been demonstrated to participate in isotype switching events. These results suggest that IRF9 may play a role in modulating these proteins.

Disclosure: A. D. Chu, None; **J. V. Price**, None; **P. J. Utz**, Bayhill Therapeutics, 1, Bayhill Therapeutics, 5, Biogen/IDEC, 5, Genentech and Biogen IDEC Inc., 5, Gilead, 5, UCB, 5, Amgen, 5, Regimmune, 5, Centocor, Inc./Johnson and Johnson, 5, Bayhill Therapeutics, 7 .

1032

Conditional Ablation of Langerhans Cells Exacerbates Lupus Dermatitis: A Novel, Protective Role of Langerhans Cells in Autoimmunity. Jennifer K. King, Anna U. Eriksson, Karen Jou and Ram Raj Singh, UCLA, Los Angeles, CA

Purpose: Skin-resident dendritic cells, called Langerhans cells (LC) maintain tolerance to skin antigens via constant, low migration to cutaneous draining lymph nodes (cLN). However, a novel finding from our lab has shown that LC migrate poorly from skin to cLN in lupus strains (MRL-Fas$^{lpr/lpr}$ [MRL-lpr] and MRL-Fas$^{+/+}$ [MRL+/+]) that develop autoimmune dermatitis *(JI 2008).* Since the LC migration defect precedes the onset of inflammation and correlates with severity of dermatitis, we posit that LCs play a protective role against the development of lupus dermatitis.

Method: We utilized MRL-lpr mice that express enhanced green fluorescent protein (EGFP) driven by a langerin (Lang) promoter by introgressing the Lang-EGFP knock-in from B6 background. Additionally, to determine the role of LCs in dermatitis development, we generated MRL-lpr mice that express diphtheria toxin receptor (DTR) and EGFP driven by Lang promoter. This permits acute ablation of LC with injection of diphtheria toxin A (DTA) for several weeks *(Malissen and colleagues, Imm 2005)*. DTR-EGFP knock-in mice were injected with DTA or vehicle weekly from 7 to 13 weeks of age and monitored for disease. Skin lesions were scored on a scale of 0(none)-3 (severe). Tissues were analyzed for immune cell subsets and skin by histology.

Results: First, we found the proportion of LC (EGFP$^+$) cells is markedly lower in cLN of EGFP MRL-lpr mice compared to B6 mice, thus confirming our report using inbred mice. Preliminary analyses suggest that this defect involves both subsets of skin Lang$^+$ cells (epidermal LC and dermal Lang$^+$ cells), although epidermal LC may be most affected. Such reduction of LC is likely important in dermatitis pathogenesis, as depletion of LC between 7 to 13 weeks of age markedly accelerated the development of skin lesions. Cumulative frequency of any skin lesion was 93% in LC ablated mice (n = 14) as compared to 23% in control wild-type littermates injected with DTA (n = 13; p <0.0003), and 15% in knock-ins injected with PBS (n=14; p<0.0001) at 20 weeks. Cumulative frequency of severe (3+; ulcerations with hemorrhage, >10% BSA) skin lesions was 93% in LC ablated mice compared to respective controls at 7% and 8% (p<0.0001) at 20 weeks. Disease free analysis of cumulative frequency of ≥2+ skin lesions showed significant acceleration of lupus dermatitis in LC ablated mice, with a median of 18 weeks compared to 32 weeks in controls (p=0.0037; Kaplan Meier). Skin sections show increased acanthosis, vacuolar changes, lymphocytic infiltrates, apoptotic keratinocytes, and fibrosis in LC ablated mice compared to controls. No difference in T cell activation, Tregs, or Th1 cytokines were found in cLN. Ongoing studies are determining mechanisms underlying this effect.

Conclusion: We demonstrate that temporal ablation of LC accelerates and worsens onset of lupus dermatitis, suggesting a protective role of LC in the pathogenesis of autoimmune dermatitis.

Disclosure: J. K. King, None; **A. U. Eriksson**, None; **K. Jou**, None; **R. R. Singh**, None.

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Pro-Inflammatory High Density Lipoproteins (piHDL) and Atherosclerosis Are Induced in Lupus-Prone but Not Normal Mice by High Fat Diet and Leptin. B. H. Hahn, Elaine V. Lourenco, Maureen A. McMahon, Brian J. Skaggs, Noriko Iikuni and Antonio La Cava, Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: Atherosclerosis is accelerated in people with systemic lupus erythematosus (SLE), and the presence of dysfunctional, pro-inflammatory HDL are a marker of increased risk.

Method: We developed a mouse model of multigenic lupus exposed to environmental factors known to accelerate atherosclerosis in humans – high fat diet with or without injections of the adipokine leptin. (NZB x NZW)F_1 (NZB/W) mice were the lupus-prone model; BALB/c were non-autoimmune controls.

Results: High fat diet increased total serum cholesterol in both strains, in BALB/c non-HDL cholesterol levels increased; they did not develop atherosclerosis. In contrast, NZB/W mice on high fat diets developed increased quantities of HDL (P<0.001) as well as high HDL scores (P<0.001) indicating pro-inflammatory HDL; they also developed atherosclerosis (P<0.05 vs controls). Thus, high fat diet rendered more susceptible to pro-atherosclerotic events the NZB/W mice than the BALB/c control mice. Moreover, in the lupus-prone strain, addition of leptin increased piHDL scores (P<0.03) and atherosclerosis (P<0.03) and accelerated proteinuria (P<0.05 vs controls).

Conclusion: These data suggest that environmental factors associated with obesity and metabolic syndrome can accelerate atherosclerosis and disease in a lupus-prone background.

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Effects of Apolipoprotein A-1 Mimetic Peptide in the Absence/Presence of Statin in a Murine Model of Accelerated Atherosclerosis in SLE. J. M.P. Woo[1], Z.F. Lin[1], C. Van Dyck[1], Y. Trejo-Lopez[1], K. M.T. Woo[1], X.P. Wang[2], N. Iikuni[1], O. J. Rullo[3], H. Wu[1], M. Navab[4], A. M. Fogelman[5], A. J. Lusis[2] and B. P. Tsao[1], [1]Division of Rheumatology, UCLA, Los Angeles, CA, [2]Divisions of Microbiology, Immunology, and Molecular Genetics, Medicine, and Human Genetics, UCLA, Los Angeles, CA, [3]Department of Pediatrics-Rheumatology, UCLA, Los Angeles, CA, [4]Division of Cardiology, UCLA, Los Angeles, CA, [5]Department of Medicine, UCLA, Los Angeles, CA

Purpose: Evaluate the effects of an apolipoprotein A-1 mimetic peptide, L-4F, in the absence/presence of pravastatin in apoE$^{-/-}$Fas$^{-/-}$ C57BL/6 mice, a murine model of accelerated atherosclerosis in SLE which spontaneously develops IgG autoantibodies, glomerulonephritis, and advanced atherosclerotic lesions on a normal chow diet.

Methods: Female mice, starting at 8-9 weeks of age, were treated for 27 weeks with 1) pravastatin, 2) L-4F, 3) L-4F plus pravastatin, or 4) vehicle control. Following euthanasia, tissues were harvested for disease assessment. Tissue damage and systemic inflammation were determined via histology and immunohistochemical staining, circulating chemokine/cytokine and autoantibody levels, and DEXA and μCT analysis.

Results: Only mice treated with L-4F in the absence/presence of pravastatin developed significantly smaller glomerular tufts ($p_{L,LP} < 0.05$), lower serum levels of IgG anti-dsDNA ($p_L < 0.05$) and anti-oxidized phospholipid ($p_{L,LP} < 0.005$) antibodies—with no significant difference in general immune suppression, elevated BMD ($p_{L,LP} < 0.005$), and lower proinflammatory plasma chemokine/cytokine levels (including CRP, CCL12, CCL19, and VCAM-1). Although all treatment groups presented 47-95% larger mean aortic root lesions, immunohistochemical staining showed a 37% decrease in mean infiltrated CD68 macrophages and a 59% increase in mean α-actin (smooth muscle) stained areas in aortic lesions of combination treatment mice compared to vehicle controls.

Conclusion: Serological and histological analysis suggests that treatment with L-4F in the absence/presence of pravastatin significantly reduces systemic inflammation in our murine model with no significant difference between treatment with L-4F alone and the combination treatment. Compared to vehicle controls, treatment with L-4F plus pravastatin effectively reduced manifestations of lupus-like autoimmunity, glomerulonephritis, and osteopenia. In addition, cellular composition of atherosclerotic lesions was suggestive of plaque stabilization due to the increased smooth muscle tissue content and lower infiltrated CD68 macrophage population, despite larger lesion area, compared to vehicle controls.

Manifestation	Control[a] (n = 23)	L-4F[a] (n = 25)	p[b,c]	Pravastatin + L-4F[a] (n = 9)	p[b,c]
Glomerular tuft size (μm^2)	7,645 ± 1,200	6,845 ± 1,060	0.04	6,226 ± 1,007	0.004
IgG anti-dsDNA (AU)	132 ± 50	85 ± 43	0.007	120 ± 40	NS
IgG anti-oxidized phospholipid (AU)	29 ± 18	15 ± 9	0.002	9.3 ± .04	0.005
Total IgG (mg/ml)	4.5 ± 0.3	4.4 ± 0.7	NS	4.0 ± 0.7	NS
Lumbar BMD (mg/cm^2)	0.042 ± 0.007	0.051 ± 0.005	$6x10^{-6}$	0.053 ± 0.003	0.0002
Plasma cytokine/chemokines	(n = 16)	(n = 16)		(n = 8)	
CRP	8.3 ± 2.2	6.2 ± 1.4	0.005	7.8 ± 1.5	NS
CCL12 (MCP-5)	201 ± 117	120 ± 70	0.03	110 ± 44	0.01
CCL19 (MIP-3β)	15 ± 7	5.5 ± 2.8	0.00004	5.3 ± 3.5	0.0001
VCAM-1	6221 ± 1600	3940 ± 1400	0.0002	4868 ± 1300	0.04
	(n = 5)	(n = 5)		(n = 4)	
Aortic root lesion size (μm^2)	0.19 ± 0.10	0.27 ± 0.13	0.019	0.37 ± 0.13	0.0003
CD68 stained area per lesion area (%)	9.8 ± 0.8	8.9 ± 2.0	NS	6.2 ± 1.2	0.006
α-actin stained area per lesion area (%)	4.9 ± 2.3	7.1 ± 1.0	0.08	7.8 ± 0.5	0.04

dsDNA; double-stranded DNA; BMD, bone mineral density
[a] Values expressed as Mean ± SD
[b] p-values taken in comparison to Control values and considered significant at $p < 0.05$
[c] NS; not significant

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Induction of Lupus Like Symptoms in Human 60kD Ro Transgenic Mice by Passive Transfer of Human SLE Ro/SSA Autoantibodies. Timothy F. Gross[1], Harlan M. Gross[1], Jourdan R. Anderson[1], Sherry Hubbell[1], R. Hal Scofield[1], Shannon Maier[2], Joel M. Guthridge[1], Kenneth M. Kaufman[1], John B. Harley[1] and Judith A. James[1], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Oklahoma Health Sci Center; Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Anti-Ro/SSA antibodies are common, early autoimmune responses in systemic lupus erythematosus (SLE). Autoantibodies to Ro/SSA occur in nearly half the patients with SLE and are associated with leukopenia, thrombocytopenia, photosensitive dermatitis, and renal disease. Extensive work has mapped common antigenic humoral targets of the 60kD Ro response. Although described many decades ago, complete pathogenic mechanisms of these autoimmune responses are still unknown. This study uses human Ro transgenic mice and passive transfer of anti-Ro responses to assess clinical pathogenesis of these human responses.

Methods: Human 60kD Ro/SSA transgenic mice were generated and crossed for 30 generations onto the NOD/ShiLtJ autoimmune-prone background. Human anti-Ro IgG was isolated by affinity purification from SLE patients for passive transfer, and human IgG from healthy controls was used for controls. Human Ro transgenic mice received anti-Ro IgG, human IgG or anti-BSA intraperitoneally at baseline and day 14. Blood was collected at baseline and serially after passive transfers. Each serial blood sample was analyzed for leukocytes, erythrocytes, and thrombocytes. Serial autoantibody evaluations were also performed. Blood samples from each mouse were analyzed by flow cytometry for CD19, CD8 and CD4 cell subsets. At terminal dates, kidneys were collected and antibody eluted for testing for antibodies against Ro/SSA and specific known antigenic peptides of 60kD Ro/SSA.

Results: Human 60kD Ro transgenic mice showed no increased levels of autoantibody production or clinical disease compared to non-transgenic NOD controls. Human 60kD Ro transgenic mice receiving anti-Ro antibodies were more likely to develop leucopenia and

lymphopenia compared to control mice. Select anti-peptide responses were eluted from mouse kidneys passively transferred with human patient anti-Ro. For example, kidney eluates contained antibodies against 60kD Ro humoral epitopes 166-180 and Ro480-498 more commonly than controls. Both of these epitopes were also present in the affinity purified serum anti-Ro of the SLE patients.

Conclusion: Transfer of purified human anti-Ro/SSA antibodies into genetically engineered 60kD human Ro NOD mice resulted in reproduction of select aspects of human SLE-like disease phenotype. In addition, select humoral anti-Ro epitopes deposit in kidneys potentially providing insights to pathogenic mechanisms of anti-Ro SLE disease.

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Use of Laser Microdissection in the Analysis of Renal-Infiltrating T Cells in Murine Lupus. Yingge Wang[1], Satoshi Ito[1], Mizuho Suziki[1], Makoto Sugihara[1], Taichi Hayashi[1], Daisuke Goto[1], Isao Matsumoto[1], Sachiko Hirose[2] and Takayuki Sumida[1], [1]University of Tsukuba, Tsukuba, Japan, [2]Juntendo University School of Medicine, Tokyo, Japan

Purpose: To clarify the role of T cells in the kidneys of murine lupus models, cytokine mRNA expression was analyzed, and tissue localization of T cells was examined by immunohistochemistry.

Method: 1) Cells infiltrating the glomeruli and perivascular areas in MRL/lpr (10 female), NZB/W F1 (B/WF1) (4 female), and BXSB (2 male) mice were captured by laser microdissection (LMD). 2) Nested reverse transcription polymerase chain reaction (RT-PCR) of samples was performed with primers specific for β-actin, T-cell receptor β chain (TCR-Cβ), Thy-1, B220, CD4, CD8, interleukin (IL)-2, IL-4, IL-10, IL-13, IL-17, and interferon (IFN)-γ. 3) Frozen sections of lesions were also stained immunohistochemically.

Results: 1) T cells infiltrating the glomeruli and perivascular areas produced IFN-γ, IL-13, and IL-17 predominately. 2) IL-10 was detected only in the perivascular areas of MRL/lpr and B/W F1 mice but not in glomerulus. 3) Thy-1, CD4, CD8, B220, IFN-γ, and IL-17 staining was observed in glomeruli and perivascular areas from MRL/lpr, B/W F1, and BXSB mice. However, IL-10 staining was observed only in perivascular areas from MRL/lpr and B/W F1 mice.

Conclusion: Results of our study suggest that the cytokine balance is complex and not due simply to the Th1 and Th2 balance and IL-17 might play a critical role in murine lupus models. These findings also support the concept of different molecular mechanisms for glomerulonephritis and vasculitis in these mice.

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Toll Like Receptor 7 Agonist Promotes the Induction of Ultraviolet Light B Induced Lupus Like Disease in Autoimmune Prone NOD Mice. Mehran Ghoreishi and Jan P. Dutz, Univ of BC, Vancouver, BC

Purpose: The role of environmental precipitants in autoimmunity such as systemic lupus erythematosus (SLE) remains unclear. We wished to determine whether ultraviolet light B (UVB) alone or in the presence of topical TLR7 stimulation would induce lupus-like disease in an autoimmune prone mouse model. Further we wished to determine whether anti-malarial therapy could prevent the skin mediated induction of lupus autoimmunity.

Method: We studied non obese diabetic (NOD) mice, a strain known to have a defect in apoptotic cell clearance and prone to autoimmunity. 6 week old female NOD mice received weekly 5000 j/m^2 UVB radiation with or without 25 μg topical imiquimod. MYD88-/- NOD mice and TLR9 -/- NOD mice were also treated with combination therapy. Sera were collected bi-weekly for detection of anti-nuclear antibodies (ANA) using HEP cells, desmoglein 3 (skin –specific) antibodies by ELISA, blood sugar determination and detection of pro-inflammatory cytokines by cytokine bead array. Treatment was continued until mice were 24 weeks of age. Skin and kidney were then harvested for immunohistochemical and immunofluorescence analysis. Blood was collected for cell surface or intra-cellular staining using flow cytometry

(FACS). Apoptotic cells in the skin were detected using TUNEL assay and IgG deposition in the kidneys was detected by direct immunofluorescence. Immunohistochemical studies were conducted to determine the expression of IFNαinducible gene, myxovirus A (MxA), and high mobility group box 1 (HMGB1) in skin. PAS staining of kidney identified the presence of glomerulosclerois.

Result: UVB exposure but not imiquimod increased apoptotic cells in the skin. Either UVB or imiquimod treatment induced ANA in NOD mice. Combined UVB and imiquimod (UV+Imiq) induced high titers of ANA and Dsg3 Ab. UV+Imiq enhanced MXA expression and HMGB1 expression in the skin. Combined but not single agent therapy induced elevated serum IL-6, TNFα, IFNγ and MCP-1. This treatment resulted in glomerulosclerosis and immune complex depositions in glomeruli. UV+Imiq therapy up-regulated TLR-7 expression on circulating B cells and TLR-7 and IFNα expression in peripheral blood plasmacytoid DCs. These effects were not detectable in MyD88-/- NOD mice. TLR9-/- NOD mice treated with UV+Imiq showed enhanced serum ANA, TNFα, IL-6 and IFNα compared to NOD mice. Conversely, addition of TLR-9 agonist CPG to UVB therapy decreased auto-antibody production in NOD mice. Chloroquine (an inhibitor of endosomal TLR-7 and TLR-9) prevented UV mediated auto-antibody production in NOD mice.

Conclusion: UVB and skin application of TLR7 agonist induce lupus-like autoimmunity in NOD mice and the combination of UVB and TLR7 activation is synergistic in this effect. The skin may thus be a site for the initiation of systemic lupus like disease. Anti-malarial therapy prevents the development of UVB induced autoimmunity in this model.

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TLR7-Dependent Accelerated Development of Systemic Lupus Erythematosus in TLR9-Deficient Lupus-Prone Mice. Marie-Laure Santiago-Raber[1], Isabelle Dunand-Sauthier[1], Tianfu Wu[2], Chandra Mohan[2], Brian L. Kotzin[3] and Shozo Izui[4], [1]Medical School, Geneva, Switzerland, [2]Univ of Texas SW Med Ctr, Dallas, TX, [3]University of Colorado Health Sciences Center, Denver, CO, [4]CMU, University of Geneva, Geneva, Switzerland

Purpose: SLE is a systemic autoimmune disorder characterized by the formation of various autoantibodies and subsequent development of immune complex glomerulonephritis. The pathogenesis of SLE is a complex process, in which MHC-linked and multiple non-MHC-linked genetic factors contribute to the overall susceptibility of the disease. More recently, the possible roles of TLR7 and TLR9 in the development of anti-nuclear autoantibodies, because of their respective recognition of RNA and DNA, has been suggested.

Method: To better define the respective contributions of TLR7 and TLR9 to the development of SLE, we introduced the TLR7 or/and TLR9 null mutation into C57BL/6 mice congenic for *Nba2 (NZB autoimmunity 2)* locus (B6.Nba2) and followed the development of SLE (autoantibody production and mortality due to glomerulonephritis).

Results: B6.Nba2.TLR9$^{-/-}$ female mice displayed a markedly accelerated development of SLE (54% mortality at 9 months of age vs. none at 14 months in B6.Nba2 females). This acceleration was associated with an increased production of autoantibodies against nuclear antigens (DNA, histones and ribonucleoproteins, but not chromatin), serum retroviral gp70 and glomerular matrix antigens. Strikingly, the expression of TLR7 was up-regulated in B cells and plasmacytoid dendritic cells in these mice. In a marked contrast, the development of SLE in B6.Nba2.TLR9$^{-/-}$ females was completely prevented by the presence of TLR7 null mutation. No mortality due to GN was observed by 14 months of age, and serum levels of autoantibodies including anti-chromatin autoantibodies were comparable or even lower than those of B6.Nba2 female mice.

Conclusion: Our results indicate that TLR7 played a critical role in a wide variety of autoimmune responses against nuclear, retroviral and glomerular matrix antigens, while TLR9 was only involved in the development of anti-chromatin autoantibodies, and that the accelerated development of SLE in TLR9-deficient mice was due to an enhanced TLR7-dependant B cell and plasmacytoid dendritic cell activation.

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Role of Toll-Like Receptor-4 for the Pathogenesis of Lupus-Like Autoimmune Diseases. Takehito Imado[1], Tsuyoshi Iwasaki[2], Sachie Kitano[1], Atsushi Satake[1] and Hajime Sano[1], [1]Hyogo College of Medicine, Nishinomiya, Japan, [2]Hyogo University of Health Sciences, Kobe, Japan

Purpose: Pathogenic T cells that recognize self-antigens and drive B cell hyperactivity play a central role in the pathogenesis of both human and murine lupus. Injection of parental C57/BL6 (B6) (H-2^b) spleen cells into (B6 x Balb/c)F1 (CBF1) (H-$2^{b/d}$) mice resulted in acute immune suppressive disease associated with the replacement of the CBF1 spleen cells with B6 spleen cells. Activated parental B6 $CD8^+$ T cells and Th1 cytokines predominate in this reaction, while this acute disease resolved and parental B6 $CD4^+$ T cells initiate Th2 cytokine profile, inducing detectable autoantibodies to DNA and extractable nuclear Ags, lupus-like nephritis, exhibiting autoimmune disorders that resemble human systemic lupus erythematosus (SLE) (J Immunol 165;2000). Toll-like receptor (TLR)-4 is the receptor for the gram-negative bacterial cell wall component LPS. Unchecked TLR-4 activation might result in autoimmune diseases. The present study we investigated the role of TLR-4 on parental $CD4^+$ T cells for the induction of lupus-like nephritis using this lupus model.

Method: Lupus-like nephritis was induced by the injection of spleen cells from either B6 or C57BL10/ScNB10 (B10/ScNCr) which lacks TLR-4 into CBF1 mice. Proteinuria was assessed semiquantitatively using urine dip sticks. Histopathological examinations were performed using renal tissues stained with hematoxylin and eosin. The numbers of $CD4^+$ T cells and B cells were examined by flow cytometry. Anti-DNA antibodies were examined by ELISA. Cytokine mRNA expressions were examined RT-PCR analysis.

Results: CBF1 mice injected by spleen cells from TLR-4 intact B6 mice developed proteinuria and histopathological changes representing lupus nephritis. In contrast, CBF1 mice injected with spleen cells from B10/ScNCr mice lacking TLR-4 developed less proteinuria and histopathological changes. The numbers of $CD4^+$ T cells and $B220^+$ B cells were significantly increased in the spleen from CBF1 mice injected by B6 spleen cells, while these changes were not significant in CBF1 mice injected by spleen cells from B10ScNCr mice. Serum levels of anti-DNA antibodies and IL-4 mRNA expression in the spleen and kidneys was significantly increased in CBF1 mice injected with B6 spleen cells, while these changes were not significant in CBF1 mice injected with spleen cells from B10ScNCr mice.

Conclusion: These results indicate that TLR-4 is crucial for induction of $CD4^+$ T cells that drive B cell hyperactivity in SLE.

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Gender Dependency of Neuropsychiatric Manifestations in Lupus Mice. Hua-xin Gao, Elena Sanders and Chaim Putterman, Albert Einstein College of Medicine, Bronx, NY

Purpose: Neuropsychiatric lupus (NPSLE), is present in more than 70% of SLE patients, and is sometimes evident even before lupus diagnosis. Depression or anxiety are among the most common NPSLE manifestations. While the mechanism is still not known, autoimmunity has been suggested as a primary cause. Previously, we demonstrated that depression is an early neuropsychiatric manifestation as compared to MRL controls. While it is known that certain lupus manifestations (such as nephritis) develop much earlier and are more severe in female MRL/lpr mice than in males, the difference in the development of NPSLE between female and male MRL/lpr mice has not been compared directly. Our objectives were 1) To systemically compare the development of NPSLE in lupus-prone MRL/lpr females and males over time; 2) To further investigate the relation between autoantibody levels and the development of NPSLE.

Methods: Urine protein and serum were obtained serially during the course of the study, from 4 to 21 weeks of age. Circulating autoantibody titers were assessed by ELISA. A battery of behavior tasks, including open field, visual and spatial memory, balance beam crossing, social preference, forced swim, and elevated plus maze tests, were performed on male and female 5 and 18 week old MRL/lpr mice, and age- and gender-matched MRL/+ controls. Two-way repeated measurement ANOVA was used for the statistical analysis.

Results: Compared to control MRL/+ females (n=3), MRL/lpr female mice (n=6) exhibited significant depression-like behavior in the forced swim test as early as 5 weeks of age ($p<0.05$), when they already demonstrate elevated levels of autoantibodies not previously present. In contrast, 5 week old male MRL/lpr mice (n=6), with normal autoantibody titers, performed similarly to controls (n=3). Depressive behavior was noted only at 18 weeks of age in male MRL/lpr mice, when the autoantibody titers were dramatically higher than male MRL/+ controls ($p<0.05$). At 5 weeks of age there was a significant correlation of depression with elevated levels of anti-cardiolipin and anti-NMDAR antibodies ($p<0.05$), while at 21 weeks depression correlated with elevated anti-dsDNA, anti-cardiolipin, anti-chromatin, and anti-NMDAR antibody titers ($p<0.05$).

Both male and female MRL/lpr mice explored more actively than MRL controls in the elevated plus maze test, indicating, paradoxically, less anxiety. In addition, 18 week old female MRL/lpr mice, but not males, showed a trend toward social withdrawal. Both female and male MRL/lpr mice had normal visual and spatial memory as well as locomotor activity and coordination.

Conclusion: With more severe lupus, female MRL/lpr mice developed CNS dysfunction with depression-like behavior earlier than male MRL/lpr mice, correlating with autoantibody levels. Emotional deficits develop in MRL/lpr female mice with a subtle increase in autoantibody titers already at 5 weeks of age, a time point usually considered to be disease-free. Our results provide further support to a primary role for anti-nuclear and other autoantibodies in the pathogenesis of early neuropsychiatric deficits in this lupus model.

Disclosure: H. X. Gao, None; **E. Sanders**, None; **C. Putterman**, None.

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Epistatic Suppression of Fatal Autoimmunity in New Zealand Black Bicongenic Mice. Christina Loh[1], Yui Ho Cheung[1], Evelyn Pau[1], Carolina Landolt-Marticorena[2], Ginette Lajoie[3] and J. E. Wither[4], [1]University of Toronto, Toronto, ON, [2]University Health Network, Toronto, ON, [3]Department of Pathology, William Osler Health Centre,, Brampton, ON, [4]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: We have previously introgressed NZB chromosomal intervals containing lupus susceptibility genes onto the B6 background and shown that: NZB chromosome 1 congenic mice (denoted, B6.NZBc1(70-100cM)) developed fatal autoimmune-mediated kidney disease and NZB chromosome 4 congenic mice (denoted, B6.NZBc4(8-79cM)) exhibited a marked expansion of immunoregulatory NKT cells in the absence of autoimmunity. In this study, we sought to determine the impact of interactions between these two loci on the development of lupus autoimmunity.

Methods: Bicongenic mice (B6.NZBc1(70-100cM).c4(8-79cM)) were generated by intercrossing B6.NZBc1(70-100cM) with B6.NZBc4(8-79cM) mice and using polymorphic marker assisted breeding to produce mice homozygous for both intervals. B6, parental congenic and bicongenic mice were aged to 4 and 8 mo old. Cellular profiles were assessed by flow cytometry and serum autoantibody (Ab) production was measured by ELISA. Kidney sections were stained by PAS or with FITC anti-mouse IgG $F(ab')_2$ and graded by a renal pathologist (G.L.) that was blinded to the strain of origin.

Results: At 8 mo age, bicongenic mice demonstrated significantly decreased mortality as compared to the B6.NZBc1(70-100cM) mouse strain ($p = 0.0156$). Comparison of kidney pathology in 8 mo old B6, surviving B6.NZBc1(70-100cM), and bicongenic mice revealed equivalent IgG deposition in B6.NZBc1(70-100cM) and bicongenic mice, however the severity of glomerulonephritis (GN) was attenuated. The majority of surviving B6.NZBc1(70-100cM) kidneys displayed diffuse (endocapillary) proliferative GN, whereas bicongenic kidneys primarily demonstrated mesangial expansion and/or proliferation. Serologic analysis revealed that bicongenic mice made IgM and IgG anti-chromatin and –ssDNA Ab, but failed to produce IgG anti-dsDNA Ab ($p = 0.0016$), which was closely associated with renal failure in the parental B6.NZBc1(70-100cM) strain. Furthermore, bicongenic mice produced predominantly IgG1 anti-ssDNA Ab, whereas both IgG1 and IgG2a anti-ssDNA Ab were observed in B6.NZBc1(70-100cM) mice. A reduced proportion of NKT cells was seen in bicongenic mice, as compared to B6.NZBc4(8-79) mice, raising the possibility that chronic activation of this subset results in the switch to less pathogenic autoAb production.

Conclusion: Although a susceptibility locus has been mapped to NZB chromosome 4, this interval suppresses fatal autoimmunity driven by genetic polymorphism(s) located on NZB chromosome 1. Ongoing experiments are seeking to further characterize the role of NKT cells in this suppression.

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The Absence of Caspase-Activated Dnase Enhances the Production of Anti-Chromatin Antibodies in the Spontaneous Lupus Models Sle1 and Sle123. Neelakshi R. Jog, Lorenza Frisoni, Qin Shi and Roberto Caricchio, Temple University, Philadelphia, PA

Purpose: Apoptotic cell death has been proposed as the source of autoantigens in SLE. Using pristane induced lupus model, we previously showed that absence of Caspase-Activated DNase (CAD) interferes with apoptotic cellular modifications and prevents the generation of autoantibodies (autoAbs), though CAD-/- have a normal immune system.

Methods: To analyze the role of CAD in the spontaneous generation of lupus Abs, we backcrossed CAD-/- mice onto B6.Sle1 and B6.Sle123 background. The B6.Sle1 model is characterized by loss of tolerance to chromatin, while the B6.Sle123 strain displays high titers of anti-chromatin, anti-dsDNA Abs and proliferative glomerulonephritis.

Results: We found that B and T cell maturation in Sle1 and Sle1.CAD-/- mice was similar to B6 and B6.CAD-/- mice, but both Sle1.CAD-/- and Sle123.CAD-/- mice had significantly higher levels of anti-chromatin Abs when compared to their control CAD sufficient lupus-prone strains. The difference was apparent as early as 5 months of age and was stronger in Sle1.CAD-/- mice. The increase was specific for anti-chromatin and not for anti-dsDNA Abs. We also found that CAD-/- and CAD+/+ mice reconstituted with Sle123 bone marrow showed similar levels of anti-chromatin Abs suggesting that the absence of CAD was relevant only in the immune competent cells.

We then investigated whether the increase of autoAbs affected nephritis development. Sle123.CAD-/- mice had higher immune deposition than Sle123 mice, suggesting that absence of CAD accelerated renal disease in Sle123 mice. However, the absence of CAD did not induce immune complex deposition in Sle1, confirming that in this model anti-chromatin Abs are not nephritogenic.

The absence of CAD profoundly alters the nuclear and cytoplasmic morphological modifications during apoptotic cell death. We therefore asked whether the absence of CAD altered the ability of sera from autoimmune mice to bind apoptotic cells. AutoAbs from both Sle1 and Sle1.CAD-/- mice bound higher number of apoptotic cells from CAD-/- mice compared to apoptotic cells from CAD+/+ mice. Similarly, sera from old MRL/lpr mice, but not B6 mice, stained higher number of apoptotic CAD-/- cells. Thus lupus autoAbs bound more to CAD-/- than CAD+/+ apoptotic cells.

Conclusion: Our data suggest that in lupus prone mice the absence of CAD during B cell development increases the escape of auto-reactive B cells. Moreover better opsonization of CAD-/- apoptotic cells by autoAbs may result in more efficient uptake and presentation of nuclear antigen, which further activates peripheral autoreactive B cells to differentiate into plasma cells. In conclusion, the absence of CAD is an excellent system to investigate systemic autoreactivity in the absence of nuclear Ags' modification during apoptosis. Studies are underway in our lab to determine at which stage of maturation autoreactive B cells need to be exposed to apoptotic autoAgs to be either deleted or rendered anergic.

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Narrowing Down Lupus Susceptibility Loci On Chromosome 13: Impaired Clearance of Apoptotic Debris. Evelyn Pau[1], Christina Loh[1], Nan-Hua Chang[2] and Joan E. Wither[2], [1]University of Toronto, Toronto, ON, [2]University Health Network, Toronto, ON

Purpose: Previously, we showed that introgression of a lupus-prone New Zealand Black (NZB) chromosome 13 interval onto a lupus-resistant C57BL/6 (B6) genetic background (B6.NZBc13) recapitulated many of the NZB autoimmune and cellular activation phenotypes. In addition, B6.NZBc13 mice have increased production of antibodies against chromatin and Sm/RNP together with expansion of various dendritic cell subsets, features typically seen in mice with defective engulfment or altered responses to apoptotic debris. We therefore investigated whether these mice have impaired clearance of apoptotic debris.

Method: To localize the genetic polymorphisms that drive the abnormal phenotypes in B6.NZBc13 mice with the full 29-73cM NZB interval, subcongenic mouse strains (c13(29-51cM), c13(38-73cM) and c13(45-73cM)) were generated. Uptake of apoptotic debris was examined in vivo by injecting CMTMR-labeled apoptotic thymocytes intraperitoneally into 8-12 wk old B6 and congenic mice. Peritoneal exudate cells were isolated 15-60 min post-injection and the proportion of peritoneal macrophages (PMΦ) that had engulfed apoptotic debris was assessed by flow cytometry. To examine clearance of apoptotic debris in germinal centers (GCs), the amount of apoptotic debris associated with tingible-body macrophages (TBMΦ) was quantified by immunofluorescent staining of splenic sections from 6 mo old mice. The splenic cellular profile was also examined by flow cytometry.

Results: Uptake of apoptotic debris by PMΦ was impaired in c13(45-73cM) subcongenic mice in vivo, resulting in a delay in the clearance of apoptotic bodies in the peritoneum compared to control B6 mice. Examination of splenic sections showed large and intact TUNEL+ apoptotic bodies as well as increased numbers of these bodies associated with TBMΦ in GCs of B6.NZBc13 and c13(45-73cM) subcongenic

mice, suggesting a failure to efficiently engulf apoptotic debris. Similar numbers of TBMΦ per GC was observed across all strains, indicating that these differences did not arise from differences in the number of TBMΦ between the mouse strains. Similar to mice with clearance defects in their GCs (Mfge8-/- mice), B6.NZBc13 and c13(45-73cM) mice had an increase in GC size as compared to B6 mice. This was accompanied by a marked increased in the proportion of GC B cells compared to B6 mice.

Conclusion: The results suggest that one of the genetic polymorphisms in B6.NZBc13 mice promotes autoimmunity by impairing clearance of apoptotic debris. Phenotypic profiles from subcongenic mice suggest that the apoptotic debris clearance deficiency maps to the distal interval (51-73cM). Future studies will continue to identify the nature of the clearance defect and potential candidate genes located in this interval.

Disclosure: E. Pau, None; **C. Loh**, None; **N. H. Chang**, None; **J. E. Wither**, None.

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Sle2c1 Sublocus Synergizes with Lpr Mutation in Contributing to Lupus Development. Zhiwei Xu and Laurence Morel, University of Florida, Gainesville, FL

Purpose: The function of the *Sle2* mouse lupus susceptibility locus and its derived *Sle2c1*sublocus have been previously shown to be associated with a lower threshold of activation of the B cell receptor leading to an accumulation of B1a cells in NZM2410 model. To explore whether these loci had any effects on other immune components, we introduced *lpr* as an amplifier into B6.Sle2 and its subcongenic strains, and analyzed systemically their cellular and functional phenotypes.

Methods: Homozygous B6.Sle2.lpr and *lpr*-carrying subcongenic strains were constituted for this experiment. At age of 4-6 months, both male and female mice were sacrificed, then the size of spleen and lymph nodes was examined and the lymphocyte phenotypes were analyzed systemically. Meanwhile, the infiltrated cell components in kidney were detected by flow cytometry and nephritic pathology scores evaluated. In addition, the IL-2 production in vitro by the activated $CD4^+$ T cells from 2 month-old mice was tested with ELISA method.

Results: It was found that the co-expression of *Sle2* and *lpr* on a C57BL/6 background markedly increased weight of peripheral lymph organs compared with B6.lpr mice, but lymph nodes show more significantly than spleen in augmentation fold. The peripheral lymph organs of B6.Sle2.lpr mice have more T cells, B cells and $CD3^+B220^+CD5^+$ cells than B6.lpr mice. Controversially, B6.Sle2.lpr mice demonstrated significantly decreased $CD4^+Fop3^+$ Treg cells in spleen and lymph nodes in comparison with B6.lpr mice. On other hand, the B6.Sle2.lpr mice had more T cells and macrophages accumulation rather than B cells in kidney, and demonstrated more serious nephritis and a shorter longevity than B6.lpr mice. By comparing the effect of *lpr* mutation on shorter *Sle2a*, *Sle2b* and *Sle2c1* subloci derived from the Sle2 locus, it was discovered that only the B6.Sle2c1.lpr mice had the same pathology changes as the B6.Sle2.lpr mice, which mapped the synergistic interaction with *lpr to Sle2c*1 sublocus. Furthermore, $CD4^+$ T cells from B6.Sle2c1.lpr mice produced less IL-2 than the B6.lpr $CD4^+$ T cells.

Conclusion: With the exception of regulating B cell receptor activation threshold, the *Sle2c1* locus has a potential of decreasing IL-2 production and breaking Treg cell balance, promoting T cell expansion and aggravating lupus development. It needs to be clarified whether there is an intrinsic interrelation of these newly-identified phenotypes of the *Sle2c1* sublocus.

Disclosure: Z. Xu, None; **L. Morel**, None.

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Induction of Antigen-Specific Tolerance by DNA Vaccination Using Sm Autoantigen Combined with IL-10 in a Murine Model of Lupus. Beatriz T. Martín Márquez[1], Minoru Satoh[2], Erika A. Martínez García[1], Jose F. Muñoz Valle[1], Víctor E. Arana Argaez[1], Rogelio Hernandez Pando[3] and Monica Vazquez Del Mercado Espinosa[4], [1]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Guadalajara, Mexico, [2]Dept. of Medicine, Univ. of Florida, Gainesville, FL, [3]Instituto Nacional de las Ciencias Médicas y Nutrición Salvador Zubirán, México D.F., Mexico, [4]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Hospital Civil Juan I. Menchaca, Guadalajara, Mexico

Purpose: Anti-Sm antibodies are specific for systemic lupus erythematosus (SLE) and considered pathognomonic. The mechanisms that regulate anti-Sm antibody production are poorly understood; however, a critical role of TH1 cytokines has been suggested. Thus, induction of antigen-specific tolerance by DNA vaccination of the Sm antigen with immunoregulatory cytokine IL-10 could be a novel approach to control autoantibody production and tissue damage. Induction of antigen-specific tolerance was evaluated by immunization with DNA encoding Sm antigens in combination with IL-10 in pristane-induced murine model of lupus.

Method: DNA vaccines of Sm D1, D2, B´/B, B´/B COOH, IFN-gamma and IL-10 were prepared by direct cloning techniques and purified. Eight groups of 3 month-old female BALB/c mice (13/group) received intramuscular injections of 100 microgram of cocktail mixture of pcDNA™3.1D/V5-His-TOPO® encoding D1, D2, B´/B or B´/B COOH plus IFN-gamma or IL-10 at day 2 and 9. At day 16, mice received an intraperitoneal injection of pristane to induce experimental lupus. Serum samples were collected at day 0 and monthly thereafter. Serum autoantibodies were tested by ELISA (anti-dsDNA, chromatin, U1RNP/Sm, Su/Ago2, ribosomal P peptide) and immunoprecipitation using ^{35}S-methionine labeled K562 cell extract. IgG subclass levels were measured by ELISA. Proteinuria was assessed monthly using Multistix®. Kidney pathology and immune complex deposition were examined at 6 months.

Results: The levels of anti-U1RNP/Sm antibodies in IL-10-Sm D2 vaccinated group were lower than those of IFN-gamma -Sm D2 vaccinated group (P = 0.026 by Mann-Whitney), consistent with the IFN-gamma dependence of anti-U1RNP/Sm autoantibody production as reported. However, the prevalence and levels of other autoantibodies were not different in this pair, indicating an antigen-specific process induced by the vaccination. IgG2a levels in IFN-gamma vaccinated group appeared to be higher than those in IL-10 vaccinated group with the same Sm antigen vaccination, consistent with the IFN-gamma overexpression. Significant proteinuria (> 1.5+) was less common in IL-10 vaccinated group vs. IFN-gamma vaccinated group for the same Sm antigen (Sm D1, 15% vs 42%; Sm D2, 31% vs 54%; B'/B 46% vs 42%; B'/B-COOH, 23% vs 100%, P = 0.0001). These data suggest possible beneficial role of IL-10 in preventing immune complex glomerulonephritis.

Conclusion: DNA vaccination using lupus autoantigens and IL-10 may have a potential as a novel therapy to induce antigen specific tolerance and prevention of kidney damage in experimental lupus.

Disclosure: B. T. Martín Márquez, None; **M. Satoh**, None; **E. A. Martínez García**, None; **J. F. Muñoz Valle**, None; **V. E. Arana Argaez**, None; **R. Hernandez Pando**, None; **M. Vazquez Del Mercado Espinosa**, None.

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Allogenic Mesenchymal Stem Cell Transplantation Ameliorates Lupus Mice Via Inhibition of B-Cell Activating Factor (BAFF).

Lingyun Sun[1], Xiaolei Ma[1], Huayong Zhang[1], Zhifeng Gu[1], Richard M. Silver[2] and GS Gilkeson[2], [1]the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Medical University of South Carolina, Charleston, SC

Purpose: B cells play an important role in the pathogenesis of SLE. B-cell activating factor (BAFF) is a member of the TNF superfamily that regulates B-cell survival and autoreactivity. Recent evidence indicates that bone marrow-derived mesenchymal stem cells (BM-MSCs) possess immunosuppressive properties both in vitro and in vivo. We previously demonstrated that transplantation of human MSCs can significantly improve the autoimmune disorders in MRL/lpr mice. This study investigates whether effect and mechanism of murine BM-MSCs transplantation for MRL/lpr mice occurs by inhibiting B cell activation and BAFF expression.

Method: 18-week-old MRL/lpr mice were treated with BM-MSCs derived from BALB/C or saline. The disease-free BALB/C mice were used as negative control. Mice were monitored for 24h proteinuria. Sera were tested for levels of anti-double-stranded DNA (ds-DNA) antibodies, BAFF , IFN-γ, IL-2, IL-4, IL-10 and TGF-β. Mice were sacrificed at 26 weeks of age, and kidneys were subjected to histologic examination. The percentage and number of marginal zone (MZ), T1 and T2 B cells in spleen were detected by flow cytometry.

Results: MSCT prevented disease onset and significantly prolonged survival. The treated mice had significantly less renal damage. Eight weeks after transplantation, the levels of BAFF in serum in treated group decreased significantly than in placebo as well as the levels of serum IFN-γ and IL-10, while the levels of serum TGF-β were increased. Treated mice had significantly smaller spleens than control animals, with fewer MZ, T1, T2 and activated B cells.

Conclusion: Our findings suggest that MSCT can inhibit the excessive activation of B cells in MRL/lpr mice, including T1, T2 and MZ B cells. BAFF production was reduced in MSCs-treated mice in association with the diminished production of anti-dsDNA autoantibodies,

proteinuria, IFN-γ and IL-10. Thus, down-regulation of BAFF may play an important role in the mechanism of action by which MSCT ameliorates lupus progression.

Disclosure: L. Sun, None; **X. Ma**, None; **H. Zhang**, None; **Z. Gu**, None; **R. M. Silver**, None; **G. Gilkeson**, None.

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Targeted Inhibition of the Alternative Pathway Ameliorates Progression of Renal Disease in Murine Models of Systemic Lupus Erythematosus. Hideharu Sekine[1], Ting Ting Hsieh Kinser[1], Efrain Martinez[1], Fei Qiao[1], Phil Ruiz[2], GS Gilkeson[1] and Stephen Tomlinson[1], [1]Medical University of South Carolina, Charleston, SC, [2]University of Miami, Miami, FL

Purpose: The complement system appears to play a dual role in the progression of lupus; serving a beneficial role in enhancing the clearance of immune complexes (ICs) and apoptotic cells, while serving a pathogenic role in inducing local inflammation and injury. The alternative pathway has been identified as playing a key role in renal injury, while the classical pathway is known to have an important contributory role in IC clearance. At ACR 2008, we reported on a preliminary study using the alternative pathway specific inhibitor, CR2-fH, for treatment of renal disease in lupus-prone MRL/lpr mice. The data suggested that CR2-fH significantly ameliorated renal disease and, unexpectedly, reduced serum autoAb levels. Here, we report on an expanded study in MRL/lpr mice, and also compared the effects of CR2-fH with CR2-Crry (inhibits all complement pathways) and sCR2 (targeting vehicle only). We also report on the characterization of CR2-fH in female NZB/W F1 mice that spontaneously develop lupus-like nephritis.

Method: Groups of 8 MRL/lpr mice or 10 NZB/W F1 mice (all females) were injected with 0.4mg of CR2-fH protein i.v. twice a week for 8 wks starting from week 15 or 23, respectively (after development of proteinuria/renal disease). Groups were also treated with CR2-Crry (0.25 mg), CR2 alone (0.18 mg) or with saline biweekly. Sera and urine were collected every two weeks, and kidneys were collected for histological evaluation at 23 wks or 32 wks. Levels of serum anti-dsDNA Ab, circulating ICs and urinary albumin excretion were analyzed by ELISA.

Results: CR2-fH and CR2-Crry treatment of MRL/lpr mice resulted in improved survival and significant reductions in albuminuria, glomerular C3 deposition and circulating ICs. Similarly, CR2-fH and CR2-Crry treatment of NZB/W F1 mice resulted in improved survival and reduced glomerular C3 deposition. However, a significant reduction in proteinuria was only seen in the CR2-fH treated group. CR2-fH treatment of MRL/lpr mice, but not CR2-Crry, also resulted in significantly reduced glomerulonephritis and serum anti-dsDNA Abs. Of interest, mice treated with sCR2 alone also showed significantly reduced glomerular C3 deposition, anti-dsDNA antibodies and circulating ICs, although there was no significant reduction in glomerulonephritis or proteinuria, and there was no survival benefit.

Conclusion: These data indicate that targeted inhibition of the alternative complement pathway is an effective treatment for murine lupus, and is more effective than blocking all three complement pathways. In addition to the potential benefit of avoiding systemic complement inhibition by a targeted approach, the data indicate benefits to leaving the classical/lectin pathways intact. The data also indicate that the sCR2 targeting vehicle contributes to therapeutic activity, possibly via modulation of autoimmunity, although it does not reduce organ inflammation.

Disclosure: H. Sekine, None; **T. T. Hsieh Kinser**, None; **E. Martinez**, None; **F. Qiao**, None; **P. Ruiz**, None; **G. Gilkeson**, Taligen Therapeutics, 5 ; **S. Tomlinson**, Taligen Therapeutics, 5 .

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Amelioration of Lupus Nephritis with Dendritic Cells Using a NF-KappaB Decoy and Histone H3 Peptide in NZB/W F1 Mice. Hitoshi Hasegawa, Atsushi Inoue, Masashi Kohno, Takuya Matsumoto and Masaki Yasukawa, Ehime University Graduate School of Medicine, Toon, Japan

Purpose: The expression of costimulatory molecules on antigen-presenting cells is crucial in determining T-cell immune response and is regulated by nuclear transcriptional factor (NF)-kappa B. The peptide of core histone H3 contains T cell epitopes of NZB/W F1 mice. We investigate the effect of NF-kappaB decoy-treated dendritic cells (DCs) on the lupus nephritis in NZB/W F1 mice reducing the T cell response against Histone H3 peptide.

Method: DCs propagated from bone marrow cells of NZB/W F1 mice were used. Double-stranded NF-kappaB decoys were generated using equimolar amount of single-stranded sense and antisense phosphorothioate-modified ODN containing NF-kappaB binding sites and were added at the initiation of DC culture of mice. Female 10-week-old NZB/W F1 mice were treated with DCs pulsed with Histone H3 peptide, three times. Phenotypical expression of DC was analysed by flowcytometry. Immune stimulatory activity of DCs was examined in T cell proliferation assay. Proteinuria concentration of NZB/W F1 mice was measured weekly to monitor the development of nephritis. Serum levels of anti-DNA antibodies were measured by ELISA. For assessment of lupus nephritis, NZB/W F1 mice were sacrified at 28 weeks of age and evaluated histologically.

Results: NF-kappaB decoys suppressed suface expression of costimulatory molecules, including CD80, CD86 and CD40 of DCs, but the expression of MHC was not affected. NF-kappaB decoy-treated DCs significantly suppressed allostimulatory activity and self-antigen specific T-cell proliferative responce. Administration of NF-kappaB decoy-treated DCs reduced significantly proteinuria, anti-DNA antibodies of 28-week-old NZB/W F1 mice compared with control mice. The pathological change in the control mice included mesangial thickening and hypercellularity evolving into sclerosis. The nephritis score in the NF-kappaB decoy DCs-treated mice was significant lower than that in the control mice. This indicates that NF-kappaB DCs pulsed with Histone H3 peptide may suppress or delay renal inflammation in vivo.

Conclusion: NF-kappaB decoy-treated DCs may promote tolerance induction by reducing the antigen-specific autoimmune response and provide a therapeutic effect to lupus nephritis of NZB/W F1 mice. This strategy may be benefical for the treatment of human autoimmune diseases.

Disclosure: H. Hasegawa, None; **A. Inoue**, None; **M. Kohno**, None; **T. Matsumoto**, None; **M. Yasukawa**, None.

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Epigallocatechin-3-Gallate (EGCG) Attenuates Inflammation in MRL/Lpr Mouse Mesangial Cells. Abigail Peairs[1], Lu Gan[2], Liwu Li[2] and Christopher Reilly[1], [1]Virginia College of Osteopathic Medicine, Blacksburg, VA, [2]Virginia Tech, Blacksburg, VA

Background and Purpose: EGCG, a bioactive component of green tea, has been reported to exert anti-inflammatory effects though activation of the metabolic regulator, AMP-activated protein kinase (AMPK). Mesangial cells from MRL/lpr lupus-like mice are hyper-responsive to immune stimulation and overproduce nitric oxide (NO) and other inflammatory mediators when stimulated. In our current studies, we sought to determine the mechanism by which EGCG attenuates immune-induced expression of pro-inflammatory mediators.

Methods: Mesangial cells isolated from MRL/lpr mice were stimulated with LPS/IFN-γ following pretreatment with various concentrations of EGCG with or without various pharmacologic agents including AMPK inhibitors (AraA and 5'-iodotubercidin), the mTOR inhibitor Rapamycin, or the PI3K inhibitor LY294002. Cellular response was determined at various time points by flow cytometry, real-time RT-PCR, ELISA and Western blot.

Results: EGCG increased AMPK activation in a concentration dependent manner and attenuated LPS/IFN-γ induced inflammation (cellular iNOS expression, supernatant NO, and interleukin-6) in MRL/lpr mouse mesangial cells. Interestingly, EGCG attenuated inflammation in the presence of the AMPK inhibitors (AraA and 5'-iodotubercidin) indicating that the anti-inflammatory effects of EGCG are independent of AMPK. Furthermore, we found that EGCG effectively inhibited the immune stimulated PI3K/Akt/mTOR pathway independently of AMPK, by decreasing phosphorylation of Akt, suggesting a novel mechanism for EGCG mediated anti-inflammatory action.

Conclusion: Taken together, these studies show that EGCG attenuated inflammation in MRL/lpr mouse mesangial cells via the PI3K/Akt/mTOR pathway. Akt is a key signaling molecule in the innate immune response, and has been implicated in mesangial cell activation in lupus. Our findings suggest a potential therapeutic role for the use of EGCG to regulate inflammation and control autoimmune disease.

Disclosure: A. Peairs, None; **L. Gan**, None; **L. Li**, None; **C. Reilly**, None.

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Active Immunization with IFNα Kinoid® Induces Polyclonal Antibodies That Neutralize IFNα From Systemic Lupus Erythematosus Patients. Alexis Mathian[1], Zahir Amoura[1], Estelle Adam[2], Fabien Colaone[2], Marco F.M. Hoekman[3], Pierre Vandepapelière[2], Julien Haroche[1], Jean -Charles Piette[4], Pierre Lebon[5] and Géraldine Grouard-Vogel[2], [1]Pitié-Salpêtrière hospital, Paris, France, [2]NEOVACS SA, Paris, France, [3]Utrecht University, Utrecht, Netherlands, [4]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [5]Department of Virology, Saint-Vincent de Paul Hospital, Paris, France

Purpose: Passive administration of monoclonal antibodies (mAbs) has been shown to be effective for the treatment of autoimmune diseases such as rheumatoid arthritis, but its therapeutic use is limited by the immunogenicity of the antibodies. Additionally, several cytokines such as interferon-alpha (IFNα), the key cytokine implicated in systemic lupus erythematosus (SLE), have different subtypes, which make very difficult and unlikely their neutralization by a single mAb. The Kinoid® immunization process developed by Neovacs is a novel approach that targets cytokines by inducing natural polyclonal antibody response and circumvents the induction of the anti-mAbs response. Kinoids® are heterocomplexes made by conjugating the targeted cytokine to a carrier protein such as the keyhole limpet hemocyanin (KLH).

Method: In the current study, FVB human IFNα2b transgenic mice were immunized with IFNα2b Kinoid (IFN-K) formulated in ISA51 adjuvant (SEPPIC). Control mice were immunized with inactivated IFNα2b emulsified in ISA51. This inactivated IFNα2b control was manufactured the same way as IFN-K but in absence of KLH.

Results: Only mice immunized with IFN-K generated neutralizing antibodies against IFNα2b. Furthermore, these antibodies neutralized all the 13 human IFNα subtypes, as assessed by the compendial Madin Darby bovine kidney-vesicular stomatitis virus infection assay. When the assay was performed with sera from SLE patients as a source of IFNα, the protective IFNα activity was neutralized by these polyclonal antibodies. However, the antibodies induced by IFN-K immunization neutralize neither IFNβ nor IFNγ. *In vitro* stimulation with native human IFNα2b of splenocytes from IFN-K immunized mice did not induce a cellular response, whereas it did with IFN-K and KLH antigens.

Conclusion: Our study shows that in mice tolerant to human IFNα2b:
Active immunization with IFN-K induces polyclonal antibodies that specifically neutralize all subtypes of human IFNα,
Active immunization with IFN-K breaks B-cell but not T-cell tolerance to IFNα thus demonstrating the safety of the product,
Polyclonal antibodies produced by active immunization with IFN-K are able to neutralize human IFNα present in sera from SLE patients,
The IFNα2b-kinoid vaccine is a promising new therapeutic strategy for the treatment of SLE.

Disclosure: A. Mathian, None; **Z. Amoura**, None; **E. Adam**, Neovacs SA, 3 ; **F. Colaone**, Neovacs SA, 3 ; **M. F. M. Hoekman**, Neovacs SA, 5 ; **P. Vandepapelière**, Neovacs SA, 3 ; **J. Haroche**, None; **J. -. C. Piette**, None; **P. Lebon**, Neovacs SA, 5 ; **G. Grouard-Vogel**, Neovacs SA, 3 .

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Delayed Antigen-Specific Responses and Increased Disease Activity in MRL-Lpr Mice Following Influenza Infection. Judith A. James, Jourdan R. Anderson, Erica V. Edwards and Sherry R. Crowe, Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Influenza virus infections result in significant morbidity and mortality, especially in individuals with impaired immune systems, such as those with systemic lupus erythematosus. It is unclear, however, whether this increased morbidity is due to intrinsic immune defects or immunosuppressive therapy. To address this question, we utilized the MRL-*lpr* mouse model and examined viral susceptibility, antigen-specific responses, and autoimmune disease activity following intranasal influenza infection.

Method: MRL and MRL-*lpr* mice were inoculated with saline or a sub-lethal dose of a mouse adapted influenza virus at 10 weeks of age. Mice were monitored for two weeks post-infection and morbidity and mortality were recorded. Viral titers from lung were determined by a standard egg assay. To assess the antigen-specific response, intracellular cytokine staining and antigen-specific ELISAs were performed. H&E staining was used to monitor organ pathology and flow cytometry and immunohistochemistry was used to characterize cellular infiltrates. Finally, pre- and post-infection serum autoantibody levels were monitored by ELISAs.

Results: MRL-*lpr* mice had increased morbidity ($p = <0.001$), as measured by weight loss, as compared to MRL. Additionally, MRL-*lpr* mice had significantly increased cellular infiltrates in the lungs ($p = 0.05$). These signs of increased susceptibility were not due to increased viral replication, as there were no differences in viral titers or viral clearance between the strains. MRL-*lpr* mice did mount different T cell cytokine responses compared to MRL. MRL-*lpr* mice made significantly less TNFa and more IFNg both pre- and post- infection ($p < 0.001$). Both groups of mice had high levels of anti-influenza antibodies, but the MRL-*lpr* mice had significantly less antigen-specific antibodies at each time-point ($p < 0.05$). MRL-*lpr* mice also had decreased numbers of influenza-specific $CD8^+$ T cells at the peak of the

immune response ($p < 0.05$). Interestingly, influenza infection of MRL-*lpr* mice also resulted in significant peri-vascular cellular infiltrates in the kidneys ($p < 0.05$), composed primarily of $CD4^+$ T cells. MRL-*lpr* mice also showed a transient but significant increase in the concentration of anti-cardiolipin antibodies ($p = 0.05$) after infection, but no changes in other autoimmune specificities studied.

Conclusion: Lupus-prone mice had increased susceptibility and pathology following influenza infection. Additionally, these mice had decreased antigen-specific humoral and cellular immunity and increased autoimmune disease activity. This model will provide a unique system to dissect the immune-pathogen interaction in an autoimmune disease setting. These data will also provide valuable information on how autoimmunity impacts the immune response to influenza.

Disclosure: J. A. James, None; **J. R. Anderson**, None; **E. V. Edwards**, None; **S. R. Crowe**, None.

ACR/ARHP Poster Session B

Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Pathogenesis, Animal Models and Genetics I

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Fibrocyte Recruitment and Myofibroblast Differentiation After Acute Lung Injury Is Blocked by Selective Inhibition of TGFbeta Signalling in Resident Pulmonary Fibroblasts. Korsa Khan, Rachel Hoyles, Emma Derrett-Smith, Xu Shiwen, David Abraham and Christopher P. Denton, UCL Medical School, London, United Kingdom

Purpose: TGFbeta overactivity is implicated in the development of lung fibrosis and may be a potential therapeutic target in fibrotic disease such as scleroderma (SSc). We have used post-natal deletion of the high affinity type II TGFbeta receptor (TbetaRII) in fibroblasts to test the role of TGFbeta signalling in resident lung fibroblasts in the fibrotic response to lung injury.

Methods: TbetaRII was deleted using a compound Cre-Lox genetic strategy with post-natal administration of tamoxifen over 5 days to activate Cre-recombinase in mice harbouring a conditional allele of TbetaRII to delete the receptor from fibroblasts exclusively. Illumina microarray gene profiling was used to confirm anergy to TGFbeta (2ng/ml) in explanted lung fibroblasts. A bleomycin lung injury model was used to induce lung fibrosis. Multichannel immunofluorescence was used to define the cell populations after lung injury at 7 and 14 days on tissue sections and fibrocytes were defined by co-expression of CD34, Col1 (Collagen I) and alphaSMA. Myofibroblasts were identified by co-expression of Col1 and alphaSMA.

Results: There was almost complete attenuation of lung fibrosis in mice treated with intratracheal bleomycin (Null-B) after deletion of TbetaRII in resident fibroblasts. At 7 days after injury there was evidence of epithelial mesenchymal transdifferentiation (EMT) but the number of fibrocytes and myofibroblasts was substantially reduced. Using high power field counts (hpf) the number of fibrocytes in Null-B lungs at 7 days was decreased compared wildtype littermate controls (WT-B;3.6±2.22 cells/hpf, 26.6±4.96 cells/hpf p=0.007 respectively). At 14 days this reduction was sustained (8.6±2.06 cells/hpf compared with 46.6±4.947 cells /hpf p=0.0007). Furthermore, myofibroblast expression was reduced in 7 day Null-B lungs compared with WT-B (134.2±28.54 cells/hpf compared to 11.4±3.25 cells/hpf, p=0.01). Again, this was maintained at day 14 (72.2±20.73 cells/hpf, 7.6±1.46 cells/hpf p=0.03). Analysis of gene expression defined a cohort of TGFbeta responsive genes that were not upregulated in fibroblasts after deletion of TbetaRII. This included the key profibrotic mediators CTGF and ET-1, raising the possibility that defective induction of these mediators may underlie the altered fibrocyte recruitment and myofibroblast differentiation that we observe (see Table).

Mean (±SEM) Normalised Gene Expression in Lung Fibroblasts

	Wildtype (n=6)			Null (n=3)		
	Basal	**TGFb**	**P value**	**Basal**	**TGFb**	**P value**
CTGF	2282 ±1781	9926 ±2115	0.031	1753 ±951	2027 ±1190	NS

ET-1	401 ±22	838 ±197	0.035	541 ±49	504 ±65	NS

Conclusion: Intact TGFbeta signalling in resident lung fibroblasts is essential for lung fibrosis to develop and our results support a key regulatory role of these cells in determining fibrocyte recruitment and myofibroblast differentiation.

Disclosure: K. Khan, None; **R. Hoyles**, None; **E. Derrett-Smith**, None; **X. Shiwen**, None; **D. Abraham**, None; **C. P. Denton**, None.

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Critical Requirement of RAGE for Development of Lung Fibrosis in An Experimental Model of Systemic Sclerosis. Tracy Delaney, Jennifer Kearley, Ebony Benjamin, Cindy Chen, Gary P. Sims, Daniel Rowe, Phillip Brohawn, Yihong Yao, Jane Connor, Ronald Herbst, Bahija Jallal and Anthony J. Coyle, MedImmune LLC, Gaithersburg, MD

Purpose: Receptor for advanced glycosylated ends (RAGE) is involved in cellular detection of immune complexes containing DNA/RNA, which are associated with autoimmune diseases such as systemic sclerosis (SSc). To determine whether RAGE plays a role in autoimmune-driven fibrosis, mice deficient in RAGE were compared to wild type (WT) in an *in vivo* model of SSc.

Methods: RAGE-/- and WT mice were immunized with 100ug human collagen V on days 0 and 21, and on day 50 lung function was assessed by Flexivent using both pressure/volume (P/V) loops and airway hyperresponsiveness (AHR) to methycholine challenge methods. Lymph nodes were phenotyped by multicolor FACS analysis, and qPCR analysis of lung mRNA was performed by Fluidigm array. Lung RAGE expression and ectopic germinal centers were visualized by immunohistochemistry on frozen tissue sections, and collagen quantified by Sircol assay.

Results: Lung elastance and airway resistance were significantly deviated from controls in immunized WT mice but not RAGE-/- mice. Increased parenchymal collagen, intersititial neutrophils, and alveloar wall thickening were observed in immunized WT but not RAGE-/- animals. Ectopic CD4+/IgG+/PNA+ aggregates present in WT lungs were absent in RAGE-/- lungs, as was overexpression of IL-4, TGFb, IL-13, and MMPs. Immunization-induced B cell expansion in lymph nodes and autoantibody production were unaffected by RAGE deficiency.

Conclusion: Development of lung inflammation and fibrosis, but not expansion of autoreactive B cells, is RAGE-dependent in an experimental murine model of SSc.These data support a key role for RAGE in autoimmune-driven lung fibrosis and suggest a pathogenic role for RAGE-mediated signaling within lung epithelium in this model.

Disclosure: T. Delaney, MedImmune, 3 ; **J. Kearley**, MedImmune, 3 ; **E. Benjamin**, MedImmune, 3 ; **C. Chen**, MedImmune, 3 ; **G. P. Sims**, MedImmune, 3 ; **D. Rowe**, MedImmune, 3 ; **P. Brohawn**, MedImmune, 3 ; **Y. Yao**, MedImmune, 3 ; **J. Connor**, None; **R. Herbst**, MedImmune, 3 ; **B. Jallal**, MedImmune, 3 ; **A. J. Coyle**, MedImmune, 3 .

1054

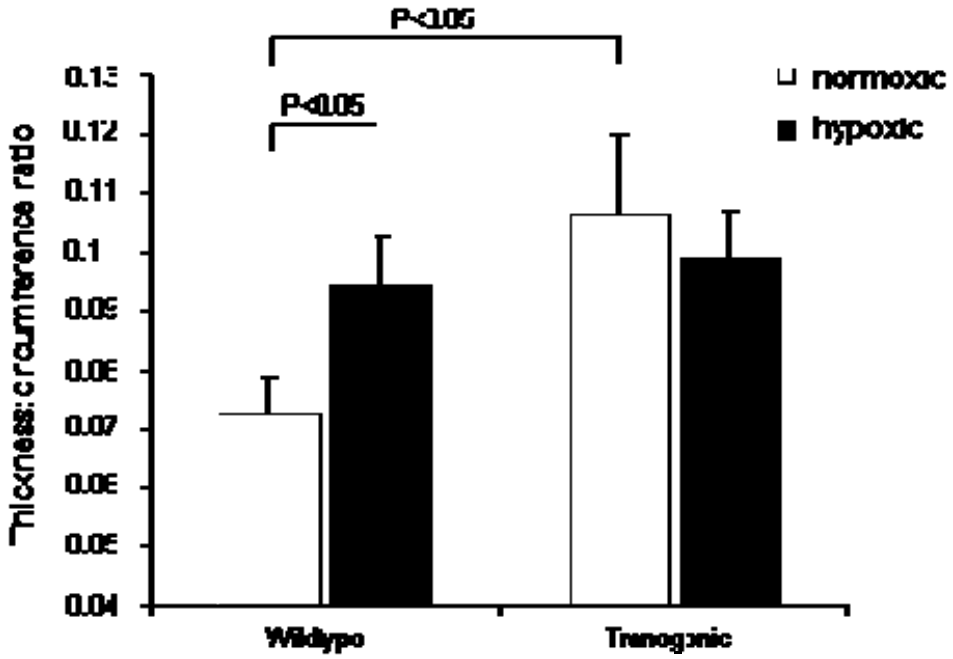
Fibroblast-Specific Activation of TGF-Beta in Transgenic Mice Recapitulates a Histological Phenotype of Hypoxic Pulmonary Hypertension In Vivo. Emma Derrett-Smith[1], Xu Shi-wen[1], Reshma S. Baliga[2], Korsa Khan[1], David Abraham[1] and Christopher P. Denton[1], [1]UCL Medical School, London, United Kingdom, [2]UCL, London, United Kingdom

Purpose: Vascular complications of systemic sclerosis (SSc) are a major cause of mortality and morbidity and are initiated by endothelial injury. The transgenic mouse strain TβRIIΔk-fib expresses a kinase-deficient type II TGF-β receptor linked to a fibroblast-specific promoter leading to balanced ligand-dependent upregulation of TGF-β signalling. We have examined changes in pulmonary vascular structure and signalling in this model of systemic sclerosis and compared responses to hypoxic stress with wildtype control mice.

Methods: Transgenic (n=6) or littermate wildtype mice (n=6) were exposed to hypoxic stress (10% O_2 for 21 days) and pulmonary vascular responses were compared with normoxic transgenic and control animals (n=6 in each group). We evaluated vascular and perivascular architecture by H&E and special stains, and used immunohistochemistry to examine TGF-β and endothelin expression. Vascular smooth

muscle cell (vSMC) proliferation and biochemical phenotype was also studied in vitro by culturing under hypoxic and normoxic conditions, including signalling responses to exogenous TGF-β1 and endothelin-1.

Results: Increased TGF-β1 immunostaining was confirmed in transgenic lung vessels with an associated reduction in endothelin receptor A expression in cultured vSMCs (mean wildtype copy number 2517±1261, mean transgenic copy number 315±73, $p<0.05$). There was no change in these variables between normoxic or hypoxic mouse tissues. As previously reported, in normoxic transgenic mice medial thickness was significantly increased in pulmonary arterial vessels compared with wildtype littermates. After exposure to hypoxia there was significant thickening of the pulmonary vascular smooth muscle cell layer in wildtype mice but no further increase in transgenic vessel wall thickness. These results are summarised in Figure 1. There was increased extracellular matrix deposition and marked perivascular infiltration with mononuclear inflammatory cells in hypoxic transgenic mice compared with hypoxic wildtype littermate animals (mean cell number per high power field in wildtype lung 128.8±21.9, in transgenic lung 176.0±20.3, $p<0.05$).



Conclusion: In this study we confirm that the pulmonary vascular phenotype previously reported in this mouse model of scleroderma recapitulates the histological response of wildtype littermates to hypoxia, an established murine model of pulmonary hypertension. Our results support a role for TGF-β overactivity in the pulmonary vasculopathy of systemic sclerosis.

Disclosure: E. Derrett-Smith, None; **X. Shi-wen**, None; **R. S. Baliga**, None; **K. Khan**, None; **D. Abraham**, None; **C. P. Denton**, None.

1055

Insulin-Like Growth Factor-II Promotes Fibrosis in Systemic Sclerosis-Associated Pulmonary Fibrosis Via Both IGF-IR and IR.

Eileen Hsu and Carol A. Feghali-Bostwick, University of Pittsburgh, Pittsburgh, PA

Purpose: Although the cause of systemic sclerosis (SSc) remains unknown, fibrosis is believed to result from the interaction of soluble mediators with fibroblasts. We recently reported increased expression of insulin-like growth factor-II (IGF-II) in vivo in lung tissues of patients with SSc. In addition, IGF-II induces a fibrotic phenotype in vitro in primary lung fibroblasts. Our goal is to examine the mechanisms mediating IGF-II-induced extracellular matrix (ECM) production and fibrosis.

Methods: Primary fibroblasts were cultured from explanted lung tissues of patients with SSc and normal lung donors. Real time PCR was used to measure IGF-II mRNA levels in fibroblasts. Fibroblasts were transfected with sequence-specific siRNA or scrambled RNA control

prior to stimulation with recombinant IGF-II. ECM production was assessed in cell lysates and supernatants by western blot. Insulin-like growth factor-I receptor (IGF-IR) and insulin receptor (IR) were immunoprecipitated, and receptor levels and phosphorylation status were examined by western blot.

Results: IGF-II mRNA was increased 10-fold in primary pulmonary fibroblasts of SSc patients with mild fibrosis compared to normal lung fibroblasts (p=0.053). Fibroblasts from SSc lungs with severe fibrosis had a 64-fold increase in IGF-II mRNA levels (p=0.002). Neutralizing IGF-II activity decreased fibronectin production in a dose-dependent fashion, suggesting that IGF-II acts in an autocrine fashion to promote ECM production. Primary fibroblasts from SSc and normal lungs expressed both IGF-IR and IR. Co-precipitation studies revealed that these receptors exist as IGF-IR/IR heterodimers in primary lung fibroblasts. Both IGF-IR and IR β subunits were phosphorylated within 10 minutes of IGF-II stimulation. IGF-II-dependent ECM production was blocked in the presence of neutralizing anti-IGF-IR and IR antibodies. Further, IGF-II-dependent ECM production was decreased by inhibition of IGF-IR and IR with sequence-specific siRNA.

Conclusion: Our findings implicate IGF-II and its receptors in SSc-associated lung fibrosis. Inhibition of IGF-II decreases ECM production, demonstrating that IGF-II is an important mediator of fibrosis that acts in an autocrine or paracrine fashion. Primary lung fibroblasts expressed both IGF-IR and IR in hybrid forms that were activated by IGF-II. IGF-II-induced ECM production depends on both of these receptors. IGF-II and its receptors may serve as potential therapeutic targets in SSc-related pulmonary fibrosis.

Disclosure: E. Hsu, None; **C. A. Feghali-Bostwick**, None.

1056

Transforming Growth Factor-ß1 (TGF-ß1) Induction of Endothelial-to-Mesenchymal Transition in Cultured Murine Pulmonary Endothelial Cells: A Novel Mechanism of Systemic Sclerosis Fibroproliferative Vasculopathy? Zhaodong Li and Sergio A. Jimenez, Jefferson Institute of Molecular Medicine, Thomas Jefferson Univ, Philadelphia, PA

Purpose: Tissue fibrosis, most prominent in the skin, lungs, and microvasculature, is the pathological hallmark of systemic sclerosis (SSc). Resident fibroblasts and bone-marrow-derived mesenchymal cells (fibrocytes) are thought to be the main cells involved in the fibrogenic process. However, other mesenchymal cell populations may exist including cells originated from epithelial-to-mesenchymal transition (EMT). The possibility that tissue fibroblasts may also be derived from endothelial cells via a process of endothelial-to-mesenchymal transition (EndoMT) has recently been implicated in cardiac and renal fibrosis. Here we investigated the occurrence of EndoMT in murine lung endothelial cells and examined the role of TGF-β and Endothelin-1 (ET-1) in this process. We also examined the participation of caveolin-1 (Cav-1), a protein involved in TGF-β receptor internalization, on pulmonary endothelial cell transition into myofibroblasts.

Method: Primary mouse pulmonary endothelial cells (PEC) from Wild-type (WT) and Cav-1 knockout mice (Cav-1 KO; provided by Dr. Michael Lisanti, Thomas Jefferson Univ) were isolated by immunomagnetic methods employing sequential anti-CD34 and anti-CD102 antibody selection and cell sorting. The purified PEC were examined by cell morphology and Dil-Ac-LDL uptake assays. The effects of TGF-β1 and ET-1 on EndoMT were tested in cultured PEC from WT and Cav-1 KO mice. EndoMT was assessed by immunofluorescence and Western blot for α-smooth muscle actin (α-SMA) expression. The role of Cav-1 expression was examined in PEC from Cav-1 KO following restoration of Cav-1 function employing cell permeable Cav-1 scaffolding domain peptides.

Results: The results showed that pure PEC populations can be isolated from WT and Cav-1 KO and expanded in culture. TGF-β1 induced significant α-SMA expression in PEC from WT mice. ET-1 alone had no effect, however, it acted synergistically and potentiated TGF-β1 effects. In contrast, bFGF did not cause increased upregulation of α-SMA expression. PEC from Cav-1 KO mice showed very high levels of spontaneous α-SMA expression, which was downregulated by restoration of Cav-1 function.

Conclusion: Murine PEC are capable of undergoing EndoMT *in vitro* in response to TGF-β and ET-1 potentiates these TGF-β effects. Cav-1 deficient PEC display high level of spontaneous EndoMT which is abrogated by restoration of Cav-1 function. These results suggest that a process of EndoMT may participate in the development of tissue fibrosis and proliferative vasculopathy characteristic of the pulmonary involvement in SSc. Further studies are needed to clarify the downstream signaling pathways and the potential role of EndoMT in SSc-associated tissue fibrosis and vasculopathy *in vivo*. Supported by NIH Grant RO1 AR055660.

Disclosure: Z. Li, None; **S. A. Jimenez**, None.

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Distinct Deregulated Pathways Underlie the Molecular Subsets of Scleroderma and Are Recapitulated in Select Animal Models. Jennifer L. Sargent[1], Antonios O. Aliprantis[2], Matthew B. Greenblatt[2], Minghua Wu[3], Giuseppina Alessandra Farina[4], Raphael Lemaire[4], Laurie H. Glimcher[2], Stephen H. Clark[5], John Varga[6], Robert A. Lafyatis[4] and Michael Whitfield[7], [1]Dartmouth Medical School, Hanover, NH, [2]Harvard School of Public Health, Boston, MA, [3]Feinberg School of Medicine, Northwestern University, Chicago, IL, [4]Boston University School of Medicine, Boston, MA, [5]University of Connecticut Health Center, Farmington, CT, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, [7]Hanover, NH

Purpose: Scleroderma (systemic sclerosis; SSc) is a devastating autoimmune disease of unknown etiology. Highly heterogeneous clinical presentation has hindered the understanding of mechanisms of disease pathogenesis. With no clear molecular markers of disease activity and severity, development of appropriate animal models of scleroderma is challenging. Milano et al. analyzed the gene expression in skin biopsies from diffuse and limited SSc patients, morphea and healthy controls (PLoS ONE 2008). Distinct gene expression groups were identified that could be mapped to specific clinical covariates such as increase skin score and ILD.

This study addressed two questions. What are molecular mechanisms and signaling pathways underlie the molecular subsets of scleroderma? And, can the molecular subsets of scleroderma be mapped to commonly used animal models of the disease?

Method: We determined the relative contribution of pro-fibrotic cytokines TGFβ, IL13 and IL4 to gene expression in SSc biopsies. Gene expression signatures associated with responses to TGFβ, IL13 and IL4 were defined in cultured primary adult dermal fibroblasts. Expression of these signatures was then examined in the molecular subsets of SSc.

Genome-wide profiles of skin from Tsk1, Tsk2, cGVHD and bleomycin-induced fibrosis murine models of SSc were analyzed. Mouse and human SSc datasets were merged using distance weighted discrimination, intrinsic genes were selected, and the samples and genes hierarchically clustered. Biological pathways shared by SSc subsets and the animal models were determined using Genomica software.

Results: TGFβ signaling underlies the diffuse-proliferation subset and IL13 and IL4-associated signaling is enriched in the inflammatory subset of scleroderma. Skin from Tsk2 mice shares gene expression features with the diffuse-proliferation subset, including enrichment of a TGFβ-responsive signature. IL13 signaling is required for expression of a disease-associated signature in cGVHD skin and reflects gene expression in skin from inflammatory subset.

Conclusion: We have shown that distinct signaling pathways underlie the diffuse-proliferation and inflammatory subsets of SSc suggesting that patients in these groups may benefit from differential treatment. Having demonstrated similar pathways deregulated in the Tsk2 and cGVHD models, we propose that these models are optimal systems in which to test new therapeutics targeting TGFβ and IL13-signaling pathways.

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Efficacy of Aminaftone in a Monocrotaline Rat Model of Pulmonary Hypertension. Alessandro Santaniello[1], Roberto Latini[2], Vanessa Zambelli[2], Lorenzo Beretta[1] and Raffaella Scorza[1], [1]Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena and University of Milan, Italy, Milan, Italy, [2]Istituto di Ricerca Mario Negri, Milan, Italy

Purpose: Pulmonary arterial hypertension (PAH) is a frequent complication of systemic sclerosis characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular (RV) failure with severe mortality and morbidity. Endothelin-1 (ET-1) is the most relevant factor in the PAH pathogenesis. We recently reported that aminaftone (AMNA) is able to down regulate ET-1 production in endothelial cells. In this work we evaluated whether AMNA may able to contrast negative effects of monocrotaline (MCT)-induced PAH in a rat model

Method: Sixty Male Wistar rats were allocated in 4 different groups:

Control group with no MCT injection (15 rats). Three other groups of rats received MCT by a single subcutaneous injection (60 mg/kg) in a volume of 3 ml/kg and were assigned to receive no treatment (15 rats), AMNA as food admix 30 mg/kg/day (15 rats) or 150 mg/kg/day (15 rats) for 4 weeks. The doses of AMNA were the maximally effective doses based on a dose-range-finding study.

Hemodynamic measurements were performed 4 weeks after MCT injection. The rats were anesthetized by intraperitoneal injection of 60mg/kg of pentobarbital. A catheter was inserted into the right jugular vein for measurement of right ventricular pressure (RVP), using the procedure previously described by Stinger. Measurements were recorded a PowerLab data acquisition system.

Heart, lungs, kidneys, and liver were removed after rats sacrifice and weighed, and the ratio of organ weight to body weight (BW) was calculated. The right ventricle (RV) and the left ventricle plus septum (LV) were separated and weighed; the ratio RV/RV+LV was used as an index of RV hypertrophy.

All data are presented as mean ± standard deviation. Statistical analyses were performed by analysis of variance (ANOVA). The null hypothesis was rejected when $P < 0.05$.

Results: In the different groups the mortality was: 0% (control rats); 25% (only MCT injection); 0% (MCT + AMNA 30 mg/kg/day); 0% (MCT + AMNA 150 mg/kg/day).

RV/RV + LV was only significantly lower in the rats treated with MCT + AMNA 30 mg/kg/day vs rats treated with MCT (0,3 ± 0,03 Vs 0,34 ± 0,02; p<0,05). No significant differences were observed in RVP and in other organ weight between groups.

Conclusion: AMNA ability to reduce ET-1 production suggested a potential beneficial effect in the treatment of PAH. Mortality percentage and RV hypertrophies reduction observed in this experimental session confirm a possible therapeutic role of AMNA in the management of PAH. This evidence might support further research to evaluate whether AMNA may be used in combination with current conventional therapy to ameliorate the prognosis of PAH patients.

Disclosure: A. Santaniello, None; **R. Latini**, None; **V. Zambelli**, None; **L. Beretta**, None; **R. Scorza**, None.

1059

The Inflammasome Is Involved in Bleomycin-Induced Dermal Fibrosis and Is Activated in Systemic Sclerosis (SSc) Fibroblasts. Judy Rieger[1], Alina Boesteanu[1], Sihem Sassi-Gaha[1], Carol A. Feghali-Bostwick[2], Peter D. Katsikis[1] and Carol M. Artlett[1], [1]Drexel University College of Medicine, Philadelphia, PA, [2]University of Pittsburgh, Pittsburgh, PA

Purpose: SSc is an autoimmune disease characterized by fibrosis of unknown etiology affecting the skin and visceral organs. The initiating events and development of fibrosis are unknown, however infection or environmental stimuli have been implicated. The newly identified inflammasome mediates the innate immune system and regulates potent proinflammatory cytokines such as IL-1b, IL-18, and IL-33. Inflammasome activation is controlled by an adaptor (ASC) and sensor (NALP3) that activate caspase-1 to cleave IL-1β, IL-18, and IL-33 into their active forms. IL-1β polymorphisms and an increase in protein have been reported in SSc as well as elevated levels of IL-18, directly suggesting the involvement of the inflammasome in SSc pathogenesis. Fibroblasts are able to modulate the innate immune system and contribute to plasma levels of IL-1β, and IL-18. We determined the role of the inflammasome in bleomycin (BLM)-induced dermal fibrosis utilizing NALP3-/- mice and investigated inflammasome activation in fibroblasts isolated from patients with SSc.

Method: Normal human fibroblasts and SSc fibroblasts derived from active lesions of SSc patients were cultured in complete DMEM. Normal fibroblasts were treated with BLM and gene expression for inflammasome transcripts was quantified by RT-PCR, and inflammasome transcripts and protein were measured in SSc fibroblasts. Localized dermal fibrosis was induced by subcutaneous injections of BLM for 28 days in NALP3 -/- and C57Bl/6 mice in one flank. The opposite flank was injected with PBS. Injection sites were harvested, stained with Masson's Trichrome and measured for skin thickness. Fibrosis was assessed as a change in skin thickness in the BLM site versus PBS site of the same mouse. Lung pathology in the mice was also assessed.

Results: In normal human fibroblasts, BLM induced genes involved in the inflammasome; IL-1β by 39% (p=0.045), IL-18 by 30.5% (p=0.02), and NALP3 by 51% (p= 0.02). Compared to normal fibroblasts, SSc fibroblasts were found to express more IL-18 (p<0.0001), IL-33 (p<0.001) and NALP3 (P<0.0001) mRNA and NALP3 protein (p<0.001). In the animal studies, BLM induced an increase in skin thickness of 41% in C57Bl/6 mice (p<0.0001) but in the absence NALP3, fibrosis was completely abolished (p=0.0026). Furthermore, BLM induced increased lung occlusion and collagen deposition in the lung of C57Bl/6 whereas NALP3-/- mice had normal lung architecture.

Conclusion: Using the BLM-induced model of fibrosis we report that the innate immune system participates in fibrosis via inflammasome activation, BLM can upregulate inflammasome specific genes, and furthermore the NALP3/ASC inflammasome is required for the development of dermal fibrosis. Finally, we found that SSc derived fibroblasts have an increased basal expression of NALP3 mRNA and protein. We conclude that the NALP3 inflammasome is an important mediator in the development of dermal fibrosis and may play a role in the pathogenesis of SSc.

Disclosure: J. Rieger, None; **A. Boesteanu**, None; **S. Sassi-Gaha**, None; **C. A. Feghali-Bostwick**, None; **P. D. Katsikis**, None; **C. M. Artlett**, Scleroderma Foundation, 2, DrexelMed CURE Grant, 2 .

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VEGF Aggravates Skin Fibrosis in Different Animal Models of Systemic Sclerosis (SSc). Britta Maurer[1], Alfiya Akhmetshina[2], Renate E. Gay[1], Georg Schett[3], Beat A. Michel[1], Michael Detmar[4], Steffen Gay[1], Jörg HW Distler[2] and Oliver Distler[1], [1]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [2]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Inst Pharmaceut Sciences, ETH Zurich, Zurich, Switzerland

Purpose: In SSc, the underlying mechanisms that link vasculopathy and fibrosis have yet to be elucidated. Recently, VEGF has been reported to induce migration of normal fibroblasts through PDGF receptor signalling due to receptor homology. Since SSc patients have high tissue and serum levels of VEGF, the aim of our study was to analyze the impact of VEGF on fibrosis in vitro and in inflammatory (bleomycin) and non-inflammatory (TSK1) animal models of SSc.

Method: Homo- (+/+) (n=8) and heterozygous (+/-) (n=9) VEGF transgenic (tg) and wildtype (wt) mice (n=6/9) were treated for 4 weeks with bleomycin or NaCl. Skin sections were analyzed by HE and Masson's trichrome staining and immunohistochemistry. Additionally, VEGF +/-/TSK1 (tight skin mice) (n=6) were generated. Furthermore, SSc and healthy skin fibroblasts (n=4 each) were treated with recombinant VEGF-A (20 ng/ml), and collagen production was measured by quantitative RT-PCR and the Sircol assay.

Results: In SSc skin fibroblasts, VEGF stimulation increased procollagen I and III mRNA by a mean ± SEM 3.4 ± 1.3 and 5.6 ± 3 fold, in healthy skin fibroblasts by 2.5 ± 0.4 and 1.5 ± 0.3 fold ($p<0.05$). Similarly, in the Sircol assay, the supernatants of VEGF stimulated SSc fibroblasts contained more collagen protein than those of unstimulated controls (77 ± 9.4 ng/ml vs. 54 ± 5.7 ng/ml). In VEGF +/- and VEGF +/+ mice treated with bleomycin, skin thickness increased by 2.3 ± 0.07 and 2.3 ± 0.08 fold compared to 1.7 ± 0.02 fold of bleomycin treated wt mice ($p<0.05$). Strikingly, VEGF +/+ mice, but not VEGF+/- mice and controls, spontaneously developed fibrosis even without bleomycin challenge with an increase of skin thickness by 1.8 ± 0.2 fold ($p<0.05$), indicating a dose-dependent in vivo effect of VEGF on skin fibrosis. Masson's trichrome staining showed that skin thickness was caused by extracellular matrix accumulation rather than skin edema. In all VEGF tg mice, inflammatory infiltrates consisting of macrophages and T cells were prominent, which was even more pronounced after bleomycin challenge. In addition, crossing VEGF +/-/ with TSK1 mice as a model for non-inflammatory SSc resulted an increased hypodermal thickness of 694.5 ± 15 µm in VEGF +/-/TSK1 compared to TSK1 and VEGF +/- controls with 456 ± 20.6 µm and 258.3 ± 22.2 µm ($p<0.05$). Most notably, VEGF tg mice displayed an altered vessel morphology with distorted capillaries that resembled the microvascular features of SSc patients.

Conclusion: Our results show that VEGF aggravates fibrosis in vitro and in vivo. Potential mechanisms include direct profibrotic effects via PDGF receptors and indirect profibrotic effects by the induction of inflammation via VEGFR1 signalling on monocytes. Thus, our data suggest VEGF as a novel link between vascular injury, inflammation and onset of fibrosis in SSc.

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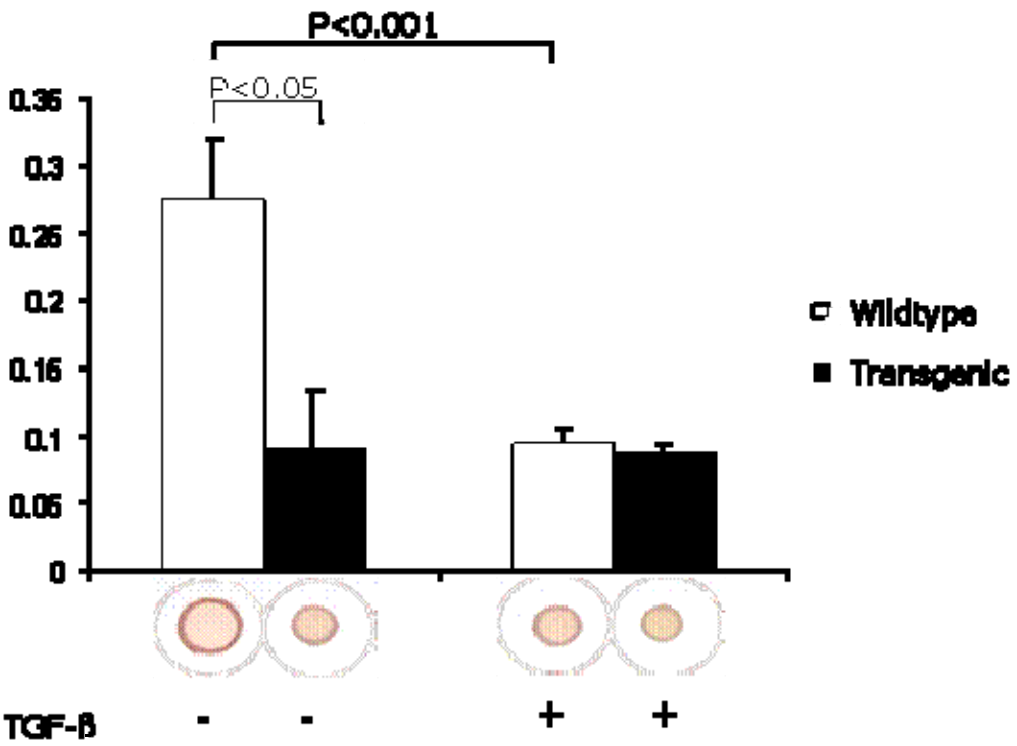
Aortic Smooth Muscle Cells Show a Pro-Fibrotic Phenotype in a TGF-Beta Dependent Mouse Model of Systemic Sclerosis. Emma Derrett-Smith, Audrey Dooley, Korsa Khan, Xu Shi-wen, David Abraham and Christopher P. Denton, UCL Medical School, London, United Kingdom

Purpose: In systemic sclerosis, the large elastic arteries have altered elasticity and compliance. We have examined the large systemic vessels in a mouse model of SSc characterised by ligand-dependent activation of TGF-β signalling in fibroblasts.

Methods: The transgenic mouse strain TβRIIΔk-fib expresses a kinase-deficient type II TGF-β receptor linked to a fibroblast-specific promoter leading to balanced ligand-dependent upregulation of TGF-β signaling. Biological replicate samples from transgenic (n=6) or wildtype littermate control mice (n=6) were compared. Aortic and cardiac tissue were examined by histological, biochemical and isolated organ bath studies. Vascular and perivascular architecture was examined by H&E and special stains including immunostaining for TGF-β1 and pSmad 2/3. Confirmatory aortic smooth muscle cell proliferation, phenotype and functional assays, including signalling responses to exogenous TGF-β and endothelin-1 were performed. Aortic ring contractile responses to direct and receptor-mediated stimulation were assessed.

Results: TGF-β1 and pSmad 2/3 staining were increased in transgenic aortic adventitia, which was increased in diameter with an associated reduction in smooth muscle layer. Non cross-linked collagen content of transgenic thoracic aortic tissue measured by Sircol assay was increased compared to wildtype (mean transgenic collagen content 22.5±1.87 mg/ml, mean wt 12.4±0.45 mg/ml, $P<0.05$). Transgenic aortic smooth muscle cells showed upregulation of TGF-β responsive genes important for cytoskeletal function, such as transgelin (mean transgenic copy number $1.06x10^6±6.6 x10^4$, mean wildtype copy number $7.6x10^5±5.5x10^4$, $P<0.05$) and smoothelin (mean transgenic copy number 11406±1306, mean wildtype copy number 5627±758, $P<0.05$), which were then resistant to further stimulation with exogenous TGF-β1. Consistent with an activated phenotype, transgenic SMC promoted significantly more contraction of free floating type I collagen lattices when compared with wildtype, but there was no further contraction after TGF-β1 stimulation (see Figure 1).



Aortic ring responses to receptor-mediated contraction with endothelin were reduced in the transgenic animals: for instance, mean change in tension from baseline with $1x10^{-9}$ endothelin-1 treatment in wildtype animals (n=3) was 21.4±9.0 mg, compared with -5.7±2.9 in transgenic animals (n=3), $P<0.05$. Bosentan reduced endothelin-mediated contraction in wild-type animals, but had no effect in transgenic animals.

Endothelin receptor A gene expression was reduced in transgenic animals (mean wildtype copy number 2517±1261, mean transgenic copy number 315±73, $p<0.05$).

Conclusion: The histological, biochemical and functional phenotype of this transgenic mouse model of scleroderma offers insight into the altered biomechanical properties previously reported for large elastic arteries in human SSc, and supports a potential role for perturbed TGF-β and endothelin activity in this process.

Disclosure: E. Derrett-Smith, None; **A. Dooley**, None; **K. Khan**, None; **X. Shi-wen**, None; **D. Abraham**, None; **C. P. Denton**, None.

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Tissue Plasminogen Activator (tPA) Restores Normal Fibrinolysis / Coagulation Balance in Kidney and Reverses Clinical Score in Skin in a Murine Graft-Versus-Host Disease Model of Scleroderma: Proof of Concept for Therapeutic Fibrinolysis in Scleroderma.
Timothy Burwell[1], Tracy Delaney[1], Cindy Chen[1], Julie Bakken[1], Isabelle de-Mendez[2], Dominic Corkill[2], Bahija Jallal[1], Jane Connor[1], Anthony J. Coyle[1] and Raphael Lemaire[1], [1]MedImmune LLC, Gaithersburg, MD, [2]MedImmune LLC, Cambridge, United Kingdom

Purpose: Scleroderma is a systemic autoimmune disease that affects skin and internal organs, including kidney and lung. Affected tissues share a common pathogenesis characterized by three key manifestations: fibrosis, inflammation and vasculopathy. Scleroderma vasculopathy features occlusion of small arteries that is due to vasoconstriction, intimal proliferation and thrombosis. Thrombosis results from an imbalance between coagulation and fibrinolysis. Whether thrombosis in scleroderma is primarily due to alteration in fibrinolysis or coagulation remains unclear. In this study, we investigated thrombosis in a murine Graft-versus-Host disease (GVHD) model of human scleroderma exhibiting an occlusive vasculopathy, along with fibrosis and inflammation. We also assessed the therapeutic value of fibrinolysis in that model.

Method: GVHD was induced by injection of spleen cells from donor B10.D2 mice into recipient RAG2-deleted BALB/c mice. Clinical skin score was assessed and proteinuria levels in urine measured by dipstick. Biomarkers of fibrinolysis and coagulation were determined in plasma, skin, kidney, and lung at weeks 2, 4 and 6 post-graft using qPCR, ELISA and IHC. The therapeutic value of augmenting fibrinolysis in the GVHD model was evaluated utilizing tissue Plasminogen Activator (tPA) and evaluating effects on thrombosis, fibrinolysis and coagulation biomarkers, and clinical skin score.

Results: Induction of scleroderma-like GVHD in mice led microthrombi formation in blood vessels of deep dermis. The presence of microthrombi was associated with dramatic increases in expression of key regulators of fibrinolysis (active plasmin, PAI-1, uPA, tPA, uPAR, kallikreins) and coagulation (Factor VII and X) in skin. Murine scleroderma-GVHD caused similar large alterations in fibrinolysis and coagulation pathways in kidney, lung and plasma. Additionally, increase in proteinuria in urine upon GVHD induction was associated with increase in coagulation factors TF and vWF in kidney. Importantly, intra-peritoneal injection of tPA on the third and fourth weeks after initiation of GVHD significantly reduced expression levels of uPA, TF and vWF in kidney and clinical score in skin between 4 and 6 week post-graft.

Conclusion: These data strongly suggest that systemic alterations in both fibrinolysis and coagulation cause thrombosis in murine scleroderma-GVHD, eventually impacting in progression of the pathology. Restoration of normal fibrinolysis/coagulation balance in kidney and reversal of clinical score in skin by tPA demonstrate the therapeutic value of fibrinolysis in murine scleroderma GVHD, and ultimately in human scleroderma.

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Platelet Derived Serotonin (5-HT) Plays a Crucial Role for Experimental Fibrosis.
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Purpose: Systemic sclerosis (SSc) is characterized by progressive vascular disease and organ fibrosis. We have shown previously that 5-hydroxytryptamine (5-HT) exerts pro-fibrotic effects via 5-HT2B receptors. Tryptophanhydroxylase-1 (tph-1) is the rate-limiting enzyme for the synthesis of 5-HT. After synthesis, 5-HT is stored in large amounts within platelets and can be released upon platelet activation. The aim of the present study was to investigate the role of platelet activation and release of 5-HT for fibrosis.

Method: The 5-HT content in lesional skin was analyzed by competitive ELISA. Clopidogrel, an inhibitor of the glycoprotein IIb/IIIa pathway, was used to prevent platelet activation. Depletion of 5-HT from platelets was achieved by knockdown of tph-1. The role of platelet derived 5-HT for fibrosis was evaluated in the mouse model of bleomycin-induced dermal fibrosis, a model for early, inflammatory stages of SSc, and in tight-skin-1 (tsk-1) mice, which serve as a model of later, less inflammatory stages of SSc.

Results: In the mouse model of bleomycin-induced dermal fibrosis, the concentration of 5-HT in lesional skin significantly increased to 5.8 ± 0.5 ng/mg compared to 3.2 ± 0.2 ng/mg in control mice ($p < 0.05$). The levels of 5-HT were also upregulated from 3.5 ± 0.4 ng/mg to 4.8 ± 0.2 ng/mg ($p < 0.05$) in the skin of tsk-1 mice. Treatment with clopidogrel significantly reduced the 5-HT content of the skin in both models. Along with reduced levels of 5-HT, treatment with clopidogrel decreased dermal thickening upon bleomycin-challenge by 61 ± 13 % ($p < 0.05$). Inhibition of platelet activation prevented also hypodermal thickening in tsk-1 mice with a mean reduction of hypodermal thickness by 51 ± 16 % ($p < 0.05$). Moreover, treatment with clopidogrel significantly reduced the number of myofibroblasts in bleomycin treated mice and tsk-1 mice. Selective depletion of 5-HT from platelets by knockdown of tph-1 exerted also potent anti-fibrotic effects and confirmed the results obtained with clopidogrel. Dermal fibrosis was significantly ameliorated in mice lacking tph-1 with a mean reduction in dermal thickening of 61 ± 6 % ($p < 0.05$) and almost complete prevention of myofibroblast differentiation.

Conclusion: We demonstrate increased levels of 5-HT in different animal models of SSc. Inhibition of platelet activation decreased the release of 5-HT and prevented dermal fibrosis in the model of bleomycin-induced fibrosis and in tsk-1 mice. In addition, mice lacking 5-HT in platelets are less sensitive to experimental fibrosis. Thus, platelet activation in affected vessels and subsequent release of the pro-fibrotic mediator 5-HT might provide a novel link between vascular manifestations and tissue fibrosis in SSc.

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Fli1 Is a Negative Regulator of Estrogen Receptor α in Dermal Fibroblasts. Tomoyasu Hattori, Yoshihide Asano, Lukasz Stawski and Maria Trojanowska, Medical University of South Carolina, Charleston, SC

Purpose: Fli1, a member of the Ets family of transcripion factors, has been shown to play a pivotal role in the regulation of extracellular matrix genes in dermal fibroblasts. Furthermore, Fli1 has been shown to be persistently down-regulated in fibrotic scleroderma skin. Estrogen has also been shown to positively regulate collagen synthesis in dermal fibroblasts. Estrogen mediates its effects through estrogen receptors (ERs), ERα and ERβ, however the roles of ERs in dermal fibroblasts remain unknown. The goal of this study was to examine a possible interaction between the estrogen and Fli1 pathways focusing on the cross-talk between Fli1 and ERα.

Method: The protein expression of ERα *in vivo* was examined by immunohistochemistry using skin samples taken from 3 $Fli1^{+/-}$ mice (1 male, 2 females). Primary dermal fibroblasts were isolated from $Fli1^{+/-}$ mice (2 females). The level of ERα expression was determined by quantitative reverse transcriptase-PCR and Western blot techniques. $Fli1^{+/+}$ littermates were studied in parallel as controls. Human dermal fibroblast cultures were established from skin biopsies taken from 4 adult young women (range 19-28 years old) in compliance with the Institutional Review Board for Human Studies. Endogenous Fli1 levels were suppressed in human dermal fibroblasts using specific small interfering RNA (siRNA). Human dermal fibroblasts were incubated in serum-free medium for 48 hours followed by 24 hour stimulation with 2ng/ml of human recombinant transforming growth factor (TGF)-β1. The binding of Fli1 to the human ERα promoter was examined by chromatin immunoprecipitation assay (ChIP).

Results: Dermal fibroblasts expressed higher levels of ERα protein in the skin of $Fli1^{+/-}$ mice as compared to the $Fli1^{+/+}$ mice. The proportion of the ERα- positive fibroblasts was 5.7-fold, 4.0-fold and 2.1-fold higher in the individual $Fli1^{+/-}$ mice as compared to control $Fli1^{+/+}$ mice. The expression level of ERα was also higher in cultured mouse fibroblasts obtained from $Fli1^{+/-}$ mice as compared to $Fli1^{+/+}$ mice at both mRNA (3.1-fold) and protein (4.6-fold) levels. Endogenous Fli1 expression was suppressed >80% by specific siRNA in

cultured human dermal fibroblasts. Down-regulation of Fli1 by siRNA resulted in up-regulation of ERα mRNA (1.9-fold) and protein (1.5-fold). Consistent with these observations, TGF-β1 that is known to inactivate repressor function of Fli1, increased the level of ERα protein in human dermal fibroblasts (1.4-fold). Fli1 was found to occupy the Ets binding site within the human ERα promoter *in vivo* by ChIP assay.

Conclusion: This study demonstrates for the first time that Fli1 functions as a suppressor of ERα in dermal fibroblasts, suggesting that estrogen/ERα pathway might contribute to the profibrotic effects induced by activation of the TGF-β/Fli1 signaling. Activation of estrogen/ERα pathway may also potentiate fibrosis in patients with scleroderma.

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Depletion of Inducible Co-Stimulator (ICOS) Bearing T Cells Inhibits Expansion of T Follicular Helper Cells (T_{FH}) and Prevents Disease in a Graft Versus Host Mouse Model of Scleroderma. Gianluca Carlesso[1], Raphael Lemaire[1], Devon Taylor[1], Nanette Mittereder[1], Ellen Kuta[1], Timothy Burwell[1], Tracy Delaney[1], Jane Connor[1], Jie Zhu[1], Huifang Dong[1], Michael A. Bowen[1], Jia Lin[1], Changshou Gao[1], Rob Woods[1], Jodi Karnell[1], Rachel Ettinger[1], Philip Brohawn[1], Yihong Yao[1], Bahija Jallal[2], Ronald Herbst[1] and Anthony J. Coyle[1], [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, Gaithersburg, MD

Purpose: Human cluster of differentiation antigen 278, also called inducible T-cell co-stimulator (ICOS) is a T cell-specific surface antigen selectively expressed by recently activated, memory, and T follicular helper (T_{fh}) T cells. In this study, the function of ICOS in the pathogenesis of a graft-versus-host disease (GvHD) mouse model of scleroderma (SSc) was investigated using a glycoengineered anti-mouse ICOS MAb with enhanced antibody-dependent cellular cytotoxicity (ADCC).

Methods: We have generated a glyco-engineered rat anti-ICOS monoclonal antibody (MAb) directed against the ligand binding domain of murine ICOS as mouse IgG2a. The antibody was produced in a fucosyltransferase 8-deficient Chinese Hamster Ovary (CHO) producer cell line (BioWa Potelligent® Technology), a procedure that generates a homogenously afucosylated antibody (anti-ICOS-aFuc) with enhanced ADCC. The activity of the afucosylated anti-mouse ICOS MAb, was evaluated in a murine GvHD model, which recapitulates key aspects of human SSc, including inflammation, fibrosis, and vasculopathy.

Results: Dosing of the anti-ICOS-aFuc MAb reduced severity and incidence of dermal lesions when compared to isotype control MAb and control syngeneic graft. Mean clinical scores were significantly reduced in anti-ICOS-treated groups compared to isotype control MAb-treated mice, as early as 12 days post-graft (3.4-fold, $p<0.002$), and thereafter up to 4 weeks post graft (8.1-fold, $p<0.0001$). The anti-ICOS-aFuc MAb also prevented the disease-associated accumulation of T_{FH} cells and the associated expansion of germinal center B cells and immunoglobulin secreting B cells. There were no ICOS MAb-related clinical signs or changes in body weight in animals during the study.

Conclusion: The results from this study indicate that ICOS plays an important role in dermal pathology of murine GvHD-SSc, as depletion of $ICOS^+$ T cells reduced the overall clinical disease score. The identification of dysregulated $ICOS^+$ T_{FH} cells in GvHD-SSc underscore their critical function in driving the generation of pathogenic B cells into germinal center B cells in secondary lymphoid tissues and in the differentiation of immunoglobulin secreting B cells in the skin. Importantly, treatment with the anti-mouse ICOS-aFuc MAb resulted in a significant reduction of the clinical signs of disease and represents an innovative therapeutic strategy for the treatment of T helper associated autoimmune GvHD-SSc.

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Anti-Inflammatory and Anti-Fibrotic Effect of Angiotensin AT2 Receptors Stimulation or AT1 Receptors Blockade in Scleroderma. Francesca Santi[1], Katja Ströder[2], Franziska Rompe[2], Anja Wieland[2], Metin Artuc[3], Christa Thöne-Reineke[2], Nazzarena Malavolta[1], Claudio Borghi[1], Thomas Unger[2] and Ulrike Muscha Steckelings[2], [1]University of Bologna - Rheumatology Unit, Bologna, Italy, [2]CCR - Centre for cardiovascular research Berlin - Germany, Berlin, Germany, [3]Dermatology Department - La Charité Hospital Berlin, Germany

Purpose: Skin harbours a complete renin-angiotensin-system (RAS). There is evidence for an upregulation of RAS in Scleroderma lesions. Our project aimed at investigating whether pharmacological interference with the RAS (angiotensin AT1 receptor blockade or AT2 receptor stimulation) may be effective in reducing inflammation and fibrosis in a scleroderma murine model.

Method: Female C3/H mice were treated with bleomycin injection (100 µl of a 100 µg/ml solution s.c.) every second day over a period of 4 weeks. Animals were randomised in 4 treatment groups (n=6 each): (i) control group (only vehicle), (ii) Bleomycin; (iii) Bleomycin+ AT1R blocker, Candesartan (0,1 mg/kg bw, s.c. every day); (iv) Bleomycin + AT2R agonist, Compound21 (0,3 mg/kg bw, s.c. every day). Subsequently, tissue samples were collected and analysed for markers of inflammation and fibrosis by real time RT-PCR, Western Blotting and conventional histological staining (HE).

Results: After 4 weeks of Bleomycin injection, histological analysis showed an increased in extracellular matrix primarily within the subdermal layers. This fibrotic reaction was ameliorated both by Compound21 and Candesartan treatment. Histological reduction of fibrosis as a results of Compound21 or Candesartan treatment coincided with a reduced expression of precollagen I&alphaI and TGF&beta as estimated by Western Blot. Furthermore, Bleomycin elicited an increase in IL-6 and MCP-1 mRNA expression, which could be significantly reduced by Compound21 and Candesartan. Experiments in vitro on human fibroblasts both from healthy donors and from scleroderma patients show results similar to our murine model.

Conclusion: Our data indicate that pharmacological interference with the cutaneous RAS by AT1R blockade or by AT2R stimulation could be a potential therapeutic approach to reduce inflammation and fibrosis in scleroderma and, potentially, in other pathological settings with similar pathomechanism.

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Autoimmune-Driven Skin Fibrosis: The Critical Requirement for IFNAR1 in An Experimental Model of Systemic Sclerosis. Tracy Delaney[1], Christopher Morehouse[1], Philip Brohawn[2], Yihong Yao[1], Cindy Chen[1], Ricardo Cibotti[1], Jane Connor[1], Ronald Herbst[1], Bahija Jallal[2] and Anthony J. Coyle[1], [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, Gaithersburg, MD

Purpse: Diffuse systemic sclerosis (dSSc) is an autoimmune disorder featuring progressive fibrosis in skin and in visceral organs such as lung and kidney. Type I interferons (IFNs) have been associated with autoimmunity, but their role in dSSc pathogenesis remains unclear. To determine whether Type I IFNs contribute to autoimmune-driven fibrosis, mice deficient in their shared receptor IFNAR1-/- were compared to wild type (WT) in an experimental model of dSSc.

Methods: IFNAR1-/- and WT mice were immunized with human collagen V on days 0 and 21 and monitored by dipstick for signs of proteinuria for an additional 4 weeks. On day 50 animals were assessed for target tissue inflammation, fibrosis, and serum autoantibodies. qPCR analysis of lung, skin, and kidneys was performed by Fluidigm array, and autoantibody titers by ELISA. Fibrosis was evaluated by trichrome staining and Sircol assay.

Results: Human collagen V immunization induced a sustained elevation in proteinuria between day 35 and day 50 in both WT and IFNAR1-/- mice. Inflammation and fibrosis in kidneys and lungs of WT and IFNAR1-/- mice were equivocal by histological analysis on day 50. By contrast, skin inflammation and fibrosis scores were markedly reduced in the immunized IFNAR1-/- group compared to WT; these differences were confirmed by Sircol assay for collagen. Overexpression of pro-inflammatory cytokines, leukocyte surface markers, and pro-fibrosis genes was highly significant in WT SSc skin compared to control skin, whereas little upregulation was detected in IFNAR1-/- SSc skin. Elevated serum titers of autoantibodies against the SSA, SSB, and the a and b subunits of the PDGF receptor were similar in both immunized WT and IFNAR1-/- mice.

Conclusion: Type I IFN signaling through IFNAR1 is required to drive skin fibrosis, but not lung or kidney fibrosis, in experimental dSSc. These data implicate Type I IFNs in an as yet unidentified key pathway that supercedes the production of pathogenic autoantibodies in importance in skin involvement in this model.

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Hydrogen Sulfide Attenuates the Development of Skin Fibrosis in Tight-Skin Mice. Eiji Muroi, Ayumi Yoshizaki, Koichi Yanaba, Toshihide Hara, Fumihide Ogawa, Motoi Takenaka, Kazuhiro Shimizu and Shinichi Sato, Nagasaki Univ Schol of Biomed, Nagasaki, Japan

Purpose: Oxidative stress has been suggested to contribute to clinical manifestations associated with systemic sclerosis (SSc), such as vascular damage, fibrosis, and autoantibody production. The generation of oxygen free radicals and reactive nitrogen species is not only due to inflammation processes, but also greatly enhanced by frequent episodes of reperfusion injury (Raynaud phenomenon). This has led to hypothesize that oxidative stress is the pivotal event in the early phase of disease. Therefore, it is likely that antioxidant treatment is useful for treatment of SSc, especially the early phase when oxidative stress is at maximal levels. Hydrogen sulfide (H2S) can neutralize a variety of reactive species and thereby exhibits the cytoprotective (antinecrotic or antiapoptotic) effects. In this study, we assessed the therapeutic effect of H2S on a tight-skin (TSK/+) mouse, a mouse model for human SSc.

Method: One-week-old TSK/+ mice were intraperitoneally injected with NaHS (H2S donor) at 100 μmol/kg each day for 4 weeks. Hypodermal thickness of 5-week-old mice was measured under a light microscope. Serum autoantibody levels were determined by enzyme linked immunosorbent assay. Fibroblasts from TSK/+ mice were cultured with or without NaHS for 24 hours. Skin expression levels of mRNA were determined by real-time reverse transcription polymerase chain reaction.

Results: NaHS treatment significantly reduced hypodermal thickness by 70%. Consistent with this finding, NaHS treatment in TSK/+ mice also decreased skin content of hydroxyproline, a modified amino acid uniquely found at a high percentage in collagen. Since H2S can function as an antioxidant by up-regulating heme oxygenase-1 (HO-1), an anti-inflammatory and cytoprotective molecule, we investigated skin HO-1 expression. The fibrotic skin from TSK/+ mice exhibited reduced HO-1 expression relative to the wild type skin. NaHS treatment significantly increased HO-1 expression in the TSK/+ skin to a similar level of the wild type skin. Furthermore, H2S can inhibit the generation of nitric oxide, which is a cytodestructive molecule in various pathological conditions, through down-regulation of endothelial nitric oxide synthase (eNOS) expression. Consistent with this, NaHS treatment significantly reduced eNOS expression in the TSK/+ skin. Finally, proα2 (I) collagen gene expression by cultured TSK/+ fibroblasts was significantly inhibited by NaHS treatment.

Conclusion: In the current study, NaHS treatment showed remarkable effectiveness in TSK/+ mice, suggesting that oxidative stress is critical for the development of skin fibrosis in TSK/+ mice.

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Th17 Polarization in Systemic Sclerosis Is Influenced by Immunosuppressive Treatment Regardless Time of Evolution. Tatiana S. Rodriguez-Reyna, Janette Furuzawa-Carballeda, Javier Cabiedes, Luís Daniel Fajardo-Hermosillo, Mariana Díaz-Zamudio and Luís Llorente, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis and vasculopathy. A key feature of the inflammatory lesions is the presence of T cells. Several studies suggest that the T-cell activity in SSc takes place outside the conventional Th1/Th2 subsets and high levels of IL-17 have been reported. Our aim was to establish the differences in T helper subsets and Tregs between SSc patients with different disease subsets and time of evolution, and contrast groups.

Method: Blood samples from 135 SSc patients were obtained. Clinical evaluation was determined using the Medsger severity scale. SSc patients were classified in: diffuse cutaneous (dc) (n=57) and limited cutaneous (lc) disease (n=78). As contrast groups age- and sex-matched healthy volunteers (n=16), active systemic lupus erythematosus (aSLE) (n=13) and active rheumatoid arthritis (aRA) patients (n=12) were included. Peripheral blood mononuclear cells were analyzed by flow cytometry to determine Th1 ($CD4^+$/IFN-γ^+), Th2 ($CD4^+$/IL-4^+), Th17 ($CD4^+$/IL-17^+) and Treg ($CD4^+$/$CD25^+$/$Foxp3^+$) subsets. Statistical analysis was performed using Mann-Whitney Rank Sum Test, student´s t test, Chi square test and multivariate ANOVA.

Results: Th17 subset was 3 to 5-fold increased in SSc groups vs healthy controls (dc=125±14 cell/mL; lc=82.9±12 cell/mL; control=27±4 cell/mL; p=0.001) and aSLE patients (13.1±3 cell/mL, p=0.001). Th1 cells were increased in SSc vs healthy controls (dc=61.3±12 cell/mL, lc=45.5±6 cell/mL, control=6±3 cell/mL $p \leq 0.001$) and aSLE patients (6±3 cell/mL, $p<0.001$). No differences in Th2 and Treg subpopulations were found between SSc patients and healthy controls; Th2 cells were higher in SSc patients (77.7±9 cell/mL) than in the

aRA (27.8±14 cell/mL; p=0.01 vs lcSSc; p=0.001 vs dcSSc) and aSLE (19.1±7 cell/mL; p=0.004 vs lcSSc; p<0.001 vs dcSSc) groups, and Treg cells were increased in the aRA group (176.4±34 cell/mL) when compared to the others (controls:79±10 cell/mL, p=0.02; dcSSc:92.1±10 cell/mL, p=0.01; lcSSc:83.1±11 cell/mL, p=0.001; aSLE:52.3±12 cell/mL, p=0.001). Interestingly, Th17 and Th2 cells were higher in SSc patients with longer time of evolution of the disease (>8.1 years; median) and also in patients that were not receiving immunosuppressive treatment (prednisone ≥5 mg/day, cyclophosphamide ≥50 mg/day or azathioprine ≥50 mg/day) at the time of the sample. In a multivariate ANOVA that included treatment and time of evolution of the disease, only the treatment remained significant (p=0.04 for the overall model; p=0.02 for the effect of treatment), suggesting that this factor explains the variability amongst subgroups.

Conclusion: Th17 and Th1 subsets are increased in patients with SSc. Immunosuppressive treatment modifies Th17 and Th2 subsets in these patients regardless time of evolution of the disease.

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Decreased Expression of Caveolin-1 Contributes to IGFBP-5′s Fibrotic Activity. Yukie Yamaguchi, Hidekata Yasuoka and Carol A. Feghali-Bostwick, University of Pittsburgh, Pittsburgh, PA

Purpose: Caveolae and Caveolin-1 (Cav-1) serve as a platform for membrane trafficking, endocytosis, and signal transduction. Recently, the physiological importance of decreased Cav-1 levels in fibrotic lung and skin of patients with systemic sclerosis (SSc) was reported. We have previously described increased expression of insulin-like growth factor binding protein- 5 (IGFBP-5) in fibrotic disorders such as SSc. IGFBP-5 is a pro-fibrotic factor that induces production of extracellular matrix (ECM) components in vitro, in vivo in lung and skin, and ex vivo in human skin. Although IGFBP-5 is a secreted protein that can translocate to the nucleus, little is known about the role of shuttling and compartmentalization of IGFBP-5 in the development of fibrosis. We therefore sought to examine the localization of IGFBP-5 and the role of Cav-1 in its compartmentalization in primary fibroblasts.

Methods: IGFBP-5 was expressed in primary human and mouse lung fibroblasts. Localization of IGFBP-5 and Cav-1 was evaluated by western blot, immunocytostaining and electron microscopy. Purified FLAG-tagged IGFBP-5 was added to WT and Cav-1 null fibroblasts and its internalization was assessed. In addition, IGFBP-5 re-uptake by cells was examined in WT fibroblasts treated with Caveolae-disrupting agents and small interfering (si)RNA. Cav-1 function was restored in Cav-1 null fibroblasts using Cav-1 scaffolding peptide (CSD). The effect of IGFBP-5 on ECM degradation was also assessed.

Results: IGFBP-5 was detected in all cell fractions and was bound to Cav-1 in lipid rafts. Cav-1 was detected within vesicular structures in the nucleus of IGFBP-5-expressing fibroblasts. Lung fibroblasts from Cav-1 null mice had reduced levels of intracellular IGFBP-5, but increased ECM levels. Internalization of IGFBP-5 was decreased in Cav-1 null fibroblasts and inhibited by both caveolae disruption and Cav-1 siRNA. In addition, restoration of Cav-1 function using CSD dramatically increased IGFBP-5 internalization, indicating that cellular uptake of IGFBP-5 occurs via a caveolin-mediated pathway. Finally, increased deposition of IGFBP-5 in the ECM resulted in excessive ECM deposition likely due to decreased degradation of ECM components such as fibronectin.

Conclusion: Cav-1 mediates the internalization and nuclear translocation of IGFBP-5. Decreased Cav-1 expression in fibrotic diseases leads to increased deposition of IGFBP-5 in the ECM and reduced ECM degradation. Our findings identify decreased internalization of IGFBP-5 and its increased extracellular deposition as novel mechanisms mediating fibrosis.

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Profibrotic Wnt Signaling in Human Mesenchymal Cells: Implications for Scleroderma. Jun Wei[1], Ethan Leng[1], Jennifer L. Sargent[2], Michael L. Whitfield[2], Anna Lam[1], Cara Gottardi[1] and John Varga[1], [1]Feinberg School of Medicine, Northwestern University, Chicago, IL, [2]Dartmouth Medical School, Hanover, NH

Purpose: Scleroderma is characterized by fibrosis in the skin and lung. Activated fibroblasts and myofibroblasts are central in pathogenesis. Wnt signaling plays an essential role in development and cell fate determination and its dysregulation is implicated in both rheumatoid arthritis and osteoarthritis. In contrast, the role of Wnt in scleroderma is largely unknown. Here we investigated Wnt expression and signaling in scleroderma.

Method: Expression of Wnt-related genes in scleroderma skin biopsies was examined by DNA microarray analysis and immunohistochemistry. Wnt ligands were used to activate Wnt signaling in cultured dermal fibroblasts. Activation of b-catenin was detected GST-ICAT (Inhibitor of Catenin And Tcf) and Western analysis. Expression of a-smooth muscle actin (a-SMA) and calponin was determined by Western blot, immunofluorescence and real-time qPCR. Cell proliferation was assayed. Adipogenic differentiation of human subcutaneous preadipocytes was evaluated by Oil Red O staining. Localization of b-catenin was examined in bleomycin-induced mouse scleroderma.

Results: DNA microarray analysis revealed elevated skin mRNA expression for Wnt receptors (FZD2) and decreased expression for Wnt antagonists (DKK2, Wif1) in subsets of patients with diffuse cutaneous scleroderma. Immunohistochemistry showed increased cytosolic b-catenin localization in scleroderma skin and lungs, indicating activated Wnt signaling. Ectopic expression of Wnt3a or Wnt10b stimulated fibroblast proliferation and Type I collagen and calponin synthesis, and induced a-SMA expression and myofibroblast differentiation in subcutaneous preadipocytes. In contrast, Wnt3a repressed adipogenic differentiation and expression of the adipocyte markers PPAR-g and FABP4 in subcutaneous preadipocytes.

Conclusion: Activated Wnt signaling in scleroderma lesions may be directly responsible for myofibroblasts differentiation and fibroblast proliferation. Furthermore, Wnt induces adipogenic precursor cell differentiation into fibroblasts. The results suggest that Wnt signaling plays an important novel role in the pathogenesis of scleroderma. Modulating Wnt activity may therefore represent a novel therapeutic approach for the treatment of scleroderma.

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Activation of the TGFbeta/c-Abl/PKCdelta/Fli-1 Pathway Is a Major Contributor to SSc Fibrosis. Andreea M. Bujor, Yoshihide Asano, Faye N. Hant and Maria Trojanowska, Medical University of South Carolina, Charleston, SC

Purpose: Scleroderma (SSc) is a connective tissue disease characterized by prominent skin fibrosis. Previous studies have linked PKCδ and Fli1 to SSc pathogenesis and the phosphorylation of Fli1(Thr312) by PKCδ downstream of TGFβ has been shown to inhibit the repressor function of Fli1 on the collagen promoter. Despite this, the upstream signaling events underlying TGFβ induced PKCδ activation remain unknown. Overexpression of c-abl was reported in SSc. Furthermore, in other cells c-abl induced PKCδ tyrosine phosphorylation and nuclear translocation. The aim of this study was to further define the molecular mechanisms that mediate the TGFβ induced Fli1 phosphorylation in dermal fibroblasts.

Methods: Protein expression of collagen type I, c-abl and P-Fli1 (Thr312) was measured in adult SSc fibroblasts from skin biopsies and matched normal controls by western blotting (n=4). Normal dermal fibroblasts were either transduced with an adenovirus overexpressing constitutively active PKCδ (CA-PKCδ) or transiently transfected with a plasmid containing bcr-abl (a constitutively activated form of c-abl) in the presence or absence of TGFβ and Imatinib. Western blot analysis was used to measure the effects on the protein levels of collagen type I and P-Fli1 (Thr312). Quantitative real-time PCR was performed to measure the mRNA levels of COL1A1 and COL1A2.

Results: Data analysis showed significantly increased expression of P-Fli1 (Thr312) in cultured SSc fibroblasts compared to normal controls in all of the pairs tested. The enhanced Fli1 phosphorylation in SSc fibroblasts correlated with an increase in the protein levels of collagen type I and c-abl in these cells. Cells transduced with the CA-PKCδ had a two fold increase in collagen levels. Blockade of c-abl using Imatinib was followed by a 70% down-regulation of the mRNA and protein levels of collagen type I which was consistently rescued by over-expression of CA-PKCδ. The levels of P-Fli1 (Thr312) where significantly increased after 2h of TGFβ addition and pretreatment with Imatinib prevented the TGFβ effect on Fli1 phosphorylation. In agreement with these observations, constitutive activation of c-abl by bcr-abl over-expression was sufficient to induce the phosphorylation of Fli1 on Thr312 to levels similar to those obtained after TGFβ treatment.

Conclusion: This study shows for the first time that Fli1 is constitutively phosphorylated on Thr312 in SSc fibroblasts in culture. Additionally we show that c-abl is required for the TGFβ induced Fli1 phosphorylation in dermal fibroblasts. Our results suggest that the constitutive activation of TGFβ/c-abl/PKCδ/Fli1 pathway in SSc fibroblasts could contribute to fibrosis by inhibiting Fli1 induced repression of collagen promoter. Blockade of the TGFβ/c-abl/PKCδ/Fli1 pathway by Imatinib further clarifies the antifibrotic mechanisms of this molecule and suggests that SSc patients with constitutive activation of this pathway could benefit from Imatinib treatment.

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ACR/ARHP Poster Session B

T cells in Autoimmune Diseases
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IL-15 Expressed On RA Synovial Fibroblasts (RASFib) Induces Proliferation of CD4+CD25+ Regulatory T Cells (Treg) and Augments Their Suppressive Potency. Y. García-Carmona, M. Benito-Miguel, Alejandro Balsa, C.P. de Ayala, E. Martin-Mola and M. E. Miranda-Carus, Hospital La Paz, Madrid, Spain

Purpose: We previously described that fibroblast-like cells from the synovium of Rheumatoid Arthritis patients (RASFib) constitutively express intracellular and surface IL-15, that induces activation of cocultured T cells. The purpose of the present study was to examine the effect of RASFib IL-15 expression on the function of human CD4+CD25+ Treg cells

Method: RASFib were obtained from synovectomy or arthroplasty specimens of RA patients. Total CD4+ T (TCD4T), CD4+CD25+ T reg and CD4+CD25- Teff cells were isolated from the peripheral blood of 30 healthy controls by Ficoll-Hypaque gradient, followed by magnetical sorting. Purity of the T cell populations was 99% by flow cytometry. Cocultures of RASFib and T cells were established in 96-well plates, in the presence or absence of IL-15 neutralizing agents. The function of Treg cells was assessed using two different approaches: A.The regulatory function of natural proportions of Treg cells was inferred by comparing the proliferative and cytokine responses of aCD3 stimulated total CD4+ versus CD25+ depleted CD4+ T cells, and B. The per cell potency of Treg was assessed in cocultures of isolated CD4+CD25+ Treg with CD4+CD25- Tresp, established at different Treg/Tresp ratios. Proliferation was determined by CFSE dilution and cytokine secretion was measured by ELISA of culture supernatants

Results: RASFib, through their constitutive IL-15 expression, were able to induce the proliferation of human Tregs stimulated through their TCR, and at the same time potentiated their suppressive action on the cytokine secretion of CD4+CD25- responder T cells (Tresp). In parallel, constitutive RASFib IL-15 expression mediated an upregulated response of Tresp cells. Subsequently, total CD4+ T cells, containing natural proportions of Treg and Tresp, secreted an increased amount of pathogenic cytokines when cocultured with RASFib despite the presence of proliferating Treg with superior regulatory potency

Conclusion: RASFib IL-15 exerts a dual action on the equilibrium between Treg and Tresp cells, by potentiating the suppressive effect of Treg while augmenting the pro-inflammatory action of Tresp; the result is a shift of the Treg/Tresp balance towards a pro-inflammatory state. This alteration of the Treg/Tresp equilibrium is not observed in the presence of OASFib or dermal fibroblasts, that do not constitutively express surface IL-15

Disclosure: Y. García-Carmona, None; **M. Benito-Miguel**, None; **A. Balsa**, None; **C. P. D. Ayala**, None; **E. Martin-Mola**, None; **M. E. Miranda-Carus**, None.

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Characterizing Natural CD4$^+$Foxp3$^+$ Regulatory T Cells by Anatomical Location. Scott M. Lieberman[1] and Laurence A. Turka[2], [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania School of Medicine, Philadelphia, PA

Purpose: Natural $CD4^+Foxp3^+$ regulatory T cells (T_R) are specialized cells which develop in the thymus and function to control naturally occurring autoreactive lymphocytes, thus preventing autoimmunity. Humans and mice with *Foxp3* mutations resulting in defective T_R, develop widespread organ-specific autoimmunity. Studies suggest T_R confer organ-specific tolerance in an antigen-specific manner; however, the exact nature of their cognate antigens is unknown. Recent studies show T_R T cell receptor (TCR) repertoires vary based on anatomical location suggesting compartmentalization based on antigen specificity; however, contributions of non-TCR dependent survival or trafficking signals may play a role. Here we evaluate T_R population homeostasis and trafficking based on anatomical location.

Method: T_R were isolated by fluorescence activated cell sorting (FACS) from mice expressing enhanced green fluorescent protein under control of the Foxp3 promoter (Foxp3-GFP knockin). T_R were isolated from spleen or lymph nodes grouped as follows: skin-draining (axillary, brachial, inguinal, popliteal), cervical, or gut-draining (mesenteric, pancreatic, gastric). For certain analyses, pancreatic/gastric and iliac lymph node groups were included separately. T_R were analyzed for steady state phenotype and proliferation by flow cytometry or were transferred intravenously to nonlymphopenic congenic ($CD45.1^+$) or lymphopenic ($RAG1^{-/-}$) hosts. Each T_R group was isolated from several donors and pooled based on anatomical location of origin before transfer to single recipients. Seven days later, recipient spleen and lymph node groups were isolated and their cellular content analyzed by flow cytometry.

Results: T_R comprise 10-20% of $CD4^+$ T cells within spleen and lymph node groups with small degree of variation. Phenotypically, they demonstrate similar steady state proliferation profiles and T_R surface markers with little anatomical variation. Surprisingly, T_R from each anatomical location, when transferred to nonlymphopenic or lymphopenic hosts, are easily recovered from all anatomical sites with no clear preference associated with anatomical site of origin.

Conclusion: T_R from skin-draining, cervical, or gut-draining lymph nodes or spleen do not vary extensively in phenotype and are able to traffic widely throughout secondary lymphoid organs upon adoptive transfer into nonlymphopenic or lymphopenic hosts. Whether T_R behave in an organ- or antigen-specific manner in this adoptive transfer system remains to be determined and studies of their differential abilities to ameliorate organ-specific autoimmunity are underway.

Disclosure: S. M. Lieberman, None; **L. A. Turka**, None.

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Regulatory T Cells Directly Suppress B Cells in Systemic Lupus Erythematosus. Noriko Iikuni, Elaine V. Lourenco, B H. Hahn and Antonio La Cava, Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: In systemic lupus erythematosus (SLE), adaptive $CD4^+CD25^+Foxp3^+$ cells (Tregs) suppress T helper (Th) cells that help autoantibody (autoAb)-producing B cells. It is not known whether naturally occurring Tregs can directly suppress B cells in SLE without an intermediate suppression of Th cells. This aspect is important for its implications in the natural course of SLE, because most if not all of the clinical and pathologic effects in SLE associate with a dysregulated production of autoAb.

Method: Lupus Tregs were incubated with B cells in the absence of Th cells, and suppression of B cells was investigated.

Results: Natural Tregs inhibited B-cell activity *in vitro* ($P<0.005$) and *in vivo* ($P<0.04$) in SLE, independently of age, through cell contact-mediated mechanisms that directly suppress autoAb-producing B cells, including those B cells that increase numerically during active disease in SLE patients such as $CD19^+CD27^{high}$ ($P<0.009$) and $CD19^+CD27^-IgD^-$ ($P<0.0007$) B cells. Using blocking antibodies and cells infected with dominant negative receptors, we identified membrane-bound TGFb on Tregs and TGFb receptor II on B cells as key molecules for the direct suppressive activity of Tregs on B cells. **Conclusion:** The dat indicate that one way by which natural Tregs attempt to limit humoral autoimmunity in SLE is by directly targeting autoAb-producing B cells.

Disclosure: N. Iikuni, None; **E. V. Lourenco**, None; **B. H. Hahn**, None; **A. La Cava**, None.

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Retinoic Acid Accelerates the Maturation of Human CD4+Foxp3+ Regulatory T Cells Induced Ex-Vivo with IL-2 and TGF-ß. Ling Lu, Julie Wang, Song Guo Zheng and David A. Horwitz, USC Keck School of Medicine, Los Angeles, CA

Purpose: Mouse CD4+ cells activated for 1 week ex-vivo with IL-2 and TGF-β are induced to become Foxp3+CD25+ regulatory T cells (iTregs) that are protective in models of SLE. Similar treatment of human CD4+ cells for one week, however, results in only partially differentiated polyclonal iTregs. Repeated re-stimulation was needed for them to become anergic, express membrane-bound TGF-β, and develop suppressive activity. Since retinoic acid (RA) enhances TGF-β induced iTregs in the intestinal immune system, we reasoned that RA might be able to accelerate the differentiation of human CD4 Foxp3+ iTregs.

Method: Naïve human CD4+ cells prepared by negative selection were suboptimally TCR activated for 6 days with anti-CD3/28 coated beads with IL-2, ± TGF-β1 and all-trans retinoic acid (atRA). The cells were then examined by FACS for surface markers characteristic of natural Foxp3+ Tregs, for intracellular cytokine production, for anergy, and for suppressive activity *in vitro* and *in vivo*.

Results: After 6 days of TCR stimulation with IL-2 and TGF-β >50% of CD4+ cells expressed Foxp3, but these cells proliferated robustly upon further stimulation, produced large amounts of IL-2, IFN-γ, and TNF-α, and lacked the ability to markedly suppress the proliferation of CFSE-labeled T cells. The addition of atRA to IL-2 and TGF-β increased Foxp3+ cells to 85%, and enhanced DR and membrane-bound TGF-β expression. Moreover, production of IL-2 and IFN-γ was markedly reduced, as was their proliferative response to restimulation. Remarkably, these cells had strong *in vitro* suppressive activity at a dilution of 1 to 32 and this effect was completely TGF-β dependent. To assess *in vivo* suppressive activity, sublethally irradiated NOD SCID IL-2R γ chain$^{-/-}$ mice were injected IV with human PBMC and additional naïve CD4+ cells. These mice spontaneously produced large amounts of human IgG after 1 week, and succumbed to a xenogenic graft-versus-host disease by two weeks. Substitution of CD4+ cells conditioned with IL-2 and TGF-β instead of naïve CD4+ cells offered minimal protection. However, the addition of CD4+ cells conditioned with IL-2, TGF-β and atRA to PBMC resulted in complete suppression of human IgG production, and significantly enhanced the survival of these mice ($p<0.01$).

Conclusion: These studies suggest that large numbers of potentially therapeutic Foxp3+ iTreg cells can be produced rapidly and expediently from naive T cells of patients with SLE and other chronic immune-mediated diseases. Following transfer back to the donor, the effects of TGF-β should enable these iTreg cells to home to both lymphoid tissues and inflammatory sites and retain their ability to expand. Studies will also be presented to indicate whether the addition of RA to IL-2 and TGF-β has also conferred resistance to proinflammatory cytokines that decrease Treg suppressive effects, and promote their conversion to effector T cells. Studies are also in progress to learn whether the addition of other epigenetic agents to RA can improve even further the generation of Foxp3+ iTregs ex-vivo.

Disclosure: L. Lu, None; **J. Wang**, None; **S. G. Zheng**, None; **D. A. Horwitz**, ExCell Therapeutics, 4, Becton Dickinson, 5 .

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Characteristics of CD8+CD25- Cells Induced to Become Suppressor Cells Ex-Vivo with IL-2 and TGF-β. Xiao H. Zhou[1], Ling Lu[1], Julie Wang[1], Hejian Zou[2], David Brand[3], Huimin Fan[4] and Song Guo Zheng[1], [1]University of Southern California, Los Angeles, CA, [2]Huashan Hospital, Fudan University, Shanghai, China, [3]VA Medical Center, Memphis, Memphis, TN, [4]East Hospital, Tongji University, Shanghai, China

Purpose: CD8+ T cells stimulated with IL-2 and TGF-β can be induced to develop suppressive activity. However, the phenotype and functional characteristics of these polyclonal regulatory T cells (iTreg) have not been well characterized. Here we want to determine characteristics of these cells primed with IL-2 and TGF-β in vitro.

Method: GFP transgenic mouse were used to distinguish expanded thymus-derived Foxp3+CD8+ cells from conventional CD8+CD25-. Splenic GFP-cells from these mice were stimulated with anti-CD3/28 coated beads and IL-2 with or without TGF-β. The phenotypes of regulatory cells were analysis by flow cytometry. Transfer DBA/2 spleen cells (80×106) to F1 (DBA/2×C57BL/6 F1 hybrid) to establish a Lupus-like graft-versus-host disease model for the in vivo suppress function analysis of iTreg.

Results: Following 4-day stimulation, 35% of CD8+ cells become CD25+GFP+ cells in the presence of IL-2 and TGF-β. Granzyme B expression was decreased compared to CD8+ cells activated without TGF-β. These cells were also anergic following restimulation. Although their Foxp3 expression is lower than TGF-β induced CD4+ cells, they displayed similar suppressive activity in cell contact-dependent, non-cytotoxic suppressive activity manner in a standard in vitro assay. Neutralization of TGF-β, IL-10 or IL-10 receptor and the TGF-β receptor□(ALK5) inhibitor was unable to abolish the suppressive activity. Similar to CD4+ iTreg, adoptive transfer of CD8+ iTregs suppressed a chronic GVHD with a lupus-like syndrome. Thus, TCR stimulation with IL-2 and TGF-β can induce CD8+ cells as CD4+ cells to become Foxp3+ Treg cells and both of these subsets have protective effects against pathologic immune-mediated inflammation.

Conclusion: Naïve CD8+CD25- cells polyclonally activated with TGF-β and IL-2 became CD28-CD103+Foxp3+ cells. These cells suppressed T cell proliferation in vitro and co-transfer of these cells markedly blocked the development of GVHD with a lupus-like syndrome. Neutralization of TGF-β or blockade of TGF-β signaling did not abolish the suppressive activity in vitro. These cells did not express granzyme or perforin and lacked cytotoxic activity. The suppressive mechanisms need to be further elucidated. Generation of CD8+ induced Tregs may have considerable therapeutic potential.

Disclosure: X. H. Zhou, None; **L. Lu**, None; **J. Wang**, None; **H. Zou**, None; **D. Brand**, None; **H. Fan**, None; **S. G. Zheng**, None.

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Generation of Tregs by Homotypic T Cell Interaction. Katja Thümmler, Andreas Ramming, Jan Leipe, Iryna Prots, Hendrik Schulze-Koops and Alla Skapenko, University of Munich, Munich, Germany

Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease driven by constantly activated CD4 effector T cells. Current evidence suggests that an insufficient activity of regulatory T cells is the prerequisite for the development of persistent inflammatory activity in RA. During the disease, activated T cells continuously circulate back and forth from the synovial tissue into the draining lymph nodes, permitting intense interactions with bystander cells (e.g. T cells, B cells, synovial fibroblasts, macrophages, etc.) in the respective tissues. We have recently described that bystander contact between activated effector T cells and resting T cells results in the production of immunoregulatory cytokines, such as IL-10 and IL-4, from the later. Here, we analyzed whether these T cells that were primed by homotypic interaction with activated effector T cells to produce immunomodulatory cytokines exert a regulatory T cell phenotype, thereby representing a potential physiological negative feedback mechanism in inflammation.

Method: Purified CD4 T cells were activated under effector T cell polarizing conditions (e.g. Th1, Th2, Th17) for five days, fixed to prevent further proliferation and effector cytokine release, and cultured with freshly isolated syngeneic CD4 T cells. Phenotype and function of the resulting cells were analyzed by FACS, ELISA, and in functional Treg assays.

Results: T cells that were primed with activated effector cells produced IL-10 (if primed with Th1 or Th17 effectors) or IL-4 (in response to contact with Th2 cells). They expressed CD25 on their surface, however, they were negative for Foxp3 protein and mRNA. Nevertheless and importantly, all primed T cells expressed a potent regulatory capacity in vitro, regardless of the nature of the priming effector T cells that was comparable with that of naturally occurring CD25+ Foxp3+ Tregs. The regulatory effect upon proliferation of CD25- responder T cells was dose dependent and could be abrogated by exogenous IL-2. Spatial separation of primed T cells from responder T cells by a transwell completely prevented the regulatory activity of Th2 cell-primed T cells. In contrast, Th1 cell-primed T cells exerted their regulatory function in part via secretion of IL-10. In vivo, D011.10 CD4 T cells that were primed by activated T cells from Balb/c mice in vitro, were able to suppress expansion of OVA-specific T cells upon antigen challenge in the D011.10 transfer model.

Conclusion: Our data indicate that activated T cells are able to prime resting T cells in a bystander fashion to exert immunoregulatory functions in contact and cytokine-dependent manners. As these T cells are functional in vivo, the data further suggest that homotypic T cell interactions may represent a physiological means to counteract sustained inflammation. Functional failure of this mechanisms may contribute to the pathogenesis of autoimmune diseases, such as RA.

Disclosure: K. Thümmler, None; **A. Ramming**, None; **J. Leipe**, None; **I. Prots**, None; **H. Schulze-Koops**, None; **A. Skapenko**, None.

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The Adhesion Receptors, ICAM1 and ICAM3 Regulate the Generation of Regulatory T Cells Induced by Homotypic T Cell Interaction. Katja Thümmler, Andreas Ramming, Jan Leipe, Iryna Prots, Hendrik Schulze-Koops and Alla Skapenko, University of Munich, Munich, Germany

Purpose: We have recently described that bystander contact between activated effector T cells and resting T cells results in the generation of regulatory T cells from the later that exert potent immunoregulatory functions in vitro and in vivo. Here, we analyzed the molecular mechanisms involved in the generation of regulatory T cells from resting T cells upon priming with syngeneic activated effector T cells.

Method: CD4 T cells were purified from the peripheral blood from healthy individuals, activated under effector T cell polarizing conditions (e.g. Th1, Th2, Th17) for five days, fixed to prevent further proliferation and effector cytokine release, and cultured with freshly isolated

syngeneic CD4 T cells. The biological activities of receptor/counterreceptor pairs as well as of individual cytokines were neutralized by monocloncal antibodies, and the phenotype and function of the resulting cells were analyzed by FACS, ELISA, and in functional Treg assays.

Results: In response to contact with activated effector T cells (stimulator T cells), resting T cells started to proliferate and to produce IL-10 (if primed with Th1 or Th17 effectors) or IL-4 (in response to contact with Th2 cells). Spatial separation of stimulator from responder T cells by a transwell completely prevented the development of cytokine producing cells. In contrast, neutralization of IL-4 or IFN-γ was without a significant effect on the appearance of cytokine producing T cells. In line, blocking of the major T cell adhesion receptor, LFA-1 prevented proliferation and cytokine production of the responder population. Notably, the interaction between LFA-1 with its individual ligands, ICAM-1, ICAM-2 and ICAM-3 determined the phenotype of the developing T cell. Whereas blocking of ICAM-1 inhibited cell proliferation and production of IFN-γ, but not that of IL-4 and IL-10, neutralization of ICAM-2 had no effect on the outcome of the priming cultures, and inhibition of LFA-1/ICAM-3 interactions prevented the secretion of IL-4.

Conclusion: The data indicate that engaging of LFA-1 is important in the generation of regulatory T cells induced upon priming with activated effector T cells. Moreover, the data also imply that interaction of LFA-1 with individual ICAMs results in the activation of distinct signaling pathways. Our results provide the first evidence of a role of ICAM/LFA-1 interactions in the generation of regulatory T cells.

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The Selective Immunoproteasome Inhibitor PR-957 Blocks Production of Inflammatory Cytokines by Polarized Th1 and Th17 Cells without Affecting TGF-β Production by Regulatory T-Cells. Erika Suzuki, Mark Bennett, Shirin Kapur and Christopher J. Kirk, Proteolix, Inc., South San Francisco, CA

Purpose: The immunoproteasome is a unique form of the proteasome predominantly found in cells of the immune system. We have recently described a selective inhibitor of the immunoproteasome, PR-957, that blocks production of interleukin (IL)-6, TNF-α, and IL-23 in human monocytes, interferon-gamma (IFN-γ) production in human T-cells and ameliorates inflammation in mouse models of rheumatoid arthritis (Nature Medicine, *in press* July 2009). PR-957 also blocked the differentiation of mouse T-cells to a T_h17 phenotype. In this study, we investigated the role of the immunoproteasome in human T-cells differentiated to T_h1, T_h17 and T_{reg} phenotypes.

Method: PBMCs and purified CD4+ T cells from normal healthy donors were stimulated for up to 12 days with plate-bound anti-CD3 and anti-CD28 antibodies in the absence or presence of polarizing cytokines. Cells were treated with brief (1 hr) and long (24 hr) exposures to PR-957 at concentrations that selectively inhibit the immunoproteasome. Culture supernatants were analyzed for cytokine levels and cells were analyzed for immunoproteasome activity and gene expression profiling.

Results: Inhibition of the immunoproteasome reduced proliferation (but was not cytotoxic) in T_h17 and T_h1 cells. Proteasome activity recovered after removal of PR-957 with an average $t_{1/2}$ of ~72 hr regardless of stimulation or differentiation conditions. Following PR-957 treatment, IL-17A production by T_h17 cells was reduced by an average of 46% (range: 28%-67%; N=3 different donors) and IFN-γ release by T_h1 cells was decreased by an average of 63% (range: 50%-84%; N=4). In contrast, TGF-β production by T_{reg} cells was unaffected by immunoproteasome inhibition. However, in the absence of polarizing cytokines, treatment of cells with PR-957 increased the production of TGF-β by an average of 82% (range:49%-100%; N=3) relative to untreated cells.

Conclusion: These results demonstrate that PR-957 blocks cytokine release by T_h1 and T_h17 cells, but not by T_{reg} cells. Furthermore, immunoproteasome inhibition in the absence of polarizing cytokines may favor development of a regulatory phenotype in T-cells. Gene expression analysis and functional assays are on-going to further understand the effects of PR-957 on the balance between T_h1, T_h17 and T_{reg} cells as this agent proceeds towards clinical development in rheumatoid arthritis.

Disclosure: E. Suzuki, Proteolix, Inc., 3 ; **M. Bennett**, Proteolix, Inc, 3 ; **S. Kapur**, Proteolix, Inc, 3 ; **C. J. Kirk**, Proteolix, 3 .

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CD4+CD25-LAG3+ Regulatory T Cells Suppress a Mouse Model of Colitis. Tomohisa Okamura, Keishi Fujio, Mihoko Shibuya, Shuji Sumitomo, Hirofumi Shoda and Kazuhiko Yamamoto, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Purpose: IL-10-secreting Foxp3-CD4+ T cells have been a focus of active investigation. However, it is difficult to assess the *in vivo* physiological function of IL-10-secreting regulatory T cells because of the lack of specific markers that can reliably differentiate them from the other T cells. LAG-3 is an MHC class II-binding CD4 homolog associated with regulatory activity of CD4+ T cells. We tried to identify IL-10-secreting regulatory T cells (Tregs) using LAG-3 as a marker molecule.

Method: Single cell suspnesion of the spleen and Peyer's patch (PP) of B6 mice were stained with anti-CD45RB, anti-LAG-3, anti-CD4 and anti-CD25. Cells were analyzed by FACS and cDNA was synthesized from sorted cell populations. Gene expressions were analyzed with qunatitative-PCR. Activated CD4+T cells were transduced with retroviral expression vectors. Colitis model of RAG1 deficient B6 mice and TEa TCR transgenic mice were used to examine in vivo suppression of CD4+CD25-LAG3+ cells. DTH model of BALB/c mice were used to examine in vivo suppression of Egr-2 transuced CD4+ cells.

Results: Approximately 2% of CD4+CD25- T cell population consisted of CD4+CD25-LAG3+ T cells in the spleen. Moreover, CD4+CD25-LAG3+ T cells are enriched to about 8% in the PP. They are hypoproliferative upon in vitro antigenic stimulation, and suppress in vivo development of colitis. Gene expression analysis reveals that CD4+CD25-LAG3+ Tregs characteristically express early growth response gene-2 (Egr-2), a key molecule for anergy induction. Retroviral gene transfer of Egr-2 converts naïve CD4+ T cells into IL-10-secreting and LAG-3-expressing phenotype and Egr-2 transduced CD4+ T cells exhibit antigen-specific immunosuppressive capacity in vivo. Unlike Foxp3+ natural Tregs, high affinity interactions with selecting peptide/MHC ligands expressed in the thymus does not induce the development of CD4+CD25-LAG3+ Tregs. In contrast, the number of CD4+CD25-LAG3+ Tregs is influenced by the presence of environmental microbiota.

Conclusion: IL-10-secreting Egr-2+LAG3+CD4+ Tregs can be exploited for the control of peripheral immunity.

Disclosure: T. Okamura, None; **K. Fujio**, None; **M. Shibuya**, None; **S. Sumitomo**, None; **H. Shoda**, None; **K. Yamamoto**, None.

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Reciprocal Regulation of FOXP3 and IL-17 Expression in Human CD4+ T Cells by 1,25(OH)2 Vitamin D3. Seong Wook Kang[1], Sang-Hyun Kim[2], Won-Woo Lee[2], Kyung-A Hwang[2], Seung-Hyun Lee[2] and Insoo Kang[2], [1]Yale University School of Medicine and Chungnam National University, Daejeon, South Korea, [2]Yale University School of Medicine, New Haven, CT

Purpose: A body of evidence supports the role for regulatory T cells (Treg) and T helper 17 (Th17) cells in developing autoimmunity and inflammatory diseases. While FOXP3+ Tregs are generated in the thymus (nTreg), FOXP3+ Treg can also be induced from non-Treg CD4+ T cells (iTreg). 1,25-dihyroxyvitamin D3 ($1,25(OH)_2VD3$) exerts an inhibitory effect on immune cells and low circulatory levels of 25(OH)VD3 are reported in patients with autoimmune diseases. However, it is unknown whether $1,25(OH)_2VD3$ can directly alter FOXP3 and IL-17 expression in human CD4+ T cells.

Method: Human naïve and memory $CD25^-CD4^+$ T cells were stimulated with anti-CD3/CD28 antibodies in the presence of cytokines and/or $1,25(OH)_2VD3$. The expression of FOXP3 and IL-17 was measured by flow cytometry and RT-PCR. IL-17 in culture supernatants was analyzed by ELISA. In order to measure the inhibitory effect of $1,25(OH)_2VD3$ induced FOXP+ cells, stimulated cells were cocultured with autologous $CD25\text{-}CD4^+$ T cells (target cells). For reporter gene assay, the promoter and enhancers of the *FOXP3* gene were cloned and transfected into human CD4+ T cells using electroporation.

Results: $1,25(OH)_2VD3$ promoted FOXP3 expression by CD25-CD4+ T cells in a dose-dependent manner with TCR triggering and IL-2. This effect was more prominent in memory CD4+ T cells, which could be secondary to higher levels of vitamin D receptor (VDR) expression in these cells compared to naive CD4+ T cells. Also, $1,25(OH)_2VD3$-treated cells had increased *FOXP3* mRNA expression. To determined whether $1,25(OH)_2VD3$-induced FOXP3+CD4+ T cells (VDiTreg) had inhibitory function, we co-cultured $1,25(OH)_2VD3$-treated cells with target CD25-CD4+ T cells. VDiTreg suppressed proliferation of target CD25-CD4+ T cells in a cell number-dependent manner. Such suppression was largely dependent on cell contact and FOXP3 expression as separating the two populations during cell culture or knockdown of *FOXP3* expression in VDiTreg blocked the inhibitory effect of VDiTreg. The direct effect of $1,25(OH)_2VD3$ on the *FOXP3* gene expression was further demonstrated by the reporter gene assay showing an enhanced promoter activity of the *FOXP3* gene in the presence of this vitamin. $1,25(OH)_2VD3$ suppressed IL-17 production from human naïve and memory CD4+ T cells, suggesting a reciprocal regulation of FOXP3 and IL-17 expression by$1,25(OH)_2VD3$.

Conclusion: 1,25$(OH)_2$VD3 promotes FOXP3 expression in CD25-CD4+ T cells, more profoundly in memory cells, with TCR triggering and IL-2 and such cells have potent inhibitory function dependently of FOXP3 and cell contact. Our findings suggest that 1,25$(OH)_2$VD3 regulates immune responses by altering IL-17 production and FOXP3 expression in CD4+ T cells in humans.

Disclosure: S. W. Kang, None; **S. H. Kim**, None; **W. W. Lee**, None; **K. A. Hwang**, None; **S. H. Lee**, None; **I. Kang**, None.

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Generating Designer Regulatory T Cells for the Treatment of Arthritis. Graham P. Wright[1], Clare A. Notley[1], Michael R. Ehrenstein[1] and Hans J. Stauss[2], [1]University College London, London, United Kingdom, [2]University College London, United Kingdom

Purpose: Regulatory T cells (Tregs) are capable of controlling and suppressing the action of multiple different immune cells. This multi-faceted suppressive ability makes them ideal candidates for the control of autoimmunity. Whilst adoptively transferred polyclonal bulk Tregs are able to suppress immune-pathology in several murine models, the superiority of antigen (Ag)-specific Tregs has been clearly demonstrated using T cell receptor (TCR)-transgenic mice. To date the potential for clinical translation of targeted Ag-specific therapy with Tregs has been hampered by difficulties of isolating rare Ag-specific Tregs from the natural polyclonal T cell repertoire. Furthermore, the initiating Ag is frequently unknown in autoimmune diseases. Here, we explored two separate strategies to generate primary T cells with Ag-specific regulatory activity.

Method: Firstly, TCR gene transfer into purified CD4+CD25+ T cells was used to redirect the specificity of naturally occurring Tregs. Secondly, co-transfer of FoxP3 and TCR genes served to convert conventional CD4+ T cells into antigen-specific regulators.

Results: Both approaches generated T cells that engrafted efficiently and retained TCR and FoxP3 expression when adoptively transferred into recipient mice. Using an established arthritis model, we demonstrate antigen-driven accumulation of the gene modified T cells at the site of joint inflammation, which resulted in a local reduction in the number of inflammatory Th17 cells and a significant decrease in arthritic bone destruction. Importantly, the specificity of the gene-modified Tregs was distinct from that of the arthritis-inducing pathogenic T cells.

Conclusion: The data indicate that adoptive therapy with gene-modified Tregs resulted in local, Ag-specific control of immuno-pathology in the absence of systemic immune suppression. Furthermore, this work highlighted the potential of Tregs to treat immuno-pathology via linked suppression without prior knowledge of the disease causing antigen.

Disclosure: G. P. Wright, None; **C. A. Notley**, None; **M. R. Ehrenstein**, None; **H. J. Stauss**, None.

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The Neuropeptide npT1 Identified by Microarray Profiling of Developing CD25+ Regulatory T Cells (Tregs) Is Specifically Expressed in Mature Human Tregs. Iryna Prots[1], Alla Skapenko[1], Katja Thümmler[1], Jan Leipe[1], Andreas Ramming[1], Peter E. Lipsky[2] and Hendrik Schulze-Koops[1], [1]University of Munich, Munich, Germany, [2]National Institutes of Health, Bethesda, MD

Purpose: Compromised development and/or function of CD25+ regulatory T cells (Tregs) are hypothesized to be of central importance for the development of autoimmune diseases, such as rheumatoid arthritis (RA). The mechanisms, however, that regulate the generation of peripheral Tregs are largely unknown. To gain insights into Treg differentiation on a molecular level, we investigated gene expression profiles at different stages of peripheral Treg development.

Method: Human peripheral Tregs were generated using a previously described in vitro system from CD4+CD25- naive T cells stimulated in the presence of autologous feeder cells and interleukin (IL)-4. Total RNA was isolated at start and from highly purified CD25+ and CD25- T cells at days 3, 5, 7, and 10 of culture, respectively, and used for DNA microarrays. CD25+ T cells generated in the absence of IL-4 constituted activated effector T cells lacking regulatory capacity and were therefore used to control for Treg-specificity. Differentially expressed transcripts in Tregs and effector T cells versus CD25- T cells were determined at each time point and Treg-specific transcripts were identified based on their differential expression between Tregs and effector T cells at each time point.

Results: A high number of transcripts were differentially expressed in Tregs compared to CD25- T cells at early time points, and markedly reduced numbers of differentially expressed transcripts were found at late time points. In contrast, the number of differentially expressed transcripts in effector T cells versus CD25- T cells was high during the whole culture period. Analysis of biological processes among

identified genes revealed significant over-representation of cell cycle and DNA-metabolic processes in Tregs and effector T cells at early time points and, in effector T cells, over the whole culture period. Of interest, Tregs at late time points were characterized by over-represented immune system and chemotaxis processes. Expression of 93 transcripts was specifically regulated in IL-4-induced Tregs compared to effector T cells at different time points. A neuromediator, npT1, transcript had the highest expression in mature Tregs and the strongest difference between mature Tregs and effector T cells. Expression of npT1 in in vitro generated Tregs was confirmed by RT-PCR in independent experiments. Moreover, npT1 was also expressed by resting and activated natural occurring Tregs purified from the peripheral blood of healthy donors.

Conclusion: Late developing and mature Tregs have less active cellular state compared to effector T cells. The neuropeptide, npT1 is specifically expressed in late developing and functionally mature peripheral and natural occurring Tregs. NpT1 represents a novel Treg-specific gene that links the control of specific autoimmunity with the neurosystem and may constitute an interesting target for novel immunomodulatory treatment strategies.

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HLA DRB1*1503: A Predominant Allelic Haplotype in SLE Correlated to Immunoregulatory Gene Expression Affecting Regulatory T Cells. Jeanann Suggs, Vikas Majithia, Julius M. Cruse and Robert E. Lewis, University of Mississippi School of Medicine, Jackson, MS

Purpose: Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune disease where the role of regulatory T cells (Tregs) is not yet fully characterized. The variability in expression levels of immunoregulatory genes and HLA DRB1 allelic haplotype composition may have effects on CD25+FoxP3+ regulatory T cell population and was evaluated in SLE patients.

Method: SLE patients followed at our institution were grouped according to HLA DRB1 allelic haplotype composition and the resulting subgroups were analyzed for Treg composition using flow cytometry. Expression levels of genes affecting immunoregulatory cells were analyzed and compared with race matched healthy controls.

Results: Molecular HLA typing revealed a prevalence of HLA DRB1*1503 allelic haplotype expression in the lupus patients (~33%). Analysis of the total CD45+CD3+CD4+ T cell population demonstrated an increased proportion of Tregs in the lupus patients compared with healthy controls. Comparison of lupus subgroups by HLA DRB1 allelic haplotype composition demonstrated increased proportions of Treg cells in both the HLA DRB1*1503 and non-HLA DRB1*1503 subgroups compared with healthy controls. Increased proportions of CD25+FoxP3- T cell populations were found in the combined lupus population, as well as each subgroup, compared to healthy controls. Gene expression analysis of the total population and both HLA DRB1 subgroups revealed increased FoxP3 gene expression compared with controls. The combined lupus population had decreased expression of immunoregulatory genes GATA3, TNFSF4, and TNFAIP3, compared with control samples. Decreased expression of GATA3 was only reproduced in the non-HLA DRB1*1503 subgroup comparison to controls. Both the HLA DRB1*1503 and non-DRB1*1503 subgroups revealed decreased TNFSF4 gene expression compared with healthy controls. TNFAIP3 was found to have decreased expression in the non-HLA DRB1*1503 subgroup only when compared with healthy controls. Furthermore, the non-HLA DRB1*1503 subgroup revealed significantly decreased expression of TNFAIP3 compared to the HLA DRB1*1503 subpopulation.

Conclusion: Increased FoxP3 gene expression, the transcription factor required for regulatory T cell differentiation, together with decreased TNFSF4 and GATA3 expression, genes that promote regulatory T cell expansion and Th2 cell expansion, respectively, correlates positively with the paradox of an increased proportion of regulatory T cells in lupus patients. Decreased TNFAIP3 expression, especially in the non-HLA DRB1*1503 subgroup, could signal a reduced suppressive capability of these regulatory T cells in lupus patients, as diminished gene expression has attenuated regulatory T cell functions in mouse models. Results of the present investigation revealed a greatly increased incidence of HLA DRB1*1503 allelic haplotype in African American females within the lupus population studied that was closely correlated with immunoregulatory gene expression affecting CD25+FoxP3+ T cells.

Disclosure: J. Suggs, None; **V. Majithia**, None; **J. M. Cruse**, None; **R. E. Lewis**, None.

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CD98hc Enables Clonal Expansion and Adaptive Immune Responses. Joseph Cantor[1] and Mark H. Ginsberg[2], [1]University of California San Diego, La Jolla, CA, [2]Univ CA SD, La Jolla, CA

Purpose: Lymphocyte clonal expansion facilitates adaptive immunity. We hypothesized that CD98hc, a lymphocyte activation marker, is important for clonal expansion.

Method: We used conditional gene targeting in mice to delete CD98 in B or T cells and tested adaptive immune responses.

Results: Deletion of B cell CD98hc did not affect B cell compartmentalization, but did result in reduced antibody responses. The mechanism of this effect did not involve interference with early signaling from antigen receptors, but instead was due to total suppression of rapid B cell proliferation, and consequent inability to form plasma cells. CD98hc can mediate both integrin signaling and amino acid transport. Reconstitution with CD98hc mutants revealed that its integrin interaction is required and its amino acid transport function is dispensable for B cell proliferation. Deletion of CD98hc in mature T cells reveals a similar role in rapid proliferation of T cells and subsequent effector functions.

Conclusion: These data establish that CD98hc enables clonal expansion and show that this function is performed by support of cell proliferation through interaction with integrins.

Disclosure: J. Cantor, None; **M. H. Ginsberg**, None.

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Allelic Imbalance of BLK Detected in CD4+ T Cells Suggesting That BLK Acts Via T Cell Pathways in Autoimmune Pathogenesis. Lina M. Olsson[1], Robert R. Graham[2] and Peter K. Gregersen[1], [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Genentech, Inc., South San Francisco, CA

Purpose: The intracellular tyrosine kinase, B-lymphocyte kinase (BLK) is associated with both Rheumatoid Arthritis and Systemic Lupus Erythematosus. Three associated SNP variants in BLK are located in the same haplotype covering the 5'UTR/ promoter region and upstream sequences. Studies in B cell lines show that the RA associated allele of the upstream SNP rs13277113 is associated with a lower mRNA expression of BLK. The SNP marker rs922483 in the 5'UTR of BLK is in high LD with all the associated variants (r^2 = 0.8-0.9). We wished to determine the effect of the Blk risk haplotype on expression in freshly isolated and separated peripheral blood cells.

Method: Transfection experiments suggest that rs922483 is a causative variant for Blk expression differences in B cell lines. Its location in the mature BLK transcript permitted us to use this variant to directly investigate allele specific expression in freshly isolated peripheral blood cells in heterozygous individuals. We separated B cells, $CD4^+$ and $CD8^+$ T cells, granulocytes, monocytes, macrophages and dendritic cells in normal subjects with defined BLK genotype.

Results: Using TaqMan assays, we documented high Blk expression in B cells, with decreased Blk after activation with anti IgM and/or CD40. T cells expressed lower levels of Blk and Blk transcript was extremely low in most other cells types. Using a sensitive pyrosequencing assay for allelic imbalance we have made two unexpected observations. First, both resting and activated B cells showed no evidence of allelic imbalance, in contrast to published reports in B cell lines. Secondly, prominent allelic imbalance was present in $CD4^+$ T cells in 5/6 individuals, with lesser degrees of allelic imbalance in $CD8^+$ T cells. Compared to the DNA reference allele ratio (A/G) of 0.4 ± 0.03, the ratio in $CD4^+$ T cells was lower and ranges between 0.1 and 0.3 in the 5 individuals showing allelic expression differences.

Conclusion: These data suggest that the causative Blk allele may play a role in disease pathogenesis by its action in T cells as opposed to, or in addition to, B cells. The contrasting data in fresh B cells compared with B cell lines suggests that if Blk plays a role in autoimmune pathogenesis in B cells, it may be in particular subsets of B cells. Future studies will investigate the role of Blk alleles in regulating expression in specific B cell subsets.

Disclosure: L. M. Olsson, None; **R. R. Graham**, Genentech and Biogen IDEC Inc., 3 ; **P. K. Gregersen**, None.

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Evidence for the Involvement of Gamma-Delta TCR+ T-Cells in Systemic Sclerosis. Adaobi I. Nwaneshiudu[1], Weon-Joo Jaung[1], Alexander Tsygankov[1], Emilia Oleszak[1], Allen R. Myers[2] and Chris D. Platsoucas[1], [1]Temple University School of Medicine, Philadelphia, PA, [2]Temple Univ Schl of Medicine, Philadelphia, PA

Purpose: Emerging evidence support a major role for T-cells in the pathogenesis of systemic sclerosis (SSc), a disease characterized by fibrosis, endothelial cell injury and immune dysfunction. The purpose of this study was to investigate whether SSc is an antigen-driven disease, by determining if γδ TCR+ T-cells are clonally expanded in skin biopsies and/or peripheral blood of patients with SSc. Human γδ TCR+ T-cells are a minor subset of T-cells in the peripheral blood but are well represented in epithelial tissues. As with αβ TCR+ T-cells, generation of the γδ TCR diversity is random during T-cell development, resulting in a repertoire of T-cells each with a unique TCR heterodimer. Therefore the probability of finding identical TCR on different T-cells is negligible, except in the context of an antigen-driven clonal expansion.

Method: Total RNA was isolated from homogenates of skin biopsies and PBMC from patients with SSc (n=7), using the Trizol® reagent. After reverse transcription for cDNA synthesis, TCR transcripts of the major subsets of the human γ-chain (i.e. VγI and Vγ9) and δ-chain (i.e. Vδ1 and Vδ2) were amplified in each sample, by gene-specific primers. Subsequently, the transcripts were cloned using the Invitrogen pCR2.1 TOPO® vector, and clones of transcripts, selected randomly, were sequenced. Predicted amino-acid sequences of the transcripts were determined using the ExPasy online software and transcripts were quantified based on the identity of productively-rearranged CDR3 region sequences of the TCR chains.

Results: Comparison of randomly-selected clones of γ- and δ-chain transcripts from each patient, revealed the presence of substantial proportions of identical VγI-chain transcripts (14.3%-37.2% identical; $p<0.05$), and Vγ9 transcripts (24%-83.3%; $p<0.05$) in skin biopsies and/or PBMC of patients with SSc. Likewise, there were multiple identical Vδ1-chain transcripts (25%-50%; $p<0.05$), and Vδ2-chain transcripts (18.1%-80%; $p<0.05$) in the samples analyzed. These results were statistically significant using binomial distribution.

Conclusion: Mulitple identical γ-and δ-chain TCR transcripts were identified in skin biopsies and peripheral blood of patients with SSc, demonstrating the presence of oligoclonal populations of γδ TCR+ T-cells in these patients. These γδ TCR+ T-cells may have undergone proliferation and clonal expansion *in vivo* in response to as yet unidentified antigens.

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Increased Expression of the High Affinity IL-7 Receptor Alpha in Inflamed Joints of RA Patients Mediates Immune Activation That Is Blocked by Soluble IL-7R. Joel A.G. van Roon, Sarita A.Y. Hartgring, Marion J.G. Wenting, Kim M.G. Jacobs, Johannes W.J. Bijlsma and Floris P.J.G. Lafeber, University Medical Center Utrecht, Utrecht, Netherlands

Purpose: IL-7, a member of the IL-2 family, is a potent T cell stimulatory cytokine. Increased IL-7 levels are found in several inflammatory diseases including rheumatoid arthritis (RA). IL-7 effects are essentially mediated through the high affinity IL-7receptor-α chain (IL-7Rα) in conjunction with the common-gamma chain (γc). IL-7 stimulates proliferation, survival and differentiation of T cells and induces T-cell dependent monocyte, B cell activation and osteoclast formation. In addition, IL-7 induces TNFα dependent and independent immune activation. Our purpose was to evaluate the expression and the functional ability of the IL-7Rα in patients with RA.

Method: IL-7Rα expression was determined by immunohistochemistry in synovial tissue of patients with RA (n=24), undifferentiated arthritis (n=27), and osteoarthritis (OA, disease control, n=15). In addition, CD3 and IL-7 expression was assessed by IHC. IL-7Rα expression on CD4 T cells, CD19 B cells and CD14 monocyte/macrophages from RA synovial fluid (SF), synovial tissue (ST) and peripheral blood (PB) was determined. Also, the proliferative capacity and FoxP3 expression of IL-7Rα^{bright} and IL-7Rα$^{dim/-}$ T cells was evaluated. Furthermore, the capacity of IL-7Rα blockade to prevent activation of CD4 T cells was studied *in vitro*.

Results: Significantly higher IL-7Rα expression in the synovial tissue of RA and UA as compared to OA patients was found (both $p<0.001$). The IL-7Rα expression significantly correlated with CD3 and IL-7 expression levels in the synovial tissue ($r = 0.769$, $p<0.001$; $r = 0.561$, $p< 0.001$, resp). CD4 T cells from RA synovial fluid and tissue strongly expressed IL-7Rα. T cells from RA ST and SF predominantly expressed the IL-7Rα. In contrast to their circulating counterparts, a substantial percentage of B cells and macrophages from the synovial fluid and tissue also expressed IL-7Rα, although less prominent than T cells.

Interestingly, we found that IL-7Rα^{bright} T cells from blood that did not express FoxP3 were highly proliferating as compared to IL-7Rα$^{dim/-}$ T cells that expressed high levels of FoxP3. Finally, soluble human IL-7Rα inhibited IL-7-induced proliferation and IFNγ production by mononuclear cells from RA patients.

Conclusion: Increased IL-7Rα expression in patients with RA could contribute to synovitis. IL-7 can activate IL-7Rα^{bright} arthritogenic T cells, overriding suppressive effects of IL-7Rα$^{dim/-}$ T cells as we have previously shown for CD25^{+} Tregs. In addition, decreased CD4 T-cell activation was achieved by inhibition of IL7Rα-mediated immune activation by soluble human IL-7Rα, indicating the therapeutic potential of targeting IL-7/IL-7Rα.

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T-Cell Receptor (TCR) Threshold Calibration by Homeostatic Cytokines in Rheumatoid Arthritis (RA). Pratima Deshpande, Karnail Singh, Cindy Wang, Cornelia M. Weyand and Jorg J. Goronzy, Lowance Center for Human Immunology and Rheumatology, Atlanta, GA

Purpose: RA patients fail to maintain tolerance and develop autoantibodies to common antigens such as IgG and citrullinated peptides. We and others have proposed that the overriding defect is a failure in TCR calibration. RA T cells respond to stimulation with increased ERK phosphorylation. The increased ERK activity sustains TCR signaling, thereby lowering the TCR activation threshold. The defect includes all T-cell subpopulations suggesting that an exogenous factor is responsible for TCR tuning.

Method: RA patients and controls were compared for phosphorylated STAT3 and STAT5 by FACS. T cells from healthy controls were incubated with IL-1β, TNFα, IL-6, IL-15 or IL-21 overnight, and washed and stimulated by CD3/CD28 crosslinking. Activation-induced ERK phosphorylation, expression of activation markers, and production of IL-2, IL-17 and IFN-g was quantified by FACS. Splenocytes from 3L2 transgenic mice were stimulated with 1 μM agonistic and partially agonistic peptides. PBMC from HLA-DR4 healthy donors were stimulated with 10 μg/ml citrullinated or regular vimentin peptides. Peptide-specific proliferation was assessed by thymidine incorporation.

Results: RA T cells express increased phosphorylated STAT3 and STAT5. T cells from healthy controls were pre-incubated with STAT3 and STAT5 cytokines (IL-6, IL-7, IL-15 and IL-21) or proinflammatory cytokines for 24 hours, and the effect of this preincubation on TCR-induced ERK phosphorylation was assessed. IL-1β and TNFα did not sensitize T cells to respond with increased pERK levels to TCR ligation. In contrast, preincubation with all homeostatic cytokines enhanced ERK responsiveness. Homeostatic cytokines did not directly activate the ERK pathway; the effect was dependent on de novo transcription. Conditioning with homeostatic cytokines had functional consequences. Conditioned T cells responded to CD3/CD28 ligation with increased expression of activation markers CD69, CD25, CD40L, and CD137 and differentiated into effector T cells producing more IL-2, IFNγ, and IL-17. Most importantly, pre-incubation with IL-15 or IL-21 lowered the TCR threshold to respond to low-affinity antigens. Proliferative responses of 3L2 TCR-transgenic splenocytes to partial agonistic peptide were increased, and PBMC from healthy HLA-DR4 donors responded to citrullinated vimentin.

Conclusion: STAT3 and STAT5-dependent homeostatic but not inflammatory cytokines prime T cells to respond with increased ERK phosphorylation, resulting in TCR threshold lowering and improved effector differentiation. This mechanism may be responsible for the autoimmunity observed in lymphopenic mouse models and be relevant for RA patients who have accelerated immune aging, elevated homeostatic cytokines and defects in TCR calibration. We propose that the exposure to homeostatic cytokines breaks T cell tolerance and paves the way to chronic inflammation.

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IL-7 Receptor Ligands IL-7 and TSLP Promote Collagen-Induced Arthritis, Associated by Differential T-Cell Activity and Induction of Proinflammatory Mediators. Sarita A.Y. Hartgring[1], Cynthia R. Willis[2], J W. J. Bijlsma[3], Floris P.J.G. Lafeber[1] and Joel A.G. van Roon[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Amgen Inc., Seattle, WA, [3]University Medical Center, Utrecht, Netherlands

Purpose: Increased IL-7 levels are found in RA. IL-7 effects are mediated by heterodimers of the high affinity IL-7 receptor-α chain (IL-7Rα) and the γc chain. IL-7 stimulates T cells and induces T-cell dependent monocyte and B-cell activation. Thymic stromal lymphopoietin (TSLP) shares the IL-7Rα for signaling, but has a distinctive receptor subunit, the TSLP receptor. TSLP acts on dendritic cells, mast cells, and CD4 T cells and plays a key role in Th2-type inflammatory responses. The effects of IL-7 and TSLP administration on collagen-induced arthritis (CIA) and immune activation and tissue destruction were studied.

Method: CIA was initiated by immunizing male DBA/1 mice with chicken type II collagen. Mice were administered PBS as a control, IL-7 or TSLP (10μg on day 21, 23, 25, 27, 29, and 31). Arthritis was determined by visual examination of swelling and redness of the paws (max 4 per paw/16 per mouse). Joint destruction on day 33 was assessed on basis of radiographs and histological examinations of the ankle joints. Proinflammatory mediators were measured by multi-analyte profiling of serum.

Results: IL-7 strongly increased arthritis severity (mean score day 33 vs. PBS; 11.3 ± 0.9 vs. 6.5, $p<0.01$). TSLP also significantly increased arthritis severity (10.1 ± 0.9, $p<0.05$). A significantly higher radiological score of 1.8 was found for the IL-7 group compared to the PBS (score 1.0). By contrast, TSLP did not alter joint destruction compared to PBS group (mean score of 1.1). This was consistent with the histological joint damage; IL-7 treatment significantly increased the intensity of cell infiltrates, bone erosions and cartilage damage, whereasTSLP did not. Absolute numbers of thymocytes were not changed by IL-7 or TSLP treatment as compared to PBS. Total splenic cell numbers, B cells and T cell subsets were also not affected by IL-7 or TSLP. However, IL-7 and TSLP treatment induced differentiation towards memory T cells ($p<0.01$), associated with an increase in percentages IFNγ- and IL-17-producing T cells in the IL-7 group, and increased IL-4-producing T cells in the TSLP group (all $p<0.05$). Both IL-7 and TSLP administration increased the serum concentrations of CD40L, indicative of T cell activity, and T cell chemoattractant MDC (both $p<0.05$).

Conclusion: IL-7R ligands IL-7 and TSLP promote clinical arthritis without expansion of thymic or splenic T cell numbers. Both IL-7R ligands increase differentiation towards proinflammatory T cells, associated with an increase of proinflammatory mediators. Importantly, IL-7 intensifies arthritis severity and joint destruction, accompanied by increased Th1 and Th17 cells, whereas TSLP promotes arthritis and joint destruction to a lesser extent, which is associated with an increase in Th2 cells. This demonstrates the differential regulation of arthritogenic responses by different IL-7R ligands.

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Autoimmune Regulator (Aire) Controls T Cell Help During Collagen-Induced Arthritis. Ian K. Campbell[1], Sarah A. Kinkel[2], Francois-Xavier Hubert[3] and Ian Wicks[4], [1]Walter & Eliza Hall Institute of Medical Research, Parkville, Australia, [2]Walter and Eliza Hall Institute of Medical Research and Department of Medical Biology, The University of Melbourne, Parkville, Australia, [3]Walter & Eliza Hall Institute of Medical Research, Australia, [4]Walter & Eliza Hall Institute of Medical Research, Parkville

Purpose: Autoimmune regulator (Aire) is a transcription factor expressed in medullary thymic epithelial cells that regulates central tolerance to peripheral self-antigens. Mutations in Aire occur in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED or APS-1). We previously showed that Aire-deficient (Aire-/-) mice on the C57BL/6 background have an enhanced susceptibility to collagen-induced arthritis following immunization with chick type II collagen (CII), a model we have shown is CD4 T cell and B cell dependent. The purpose of this study was to evaluate whether Aire-/- mice are also susceptible to autoimmune arthritis following immunization with self type II collagen (mCII).

Methods: Aire-/- and wild-type (WT) mice were given a single injection of mCII in complete Freund's adjuvant. Mice were monitored for clinical signs of arthritis for up to 41 days. Serum anti-mCII levels were determined by ELISA. The T cell response to mCII was evaluated by [3H]-thymidine incorporation and by ELISpot for interferon-γ. Follicular helper (TFH) T cells (CD4+, CXCR5+, PD-1hi) were evaluated by flow cytometry.

Results: A single immunization with mCII in complete Freund's adjuvant induced severe arthritis in 11 out of 12 Aire-/- mice but only mild disease was observed in 2 of 8 WT mice. The clinical signs of arthritis were confirmed by histology. Disease did not develop in Aire-/- mice (n = 4) that were immunized with mCII in incomplete Freund's adjuvant, showing the requirement for innate system signaling at the time of immunization. Anti-mCII antibodies (IgM and IgG) were detected in the Aire-/- but not in WT mouse sera. A conventional CD4 T cell

response to mCII could not be demonstrated for either mouse genotype. The TFH cell population in pooled spleen and draining lymph nodes was not increased in Aire-/- mice.

Conclusion: The data mirror the response we previously reported for Aire-/- mice immunized with chick CII. Reduced central tolerance to CII in Aire-/- mice manifests as increased CD4 T cell help to B cells for cross-reactive autoantibody production and enhanced CIA. Aire and central tolerance help prevent cross-reactive autoimmune responses to CII initiated by environmental stimuli, as well as spontaneous autoimmunity.

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Altered Fli1 Regulation and Expression in Lupus T Cells and Effects On T Cell Function. John L. Svenson[1] and Tamara K. Nowling[2], [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC

Background/Purpose: Lupus is a systemic autoimmune disease characterized by increased expression of several inflammatory and transcription factor genes. Mounting evidence indicates strongly that the expression level of the transcription factor gene Fli1 has a significant impact on the pathogenesis of lupus. Currently, little is understood about how Fli1 is regulated in lymphocytes and how its expression affects lymphocyte survival and/or function. To identify mechanisms involved in the transcriptional regulation of Fli1 gene expression in lymphocytes from MRL/lpr lupus mice.

Methods: We first isolated splenic T cells from MRL/lpr lupus prone mice and C57BL/6 non-autoimmune prone mice. Cells were stimulated with PMA and Ionomycin. Total RNA was collected and subjected to real-time PCR to assess effects on Fli1 expression. Next, chromatin immunoprecipitation was used to assess the in vivo binding of Ets factors to the Fli1 promoter in MRL/lpr compared to C57BL/6 T cells. Finally, Flow cytometry was used to assess proliferation when Fli1 levels were reduced or increased in T cells of C57BL/6 mice.

Results: Our results demonstrate that Fli1 expression decreases in stimulated T cells from C57BL/6 non-autoimmune prone mice but not MRL/lpr lupus mice. In vivo binding assays demonstrate that the binding of Ets1, Ets2, Fli1 and Elf1 to the endogenous Fli1 promoter in C57BL/6 T cells is altered in primary T cells from MRL/lpr lupus mice. Finally, proliferation of T cells isolated from C57BL/6 with genetically reduced Fli1 activity is increased in response to immune stimuli whereas over-expressing Fli1 in T cells isolated from C57BL/6 results in decreased proliferation.

Conclusion: These results demonstrate that Fli1 expression fails to become down-regulated in MRL/lpr T cells upon activation, likely due aberrant transcriptional regulation. The failure to become down-regulated likely leads to Fli1 over-expression in T cells and these results demonstrate that Fli1 levels impact the proliferation of T cells. Together, our results provide evidence of how changes in regulatory mechanisms may influence expression, cellular function and the pathogenesis of lupus.

Disclosure: J. L. Svenson, None; **T. K. Nowling**, None.

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Immune Complex Is Required but Insufficient for Autoimmune Tissue Injury: Essential Role of Effector CD8+ T Cell. Ken Tsumiyama[1], Akira Hashiramoto[2] and Shunichi Shiozawa[2], [1]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Sciences/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Purpose: We previously showed that repeated immunization with a conventional antigen caused systemic autoimmunity in the mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD8+ T cells by repeated immunization with antigen led to development of full-matured MHC class I-restricted, antigen-specific effector cytotoxic T lymphocyte (CTL). This CTL, generated *via* antigen cross-presentation, subsequently caused autoimmune tissue injury (Tsumiyama K, *et al.* Arthritis Rheum. 58 (suppl. 9): S705, 2008). Here we investigate the contribution of immune complex (IC) to the pathogenesis of autoimmune glomerular lesion, and show that IC is required but still insufficient for autoimmune tissue injury. Instead, full-matured effector CD8+ T cell is absolutely required.

Methods: Wild-type (WT) BALB/c mice, β_2-microlobulin (β_2m)-deficient mice, in which both MHC class I and CD8+ T cells were absent, or μMT mice, who produce no antibodies because of the lack of B cells, were repeatedly immunized with ovalbumin (OVA). Splenocytes of WT mice immunized 12x with OVA were adoptively transferred into naïve WT mice. Renal pathology was assessed by detection of proteinuria and histopathological study, and sera were collected to determine anti-OVA antibody and IC using ELISA. IFNγ-producing CD8+ T cell in spleen was detected under flow cytometry.

Results: Two following findings indicate that CD8+ T cell recognizing MHC class I is essentially required for the induction of autoimmune tissue injury: first, transfer of the $CD8^+$ T cells of mice immunized 12x with OVA induced autoimmune glomerular lesion in recipient mice. Notably, IFNγ-producing CD8+ T cell was newly generated in these recipient mice. Second, after repeated immunization 12x with OVA, massive deposition of IC was observed in the glomeruli of both WT and β_2m-deficient mice, whereas proteinuria were minute as compared to WT mice, and glomerulonephritis was never seen in β_2m-deficient mice. On the other hand, neither IC nor OVA was deposited in the glomeruli of μMT mice that lack B cells even after repeated immunization 12x with OVA. In these μMT mice, however, IFNγ-producing CD8+ T cell was increased to the levels similar to WT mice. Thus, while CD8+ T cells of μMT mice were full-matured as with those of WT mice, proteinuria were not increased and renal lesion was absent in these μMT mice, which indicated that IC is also required for generating glomerulonephritis.

Conclusion: We show that IC or immunizing antigen deposited in target organ is required but insufficient for the induction of autoimmune tissue injury. The full-matured CD8+ T cell is essentially required for the generation of autoimmune tissue injury.

Disclosure: K. Tsumiyama, None; **A. Hashiramoto**, None; **S. Shiozawa**, None.

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T Cell Upregulation of CD80 but Not CD86 Limits Peak Antigen Activated Effector CD8 T Cell Numbers. Irina Puliaeva[1], Roman Puliaev[1], Thomas J. Lang[2] and Charles S. Via[1], [1]Uniformed Svcs Univ Health Sci, Bethesda, MD, [2]Woodstock, MD

Purpose: T cell upregulation of B7 molecules CD80 and CD86 has been shown to limit T cell expansion in immunodeficient hosts however the relative roles of CD80 separate from CD86 on CD4 vs. CD8 T cells in a normal immune system have not been delineated.

Method: To address this question, we used the parent-into-F1 (P->F1) murine model of graft-vs-host disease and transferred T cells deficient in CD80 and/or CD86 into normal, wild type (WT) F1 hosts. Mice were assessed by flow cytometry at selected time points over the first 14 days after transfer for donor T cell engraftment, host cell elimination and in vivo T cell proliferation as measured by bromodeoxyuridine incorporation. Mice were tested individually (n=4-5 mice/group per time point).

Results: CD80 knock out (KO) but not CD86 KO donor cells exhibited a five-fold reduction in the number of donor cells required for complete elimination of host B cells compared to WT donor cells. Kinetic studies comparing CD80 KO to WT donor cells using optimal and sub optimal donor cell doses demonstrated no differences in T cell engraftment prior to day 10 consistent with flow cytometry results demonstrating that maximal donor T cell upregulation of CD80 occurs after day 10. At day 10, CD80 KO->F1 mice exhibited significantly greater donor CD4 and CD8 proliferation, greater day 12 peak donor CD8 T cells and greater day 14 elimination of host cells compared to WT->F1 mice. Despite the greater day 12 peak in CD80 KO donor CD8 T cell engraftment, contraction of CD80 KO T cells nevertheless occurred reflecting CD80-independent downregulatory mechanisms. Mixing of WT and KO donor T cell subsets prior to injection demonstrated that maximal host cell elimination required that CD80 be deficient on both CD4 and CD8 donor T cells.

Conclusion: These results indicate that expression of CD80 but not CD86 on both CD4 and CD8 ag-specific T cells is important in limiting maximal expansion of CD8 CTL effectors as part of a normal immune response. Our results support the therapeutic targeting of CD80 in conditions where stronger CD8 effector responses are desirable.

Disclosure: I. Puliaeva, None; **R. Puliaev**, None; **T. J. Lang**, None; **C. S. Via**, None.

ACR/ARHP Poster Session B

Treatment and Outcomes

Monday, October 19, 2009, 9:00 AM - 6:00 PM

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Placebo-Controlled Study of Rilonacept for Gout Flare Prophylaxis During Initiation of Urate-Lowering Therapy. H. Ralph Schumacher Jr.[1], John S. Sundy[2], Robert Terkeltaub[3], Howard R. Knapp[4], Scott Mellis[5], Yuhwen Soo[5], Shirletta King-Davis[5], Steven P. Weinstein[6] and Allen R. Radin[5], [1]U Penn & VAMC, Philadelphia, PA, [2]Duke Univ Med Ctr, Durham, NC, [3]VAMC/UCSD, San Diego, CA, [4]Billings Clinic Res Ctr, Billings, MT, [5]Regeneron Pharmaceuticals, Tarrytown, NY, [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Purpose: The NALP3 inflammasome/ IL-1 pathway has been implicated in crystal-induced inflammatory arthritides. We assessed weekly subcutaneous rilonacept (R) [IL-1 Trap] 160 mg, a soluble IL-1 receptor-Fc fusion protein, compared to placebo (Pbo) (1:1) for prevention of acute gout flares (GF) during the initiation of urate-lowering therapy in hyperuricemic patients with gout.

Method: A US multi-center, randomized, phase 2 study was initiated in adults with intercritical gout, urate ≥ 7.5 mg/dL, and self-reported history of ≥ 2 GFs in the previous year. Sixteen weeks (wk) of double blind study drug treatment was initiated along with allopurinol 300 mg daily (a lower initial dose was used in those with renal dysfunction), which was titrated to a serum urate < 6 mg/dL. Medications other than study drug for GF prophylaxis were not allowed. GFs (those requiring treatment with an anti-inflammatory agent) were confirmed via phone contact with the study site and reported by the patient via interactive voice response diary. GFs were treated with an NSAID or oral glucocorticoid for 5 to 10 days, with study treatments continued. Endpoints included the mean # of GFs (primary), % of patients with 1 or more GFs, and assessments of safety and tolerability during the treatment period.

Results: 83 patients were randomized, 42 to Pbo and 41 to R. Baseline parameters were similar between treatment groups and included: 80M/3F; mean age, 51 years (27-77); tophaceous gout, 10%; mean # of GFs reported in the prior year, 4.5. Fourteen patients (11 on Pbo/3 on R) withdrew prior to wk 16. Urate levels decreased similarly in both groups.

	Week 12 (primary endpoint timepoint)			Week 16 (end of prophylaxis period)		
	Placebo	Rilonacept	P value	Placebo	Rilonacept	P value
mean per patient [total] # GFs	0.79 [33]	0.15 [6]	0.0011	0.93 [39]	0.22 [9]	0.0036
% [# patients] with ≥1 GF	45% [19]	15% [6]	0.0037	48% [20]	22% [9]	0.0209
% [# patients] with >1 GF	21% [9]	0% [0]	0.0024	26% [11]	0% [0]	0.0005

During the first and last 4-wk period of prophylaxis with study drug and the subsequent 6-week post-prophylaxis period, respectively, 14, 6, and 2 GFs and 2, 3 and 2 GFs were reported in the Pbo and R groups, respectively. Reported adverse events (AE) were similar between treatment groups, with the most common categories being infections (26% on Pbo, 15% on R) and musculoskeletal system disorders (21% on Pbo, 15% on R). No deaths or serious infectious AEs were reported.

Conclusion: In this first double blind, Pbo-controlled trial of IL-1 blockade in patients with gout, rilonacept markedly reduced the occurrence of gout flares during initiation of urate-lowering therapy, and demonstrated an acceptable safety profile. The absence of a post-prophylaxis increase in GFs suggests that a 16-wk period of GF prophylaxis may be sufficient in many patients.

Disclosure: H. R. Schumacher, Regeneron, 5 ; **J. S. Sundy**, Regeneron, 5 ; **R. Terkeltaub**, Regeneron, Novartis, Pfizer, Takeda, Savient, ARDEA, URL Pharma, 5, VA, NIH, 2 ; **H. R. Knapp**, Regeneron, 2 ; **S. Mellis**, Regeneron, 1, Regeneron, 3 ; **Y. Soo**, Regeneron, 1, Regeneron, 3 ; **S. King-Davis**, Regeneron, 1, Regeneron, 3 ; **S. P. Weinstein**, Regeneron, 1, Regeneron, 3 ; **A. R. Radin**, Regeneron, 1, Regeneron, 3 .

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Evidence for a Two-Stage Approach to Urate-Lowering Therapy in Patients with Gout. Fernando Perez-Ruiz[1] and Ana M. Herrero-Beites[2], [1]Hospital De Cruces, Barakaldo, Spain, [2]Hospital de Gorliz, Gorliz, Spain

Purpose: Lowering serum urate (Sur) level under the threshold for saturation (<6 mg/dl) is considered to be the target to completely dissolve monosodium urate (MSU) crystal deposits in patients with gout (Pascual E, et al, Ann Rheum Dis 2008). Life-long therapy is recommended to avoid new crystal formation, but there is no evidence to support life-long therapy achieving Sur < 6 mg/dl after depletion of MSU deposition.

Method: A cohort of patients is followed-up after voluntary withdrawal of urate-lowering therapy (initial 98 patients reported in: Perez-Ruiz F, Arthrits Rheum 2006) with the following inclusion criteria: achieving Sur < 6 mg/dl for 5-year or 5-year after the disappearance of the last subcutaneous tophus. Sur control was made at least twice the first year and at least once a year afterwards. Average Sur during follow-up was calculated using a trapezoidal method. Both diagnosis of gout and diagnosis of recurrence were based on MSU crystal observation. Kaplan-Maier analysis for survival function was used stratifying patients on the distribution of Sur into terciles for those over 7.0 mg/dl.

Results: 194 patients. 49 (25.3%) tophaceous, 168 (87.6%) with two or more joints involved were treated a mean of 65±9 months, range 58 to 116 months, achieving mean average Sur levels 4.89±0.84, range 2.80-5.99 mg/dl. Baseline Sur was 8.84±1.29 and 8.67±1.46 mg/dl after withdrawal of ULDs. Mean time on treatment was 65±9 months (range 58-116 months), mean follow-up after ULDs withdrawal was 29 months (range 6 to 124). Recurrence of gout was observed in 73 (37.6%) patients. There were 22 (11.3%) patients showing Sur 6-7 mg/dl after ULDs withdrawal, none of them showing recurrence. Patients with Sur > 7 mg/dl were divided into groups by terciles distribution: 7.01 to 8.22, 8.23 to 9.50, >9.50 mg/dl. Results of the rate of recurrence and estimated median and 95% confidence interval limits of time to recurrence are shown in Table 1. Survival function graphic is shown in Figure 1.

Table 1. Kaplan-Meier analysis for survival for serum urate levels

Serum urate after UDLs withdrawal	N	Events	%			
				Median Estimation (months)	Lower 95% CI limit	Upper 95% CI limit
≤7.0 mg/dl	22	0	0			
7.01-8.22 mg/dl	52	13	25.0	69	44	93
8.22-9.50 mg/dl	53	27	52.9	44	40	48
>9.50 mg/dl	53	33	61.1	24	41	50

Conclusion: After long-term achievement of proper control of serum urate levels far below the saturation threshold (crystal depletion period), subsequent target for proper control of Sur level could be settled just below the saturation threshold (prevention of new crystal formation period).

Disclosure: F. Perez-Ruiz, Ipsen, 5, Pfizer Inc, 5, ARDEA Biosciences, 5, Savient, 5 ; **A. M. Herrero-Beites**, None.

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Patients' and Providers' Views of Gout Management: A Qualitative Study. Leslie R. Harrold[1], Kathleen M. Mazor[2], Sarah J. Velten[2], Ira S. Ockene[1] and Robert A. Yood[3], [1]University of Massachusetts Medical School, Worcester, MA, [2]Meyers Primary Care Institute, Worcester, MA, [3]Fallon Clinic, Worcester, MA

Purpose: Previous research has shown that gout is often not properly managed. We sought to examine patients' and providers' views on the treatment of gout to better understand why management is so challenging.

Method: In-depth telephone interviews were conducted with gout patients (n=26) who initiated treatment with a urate-lowering drug (ULD) in the prior 6 months and with providers who care for gout patients (n=15), mostly primary care physicians. The interviews were audiotaped and transcribed verbatim. Using qualitative methods, results were analyzed and themes were identified. Interviews focused on acute management, chronic management, prevention and improvement strategies.

Results: For treatment of acute gout symptoms, providers viewed the majority of patients as having excellent relief with NSAIDs, colchicine and glucocorticoids. In contrast, some patients felt the medications prescribed were ineffective. For chronic gout therapy, providers felt most patients had a good understanding of the rationale for ULD therapy and that patients responded well. Many patients were unsure of the duration of chronic therapy and some felt ULDs triggered, worsened or had no impact on their disease. Most providers thought medication adherence was relatively good. Some patients reported discontinuing medications. Discontinuations were largely purposeful and due to clinical or financial concerns. Most providers thought their patient education was adequate to teach disease self-management behaviors. Patients requested more information, more time for interactions and greater awareness by their providers of the use of natural remedies.

Table 1. Responses from the patient and provider in-depth interviews.

Themes	Provider's responses	Patients' responses
Chronic medication management		
Education and knowledge	Patients have a good understanding regarding the need for long-term medication use.	They were aware that allopurinol reduces serum uric acid levels, but had unanswered questions regarding gout etiology
Treatments	Allopurinol was prescribed; the dose was adjusted based on symptoms, serum uric acid level and renal function.	Several changed doses during attacks; many patients were unclear of the duration of therapy with allopurinol.
Response to treatment	Patients respond well to therapy.	Several believed allopurinol triggered or worsened their gout.
Prevention and adherence		
Recommendations	Dietary changes were recommended to most patients.	Most reported receiving recommendations on dietary changes to prevent gout.
Follow through on recommendations	Medication adherence is not a problem as the pain of a gout attack is a strong motivator; lifestyle changes more challenging for patients to adhere to.	Most reported incorporating the recommended lifestyle changes; medication nonadherence was due to clinical and financial factors.

Conclusion: There is a striking disconnect between how providers and patients view gout and its management.

Disclosure: L. R. Harrold, None; **K. M. Mazor**, None; **S. J. Velten**, None; **I. S. Ockene**, None; **R. A. Yood**, None.

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Methotrexate as An Alternative for Refractory Calcium Pyrophosphate Arthropathy. Francisca Sivera, Mariano Andres, Juan Miguel Lopez-Gomez, Paloma Vela and Eliseo Pascual, Dpt. Rheumatology, Hospital General Universitario Alicante, Alicante, Spain

Purpose: A series of 5 patients suffering from chronic calcium pyrophosphate dihydrate (CPPD) arthritis and responding poorly to non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine treatments has been reported to respond to methotrexate (MTX) [*Arthritis Rheum* 2007;56:688-921]. We present our experience with the use of MTX in 8 similar patients with CPPD arthropathy.

Method: Retrospectively we identified 8 patients who are currently followed at our clinics after successful treatment with low dose MTX for chronic primary CPPD arthropathy (all diagnosed by crystal identification and all had radiologic chondrocalcinosis). All patients were refractory to NSAIDs and colchicine. Treatment response was evaluated by the physician's opinion (excellent, good, medium, poor or absent response) and the patient's opinion, measured on a 10-cm visual analogue scale (0=no effect; 10=complete resolution of symptoms). Months of follow-up, initial and maximum MTX dose, administration route, the use of colchicine, glucocorticoids or NSAIDs and adverse effects was recorded on all patients.

Results: Four patients presented with persistent polyarthritis, three with persistent oligoarthritis and one patient with frequent recurrent bouts of severe acute monoarthritis ("pseudogout") in ankle, knee and wrist. Median duration of the disease since its diagnosis prior MTX was 32.5 months (range 1-96). In 6/8 patients MTX was administered orally, and subcutaneously in the remaining 2. Seven out of 8 patients received colchicine too. No patients were on NSAIDs or glucocorticoids. MTX efficacy measured by both patient and physician was in general good to excellent (Table). MTX was discontinued in 2 patients due to adverse effects (transient bone marrow aplasia and elevation of liver enzymes).

Results:

Characteristics, efficacy and adverse effects in CPPD arthropathy treated with MTX

Sex/Age (years)	**CPPD presentation**	**MTX maximum dose (mg/wk)**	**Time on MTX (months)**	**Evaluation (physician)**	**Patient opinion**	**Adverse effects**
M/69	Polyarthritis	12.5 or	7	Excellent	8	Leukopenia
F/65	Oligoarthritis	7.5 or	12	Good	7	None
F/59	Polyarthritis	20 or	18	Good	6	None
F/83	Oligoarthritis	10 sc	18	Good	9	None
F/46	Monoarthritis	15 sc	10	Good	8	None
M/76	Polyarthritis	20 sc	12	Excellent	8	None
F/70	Oligoarthritis	15 or	48	Medium	5	Liver enzymes
F/81	Polyarthritis	15 or	9	Good	9	Myelotoxicity & Stomatitis

M: male; F: female; or: orally, sc: subcutaneous.

Conclusion: Our results support the results of the reference and indicate that MTX is an effective treatment for at least some patients with chronic CPPD arthropathy. Additional studies are necessary to determine to what extent and for which patients is MTX effective.

Disclosure: F. Sivera, None; **M. Andres**, None; **J. M. Lopez-Gomez**, None; **P. Vela**, None; **E. Pascual**, None.

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Pegloticase Therapy Does Not Increase Oxidative Stress Status. Michael S. Hershfield[1], L. Jackson Roberts II[2], Nancy J. Ganson[1], Susan J. Kelly[1], John S. Sundy[3], Edna Scarlett[4] and Denise A. Jaggers[5], [1]Duke University Med Ctr, Durham, NC, [2]Vanderbilt University, Nashville, TN, [3]Duke Univ Medical Ctr, Durham, NC, [4]Durham, NC, [5]Durham

Purpose: Pegloticase, a pegylated recombinant mammalian urate oxidase, can rapidly lower plasma urate (PUA) to <2 mg/dL. Since urate is postulated to be an important free radical scavenger, and urate oxidation generates hydrogen peroxide, it has been suggested that pegloticase therapy might increase oxidative stress. To address this concern, we examined plasma concentration of F2-Isoprostanes (IsoP) in a phase 2

trial of pegloticase in 21 patients with refractory gout. IsoP result solely from free radical attack on membrane-associated arachidonic acid, and plasma IsoP is well validated as a biomarker of oxidative stress status.

Method: Plasma IsoP was measured by GC-MS, and PUA by HPLC. The clinical protocol called for 5 infusions of pegloticase (8 mg) at 3 week intervals. PUA and IsoP were assessed at baseline and 2, 48, and 168 h after infusion #1, at 7 d after the final infusion, and at a follow-up visit about 7 weeks later.

Results: At baseline, mean PUA was 10.8 +/- 1.3 mg/dL, and mean plasma IsoP was 69 +/- 40 pg/mL (normal, 35 +/- 6 pg/mL). After pegloticase infusion #1, PUA fell to 7.0 mg/dL within 2 h, and to <1 mg/dL at 48 and 168 h in all 21 subjects. In 15 subjects, mean PUA remained <1 mg/dL at 7 d after the final infusion, and was 6.3 mg/dL at follow-up. In 6 subjects who developed clearing antibodies to pegloticase, mean PUA in the final 2 samples had returned to baseline. Overall, plasma IsoP showed no relationship to PUA ($R^2 = 0.01$). As a change from baseline, mean plasma IsoP (all 21 patients) decreased by 7% by d 7 after infusion #1, and by 12% at 7 d after the last infusion of pegloticase in the 15 persistently hypouricemic patients.

Conclusion: Elevated baseline plasma IsoP suggests that hyperuricemia in refractory gout is associated with high oxidative stress. Sustained hypouricemia induced by IV pegloticase therapy was associated with a slight, but non-significant decrease in plasma IsoP, and over a wide concentration range there was no correlation between plasma urate and IsoP levels. These findings indicate that pegloticase therapy does not increase oxidative stress status, and they raise questions about the importance of urate as a free radical scavenger.

Disclosure: M. S. Hershfield, Savient Pharmaceuticals, Inc, 2, Savient Pharmaceuticals, Inc, 5, Savient Pharmaceuticals, Inc, 7 ; **L. J. Roberts**, None; **N. J. Ganson**, None; **S. J. Kelly**, Savient Pharmaceuticals, Inc, 7 ; **J. S. Sundy**, Savient, 2, Savient, 5, Takeda, 8, Ardea, 5 ; **E. Scarlett**, None; **D. A. Jaggers**, None.

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Improvement in Health-Related Quality of Life (HRQOL) in Patients with Treatment Failure Gout (TFG) Treated with Pegloticase Measured by SF-6D Derived Utility. Vibeke Strand[1], N. Lawrence Edwards[2], Herbert S. B. Baraf[3], M. A. Becker[4], John S. Sundy[5], B. Huang[6] and A. Forsythe[7], [1]Stanford University, Portola Valley, CA, [2]Univ of Florida, Gainesville, FL, [3]Arthritis & Rheumatism Associates, P.C., Wheaton, MD, [4]University of Chicago, Chicago, IL, [5]Duke Univ Medical Ctr, Durham, NC, [6]Savient Pharmaceuticals, Inc., East. Brunswick, NJ, [7]Savient Pharmaceuticals, Inc., East Brunswick, NJ

Background: Short Form-6D (SF-6D) is an indirect preference-based measure derived from responses to the Medical Outcomes Survey Short Form 36 (SF-36) to assess quality-adjusted life years (QALYs), ranging from 0.30 to 1.00; higher values indicating better health. New methodologies allow 8 mean SF-36 domain scores to be converted into utility scores (SF-6D) that can be used to calculate QALYs.[1,2]

Purpose: To assess the effectiveness of Pegloticase (PGL) 8 mg q2 wks treatment in patients (pts) with TFG over 6 and 12 months by changes in SF-36 and SF-6D.

Methods: Primary data was collected from 2 replicate phase 3 trials of 6 months duration and open label extension (OLE). PGL 8 mg IV was administered q2 or q4 wks vs placebo (Pbo), followed by PGL q2 or q4 wks or observation in OLE. Patients (N=212 at baseline) completed SF-36 at baseline, and weeks 13, 19, 25, 37 and 49.

Results: At baseline, SF-36 domain scores were 4.4 – 32.3 points lower and SF-6D: 0.646 compared with age and gender matched US norms: 0.759, reflecting the major impact of TFG upon HRQOL. Improvements in SF-6D with q2 wks PGL treatment at Week 25 were large (Table) SF-6D change = 0.084, clinically meaningful, well exceeding the minimum clinically important difference (MCID) for SF-6D of 0.041. SF-36 changes at week 25 were statistically significant in 6 domains, reflected by an increase in PCS of 6.42; ≥MCID in all domains and met or approached A/G norms in 5 domains vs. no improvement reported by subjects receiving PBO. Sustained or further improvements were evident over 49 wks treatment in OLE. Improvements in SF-36 scores were consistent with those reported in patient global, pain and physical function (by HAQ); and resulted in Number Needed to Treat values of 1.2 to 4.5 based on changes ≥MCID in 1, 2, 3 or all 4 patient reported outcomes.

Conclusion: PGL q2 wks therapy resulted in clinically meaningful improvements in SF-36 and SF-6D utilities approaching US A/G norms, reflecting that pharmacodynamic effects of PGL treatment (normalization of uric acid and resolution of tophi) result in disease modification in this TFG population.

Table: PGL q2 wks: SF-36 domain and SF-6D utility scores

Domain	PCS	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	SF-6D
A/G norms	50.0	77.5	76.7	67.5	67.1	58.8	81.8	84.2	75.0	0.759
PGL Baseline	35.16	45.2	47.2	37.4	47.4	47.3	61.9	69.4	68.6	0.646
Pbo Wk 25	22.31	40.0	45.1	35.8	45.5	45.2	63.2	75.4	75.5	0.649
PGL Wk 25	40.44*	59.5*	64.2*	61.8*	56.3*	60.0*	77.4*	79.8	79.3	0.730

* indicates $p<0.05$ vs placebo

[1, 2]. Ara and Brazier. *Value in Health* 2008:12:346 and 2009:11:7

Disclosure: V. Strand, Takeda Inc., , 5, Savient Pharmaceuticals, Inc., 5 ; **N. L. Edwards**, Savient Pharmaceuticals, Inc, 5 ; **H. S. B. Baraf**, Savient Pharmaceuticals, Inc. ; **M. A. Becker**, Savient Pharmaceuticals, Inc, 5 ; **J. S. Sundy**, Savient, 2, Savient, 5, Takeda, 8, Ardea, 5 ; **B. Huang**, Savient Pharmaceuticals, Inc., 3 ; **A. Forsythe**, Savient Pharmaceuticals, Inc, 3 .

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Evaluation of Drug-Drug Interaction Potential Between RDEA594, Allopurinol and Febuxostat in Preclinical Species. Xiaoqing Yang, Ryan Dick, Virginia Borges, Nahid Yazdani, Andrea Green, Kimberly Manhard, Barry Quart and Li-Tain Yeh, Ardea Biosciences, San Diego, CA

Purpose: RDEA594 has demonstrated serum uric acid (sUA) lowering effects in humans following dosing of either of RDEA594 or its parent, RDEA806, in over 300 healthy volunteers and patients. The lowering of sUA is directly linked to increased urinary excretion of uric acid, which is believed to result from inhibition of the URAT1 transporter. Allopurinol, its active metabolite oxypurinol, and febuxostat, are xanthine oxidase inhibitors used in the treatment of gout. Because of a different mode of action, RDEA594 could be used in combination with allopurinol or febuxostat for uric acid lowering therapy. Assessment of the drug-drug interaction potential between RDEA594, allopurinol and febuxostat was conducted in monkeys and rats.

Method: In male Cynomolgus monkeys, a two period, one-way crossover study was conducted with oral administration followed by plasma and urine collection. In Period 1, a single dose of either RDEA594 at 25 mg/kg (group 1) or allopurinol at 12 mg/kg (group 2) was administered. After a 7 day wash out, in Period 2, RDEA594 was administered concomitantly with allopurinol (group 1), or allopurinol administered concomitantly with RDEA594 (group 2). In Sprague-Dawley rats, RDEA594 or febuxostat was dosed for 3 days before concomitant administration of the other compound on Day 4. The resulting pharmacokinetics of RDEA594 or febuxostat following co-administration was then compared to rats receiving single dose of either RDEA594 at 30 mg/kg or fexobustat at 10 mg/kg.

Result: RDEA594 had no effect on the plasma PK or urinary excretion of allopurinol and oxypurinol in monkeys. Comparing allopurinol plus RDEA594 versus allopurinol alone, the C_{max} and AUC for allopurinol were 0.55 µg/mL, 1.23 µg*hr/mL and 0.65 µg/mL, 1.61 µg*hr/mL, respectively, with $P > 0.05$, indicating an absence of interaction. The C_{max} and AUC for oxypurinol were 2.1 µg/mL, 15.1 µg*hr/mL and 2.0 µg/mL, 14.0 µg*hr/mL, respectively, with $P > 0.05$. The urinary excretion of Allopurinol and oxypurinol were also found to be unaffected by concomitant RDEA594 administration. Similarly, Allopurinol was found to have no effect on the plasma PK or the urinary excretion of RDEA594. Findings from *in vivo* rat study indicated that RDEA594 had no effect on the plasma PK of febuxostat, and vice versa.

Conclusion: No drug-drug interactions were found between the xanthine oxidase inhibitors allopurinol, oxypurinol, febuxostat and RDEA594. RDEA594 coadministration did not alter plasma PK or urinary excretion of the xanthine oxidase inhibitors, and they did not affect the plasma PK and urinary excretion of RDEA594.

Disclosure: X. Yang, Ardea Biosciences, 1 ; **R. Dick**, Ardea Biosciences, 3 ; **V. Borges**, Ardea Biosciences, 1 ; **N. Yazdani**, None; **A. Green**, Ardea Biosciences, 3 ; **K. Manhard**, Ardea Biosceinces, 3 ; **B. Quart**, Ardea Biosciences, 3 ; **L. T. Yeh**, Ardea Biosciences, 3 .

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Colchicine Efficacy Assessed by Time to 50% Reduction of Pain Is Comparable in Low Dose and High Dose Regimens: Secondary Analyses of the AGREE Trial. Robert Terkeltaub[1], D. E. Furst[2], Katherine Bennett[3], Karin Kook[3], R. S. Crockett[4] and Matthew W. Davis[5], [1]VA Medical Ctr, San Diego, CA, [2]UCLA, Los Angeles, CA, [3]Salamandra, LLC, Bethesda, [4]D.A.T.A. Inc, Bayou La Batre, AL, [5]United Research Laboratories, Philadelphia, PA

Purpose: Colchicine has been used for centuries for the treatment of gout flares but until recently it has not been studied extensively for safety and efficacy in controlled trials. The randomized, double-blind (DB), placebo-controlled AGREE trial established that low-dose (LD) colchicine is as effective as high-dose (HD) colchicine in achieving flare control with a placebo-like side effect profile. This analysis focuses on the efficacy of colchicine as reflected by time to 50% joint pain reduction. Also investigated was a comparison of pain improvement scores at 24 and 32 hr following administration of study drug.

Methods: Patients (pts) with acute gout flare (ACR criteria) were randomly assigned to HD colchicine (4.8 mg: 1.2 mg initially, then 0.6 mg q1hr ×6), LD colchicine (1.8 mg: 1.2 mg initially, then 0.6 mg at 1 hr), or placebo (PBO) groups. After confirmation of gout flare, pts took study drug or placebo and recorded pain intensity as well as adverse events (AEs) for 72 hr thereafter. Efficacy was defined as ≥2-unit reduction in target joint pain score at 24 hr. Pain improvement scores were analyzed 24 and 32 hrs post first dose.

Results: 575 pts were randomized and 184 received study drug or PBO (52 HD, 74 LD, and 58 PBO). Mean baseline pain scores were 6.8 to 6.9 (0 to 10 scale). Both HD and LD colchicine groups achieved significant reduction (≥2-units) in mean pain scores relative to PBO at 24 and 32 hrs post first dose (see table). There was no statistical difference between colchicine groups in time to 50% joint pain reduction (24.5 hr for HD, 24 hr for LD). Rates of AEs were similar between LD and PBO groups, but greater than PBO in the HD group.

	(%) of Responders			**Treatment Comparisons**		
	Colchicine Dose			**(Odds Ratio and 95% CI)[1]**		
Hours Post First Dose	**High (N = 52)**	**Low (N = 74)**	**Placebo (N = 58)**	**High *vs.* Placebo**	**Low *vs.* Placebo**	**High *vs.* Low**
24	34.6	43.2	17.2	2.54 (1.04, 6.18) p = 0.0368	3.66 (1.61, 8.32) p = 0.0015	0.69 (0.33, 1.45) p = 0.3298
32	38.5	45.9	17.2	3.00 (1.24, 7.24) p = 0.0126	4.08 (1.80, 9.27) p = 0.0005	0.74 (0.36, 1.51) p = 0.4033

[1]p-value comparisons using unstratified Pearson chi-square test.

Conclusion: Unlike NSAIDs used for acute gout, colchicine has no primary analgesic properties. Yet in this first PBO controlled, DB study, colchicine provided significant joint pain relief (without adjunctive analgesic therapy) within 24 hr post-drug administration. Both HD and LD groups achieved significant gout joint pain relief by 24 hr compared to PBO. HD and LD efficacy also was observed 32 hr following initial dose. Despite similar pain relief seen in LD and HD groups, the LD colchicine safety profile was comparable to PBO. These results provide further evidence for the treatment of early acute gout flare with a LD colchicine regimen.

Disclosure: R. Terkeltaub, NIH, 2, VA., 2, Takeda, 2, Altus, 5, Ardea, 5, BioCryst, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Proctor and Gamble, 5, Regeneron, 5, Savient, 5, EnzymeRx, 5, Takeda, 5, URL Pharma, 5, UCB, 5 ; **D. E. Furst**, Wyeth Pharmaceuticals, 5, UCB, 5, Novartis Pharmaceutical Corporation, 5, Nitec, 5, Merck Pharmaceuticals, 5, GlaxoSmithKline, 5, Genentech , 5, Gilead, 5, Centocor, Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Amgen, 5, Actelion Pharmaceuticals US, 5, Abbott Laboratories, 5, Xoma Corporation , 2, Wyeth Pharmaceuticals, 2, UCB, 2, Roche

Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Nitec, 2, NIH, 2, GlaxoSmithKline, 2, Gilead, 2, Genentech , 2, Bristol-Myers Squibb, 2, Amgen, 2, Abbott Laboratories, 2, Actelion Pharmaceuticals US, 2, Xoma Corporation , 5, Abbott Laboratories, 8, Actelion, 8, UCB, 5, Abbott Laboratories, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech , 9, Gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9 ; **K. Bennett**, URL Pharma, 9 ; **K. Kook**, URL Pharma, 9 ; **R. S. Crockett**, United BioSource, 9 ; **M. W. Davis**, URL Pharma, 1, URL Pharma, 3 .

1104

Routine Serum Uric Acid (SUA) Monitoring Predicts Antibody-Mediated Loss of Response and Infusion Reaction Risk During Pegloticase Therapy. Dave Wright[1], John S. Sundy[2] and Theresa Rosario-Jansen[1], [1]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [2]Duke Univ Medical Ctr, Durham, NC

Purpose: To characterize relationship between development of anti-pegloticase antibodies (α-PGL), SUA and IRs during pegloticase therapy.

Methods: Pegloticase is a PEGylated recombinant mammalian uricase developed for treating the signs and symptoms of treatment failure gout. Subjects in 2 replicate randomized, double-blind, placebo-controlled studies received pegloticase 8 mg IV q2wks or q4wks or placebo (pbo). Persistent responders maintained SUA <6.0 mg/dL for ≥6 months; transient responders had initial SUA lowering, but SUA returned to ≥6.0 mg/dL. A validated ELISA was used to measure α-PGL during the 6 month studies. IRs were defined as any adverse event occurring during or within 2 hrs post-infusion. Relationships between α-PGL, SUA and IRs were assessed.

Results: α-PGL were detected in 88% of subjects on pegloticase q2wks and q4wks groups and in 15% pbo. Titers were mostly ≤1:2430 in persistent responders (55 of 65). In transient responders, titers usually exceed 1:2430 (67 of 104). α-PGL recognized the PEG moiety of pegloticase. Isotyping of α-PGL showed that 78% had both IgM and IgG, 20% had IgM only, and 2% had IgG only. Development of α-PGL was associated with loss of SUA response due to accelerated clearance of pegloticase. The presence of α-PGL significantly decreased peak and trough serum pegloticase, but were not directly neutralizing of pegloticase activity assayed *in vitro*. Approximately 80% of transient responders lost the SUA response in the first 5 wks of therapy, and ~90% in the first 8 wks. At the time SUA rose in transient responders, serum pegloticase was no longer detectable and α-PGL were rising, but there was no relationship to α-PGL titer at this time point. IRs occurred in 26% in q2 wk and 40% of q4wk groups. In subjects with IRs, 20/22 and 20/34 in the q2wk and q4wk groups, respectively, had SUA ≥6 mg/dL at the time of IR and high levels of α-PGL (mean titer 1:28,013). Most (71%) IRs occurred after loss of SUA response. In those receiving the recommended q2wk dosage of pegloticase, 91% of IRs would have been avoided if pegloticase treatment had been discontinued when SUA was ≥6 mg/dL.

Conclusion: Development of anti-pegloticase antibodies is associated with loss of SUA response and the majority IRs. Most IRs occurred after loss of SUA response. Therefore, routine SUA monitoring can be used to prospectively identify patients receiving pegloticase who may no longer benefit from treatment and are at greater risk for IRs.

Disclosure: D. Wright, Savient Pharmaceuticals, Inc., 3 ; **J. S. Sundy**, Ardea, 5, Takeda, 8, Savient, 5, Savient, 2 ; **T. Rosario-Jansen**, Savient Pharmaceuticals, Inc., 3 .

1105

RDEA594, a Novel Uricosuric Agent, Significantly Reduced Serum Urate Levels and Was Well Tolerated in a Phase 2a Pilot Study in Hyperuricemic Gout Patients. Ben Lasko[1], Beth Sheedy[2], Vijay Hingorani[2], Guy Tellier[3], Kimberly Manhard[2], Li-Tain Yeh[2], Jeffrey N. Miner[2], Bradley Kerr[2], Zancong Shen[2] and Barry Quart[2], [1]Manna Research, Toronto, ON, [2]Ardea Biosciences, San Diego, CA, [3]Omnispec Clinical Research, Mirabel, QC

Purpose: RDEA594 is in development for the management of hyperuricemia in gout patients. It is a uricosuric agent that acts through inhibition of the uric acid transporter (URAT1) in the proximal tubule of the kidney. RDEA594 was safe and well tolerated and demonstrated dose-dependent reductions in serum urate (sUA) in over 100 healthy volunteers in Phase I studies of up to 10 days duration. The primary objective of this pilot study was to compare the proportion of patients whose sUA level was <6.0 mg/dL following 2 weeks of continuous treatment with RDEA594 compared to allopurinol and placebo in gout patients

Method: Twenty-one gout patients with hyperuricemia (sUA ≥ 8.0 mg/dL) were enrolled. Patients were randomized in a 2:1:1 ratio to the following treatment groups: RDEA594 200 mg once daily (qd) for 1 week followed by 400 mg qd for 1 week, RDEA594 matching placebo qd for 2 weeks, or open-label allopurinol 300 mg qd for 2 weeks. The study included a 2-week run-in period, a 2-week treatment period, and

a 1 week follow-up period. To reduce the incidence of gout flares, colchicine (0.6 mg qd) was administered to all patients throughout the 5-week study. An immediate release (IR) capsule formulation was administered under fed conditions. Serum urate levels were assessed at baseline, Days 1, 8, 9, 14 and 15, and at the end of the follow-up period. Safety was assessed by adverse events (AEs), clinical laboratory test results, vital signs, 12-lead ECGs, and physical examinations. Drug exposure was assessed by measuring concentrations of RDEA594 in plasma and urine.

Results: Preliminary results suggest that RDEA594 plasma levels in gout patients were generally consistent with those observed in Phase 1 healthy volunteer studies. A large majority of the patients achieved target sUA concentrations of less than 6 mg/dL after the first week of treatment, which was comparable to patients receiving allopurinol and significantly better than placebo. On average, RDEA594-treated patients achieved a 40% reduction in serum urate levels by this early time point. RDEA594 was well tolerated in this study, with no serious adverse events and no premature discontinuations due to adverse events at the time of this assessment

Conclusion: Preliminary results in this pilot study show that RDEA594 lowers sUA and is well tolerated after dosing in gout patients with hyperuricemia

Disclosure: B. Lasko, None; **B. Sheedy**, Ardea Biosciences, Inc, 3 ; **V. Hingorani**, Ardea Biosciences, 5 ; **G. Tellier**, None; **K. Manhard**, Ardea Biosceinces, 3 ; **L. T. Yeh**, Ardea Biosciences, 3 ; **J. N. Miner**, Ardea biosciences, 3 ; **B. Kerr**, Ardea Pharmaceuticals, 5 ; **Z. Shen**, Ardea Biosciences Inc, 3 ; **B. Quart**, Abdea Biosciences, 3 .

1106

Allopurinol Hypersensitivity Reactions: A Case-Control Study of the Role of Renal Dosing. Miriam S. Silverberg[1], Rajitha Mallela[2], Alan J. Lesse[1], Matthew R. Bonner[1], Alan N. Baer[3] and Carl Li[1], [1]University at Buffalo, Buffalo, NY, [2]University of Rochester, Rochester, NY, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: The use of standard dose allopurinol in patients with impaired renal function has been linked with the development of allopurinol hypersensitivity reactions. In 1984, Hande et al (Am J Med 76:47-56) noted an increased frequency of renal impairment among reported patients with severe allopurinol hypersensitivity reactions and proposed guidelines for the reduction of the dose of allopurinol based on estimated glomerular filtration rate (GFR). The objective of this study was to determine whether allopurinol doses higher than those recommended in these guidelines are associated with an increased frequency of hypersensitivity reactions among gout patients.

Method: We conducted a case-control study among patients with a diagnosis of gout (n= 66) from 10/2004 – 11/2007 in the VA computerized chart system. Cases (n=15) were defined based on the presence of an allopurinol hypersensitivity reaction in the adverse reactions section of the patient's medical record. Controls (n = 51) were patients with gout on allopurinol who had not had an adverse reaction to allopurinol. Each study patient was categorized as to whether or not allopurinol dose was high, low, or appropriate for GFR based on published guidelines. Charts were reviewed for description of allopurinol reactions.

Results: Adverse cutaneous reactions occurred in 13 patients (rash 12, pruritus 1), agranulocytosis in one, and angioedema in one. A higher percentage of cases had allopurinol dosed low or appropriate according to the guidelines compared to controls, although the difference was not statistically significant (66.7 vs 43.1%, p=0.109). More patients in the control group were taking ACE inhibitors (51.0 vs 20.0%, p=0.034). Otherwise there was no significant difference between the 2 groups (Table).

Table (percentage appears in brackets)

	Cases n=15	Controls n=51	p Value
Mean Age (yrs) [95%CI]	72.3 [61.8,86.1]	71.3 [60.4,82.2]	0.425
Caucasian	10 (66.7)	44 (86.3)	0.125
Male gender	15 (100)	50 (98.0)	

Thiazide diuretic	0 (0)	9 (17.6)	0.106
Other diuretic	4 (26.7)	15 (29.4)	1.00
Ampicillin/Amoxicillin	0 (0)	4 (7.8)	0.567
ACE inhibitor	3 (20.0)	26 (51.0)	0.034
ARB	1 (6.7)	3 (5.9)	1.00
Allopurinol dose:			
100 mg	8 (53.3)	22 (43.1)	NS
300 mg	6 (40.0)	29 (56.9)	
other	1 (5.9)	0	
Average creatinine clearance (ml/min) [range]	54.6 [27-75]	63.5 [35-99]	
Dose low or appropriate according to guidelines of Hande et al	10 (66.7)	22 (43.1)	0.109

Conclusion: Our study did not demonstrate a relationship between the development of hypersensitivity reactions and the prescription of allopurinol at doses higher then recommended by the guidelines. Surprisingly, the cases were more likely to be taking allopurinol at appropriate doses or doses lower than recommended by the guidelines, although the difference between cases and controls was not statistically significant. These results are important as adherence to these guidelines may lead to suboptimal control of hyperuricemia and therefore recurrent flares of gout.

Disclosure: M. S. Silverberg, None; **R. Mallela**, None; **A. J. Lesse**, None; **M. R. Bonner**, None; **A. N. Baer**, None; **C. Li**, None.

1107

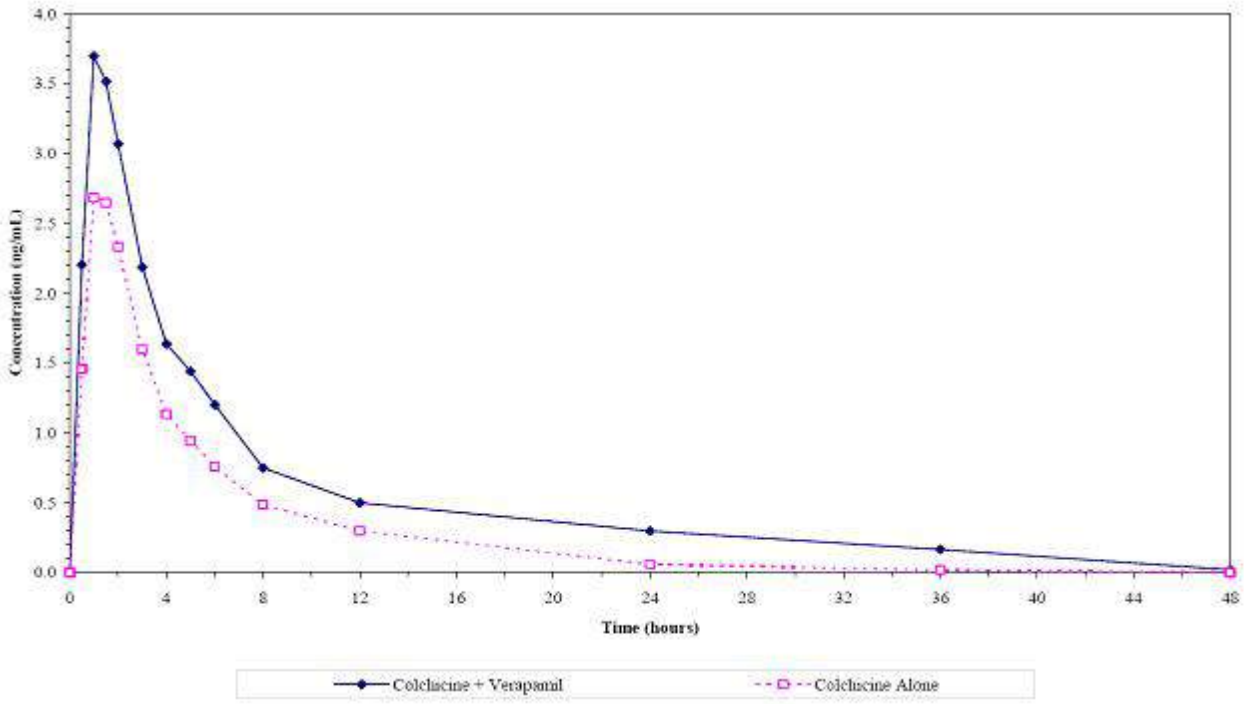
New Dosing Guidelines for Colchicine to Avoid Toxicity When Used with Ca2+ Channel Blockers: The Potent P-Gp/CYP3A4 Inhibitor Verapamil Increases Maximal Concentration of Single-Dose Colchicine by 30% and Exposure by ~100% in Healthy Subjects. Robert Terkeltaub[1], D. E. Furst[2], Karin Kook[3], Jennifer L. DiGiacinto[3] and Matthew W. Davis[4], [1]VA Medical Ctr, San Diego, CA, [2]UCLA, Los Angeles, CA, [3]Salamandra, LLC, Bethesda, [4]United Research Laboratories, Philadelphia, PA

Purpose: Despite the widespread use of colchicine for treatment of acute gout flares, there has been little characterization of colchicine (COL) drug-drug interactions (DDI). Colchicine is a substrate for both the CYP3A4 enzyme and P-glycoprotein (P-gp) transporter. Of particular interest are DDIs involving drugs often used concomitantly with COL that could impact COL metabolism. Currently, 25-50% of gout patients have hypertension. 2.5 billion tablets of verapamil (VER) are prescribed/yr in the USA, principally for hypertension. We previously described the pharmacokinetics (PK) for the calcium channel blocker diltiazem (1.7 billion tablets/yr prescribed) with COL. In that study concomitant diltiazem increased the COL C_{max} value by 31% as well as AUC values by 87% ($AUC_{0-\infty}$). Here, we examined the effects of VER, a potent P-gp/CYP3A4 inhibitor on the PK of single-dose COL.

Methods: In this open-label, 2-period, DDI study, fasting M/F subjects (N=24; 18–45 yrs.) received a single 0.6-mg oral dose of COL on Day 1. Blood samples were taken at various times for PK analysis on Days 2, 3, 4, and 5. On Day 15, following a washout period, subjects received 240 mg VER once daily x5. On Day 19, a second 0.6 mg dose of COL was given. Samples were taken for PK analysis on Days 20, 21, 22, and 23. PK parameters were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$.

Results: Co-administration of VER increases COL concentrations by 30% to a mean maximum of 3.85 ng/mL compared with 2.97 ng/mL with COL alone. COL AUC_{0-t} and $AUC_{0-\infty}$ were 13.1 ng•h/mL and 15.4 ng•h/mL, but increased to 24.6 ng•h/mL and 30.6 ng•h/mL,

respectively, when co-administered with VER. COL T_{max} (1 hr) was unaffected by VER dosing. Total apparent oral clearance decreased from 43.9 L/hr to 21.0 L/hr with co-administration.



Conclusion: Co-administration of VER increases COL C_{max} by 30% and exposure by 99% ($AUC_{0-\infty}$) and reduces its clearance by 52%. This PK profile reflects the DDI observed between COL and VER. Previously, we reported preliminary DDI data for diltiazem and COL comparable to that for VER. Taken together the data suggest COL dosing should be reduced by 50% when administered chronically and concomitantly with either VER or diltiazem. For treatment of acute gout flare, the standard dose of COL should be reduced from 3 to 2 tablets (one-third reduction) for patients on VER or diltiazem.

Disclosure: R. Terkeltaub, NIH, 2, VA., 2, Takeda, 2, Altus, 5, Ardea, 5, BioCryst, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Proctor and Gamble, 5, Regeneron, 5, Savient, 5, EnzymeRx, 5, Takeda, 5, URL Pharma, 5, UCB, 5 ; **D. E. Furst**, Wyeth Pharmaceuticals, 5, UCB, 5, Novartis Pharmaceutical Corporation, 5, Nitec, 5, Merck Pharmaceuticals, 5, GlaxoSmithKline, 5, Genentech , 5, Gilead, 5, Centocor, Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Amgen, 5, Actelion Pharmaceuticals US, 5, Abbott Laboratories, 5, Xoma Corporation , 2, Wyeth Pharmaceuticals, 2, UCB, 2, Roche Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Nitec, 2, NIH, 2, GlaxoSmithKline, 2, Gilead, 2, Genentech , 2, Bristol-Myers Squibb, 2, Amgen, 2, Abbott Laboratories, 2, Actelion Pharmaceuticals US, 2, Xoma Corporation , 5, Abbott Laboratories, 8, Actelion, 8, UCB, 5, Abbott Laboratories, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech , 9, Gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9 ; **K. Kook**, URL Pharma ; **J. L. DiGiacinto**, URL Pharma, 9 ; **M. W. Davis**, URL Pharma, 1, URL Pharma, 3 .

1108

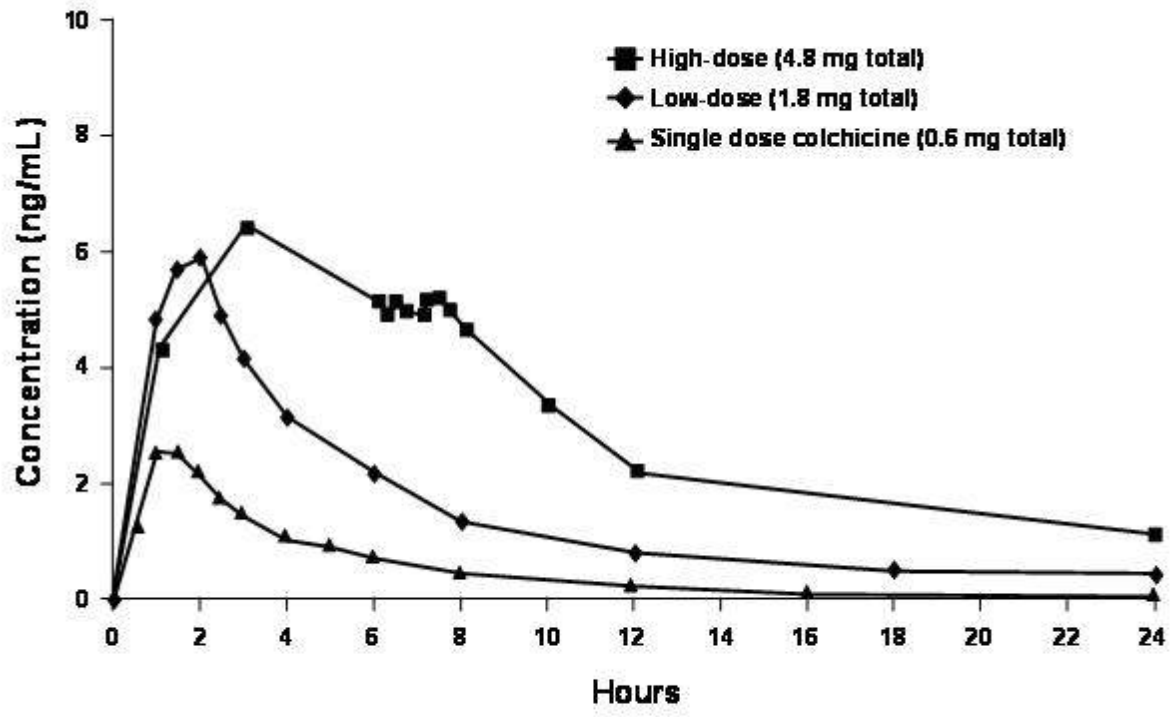
Maximal Plasma Concentrations of Low-Dose Vs High-Dose Colchicine Are Similar but Total Exposure Is Dose Dependent: Implications for Safe Administration of Colchicine to Treat Acute Gout Flare. Robert Terkeltaub[1], D. E. Furst[2], Karin Kook[3], Katherine Bennett[3], Kristin Arnold[4] and Matthew W. Davis[4], [1]VA Medical Ctr, San Diego, CA, [2]UCLA, Los Angeles, CA, [3]Salamandra, LLC, Bethesda, [4]United Research Laboratories, Philadelphia, PA

Purpose: Although colchicine is frequently used for the treatment of gouty attacks, dosing that optimizes its therapeutic index has not been defined. The AGREE trial showed that low-dose colchicine was as effective as high-dose (standard) colchicine (≥50% pain reduction at 24 hrs) but had a better safety profile. Summarized here are the results from pharmacokinetic (PK) studies that evaluated a new oral formulation of colchicine (Colcrys™, Col) as single doses or as low-dose and high-dose regimens.

Methods: A total of 75 healthy male or female subjects were enrolled across 4 phase 1 studies. Plasma samples were collected for PK analyses (LC–MS/MS) following single-dose Col (0.6 mg, fed/fasted), and low-dose (1.2 mg + 0.6 mg after 1 hr) and high-dose (1.2 mg + 0.6 mg x6) Col regimens. PK parameters included $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Adverse events (AEs) were assessed and cardiac safety was measured by ECG.

Results: PK of 0.6 mg Col was linear. Food decreased AUC ≈15% but did not affect C_{max} in subjects given 0.6 mg Col. At steady state, mean peak plasma concentration was 3.5 ng/mL ≈1.3 hours post-dose. High-dose and low-dose regimens had similar max blood levels (C_{max}=6.8 and 6.2 ng/mL, respectively). High-dose Col had 2-fold greater total exposure than low-dose, with an $AUC_{0\text{-}\infty}$ of 105 compared with 43.8 ng•h/mL, respectively. There were no clinically relevant changes in PR, QRS, or QTc intervals. The most common AEs were headache, diarrhea, dizziness, nausea, stomach pain, and vomiting. All AEs were mild to moderate in intensity and none resulted in discontinuation from any study.

C_{max} of high-dose and low-dose Col is similar but AUC is dose dependent.



Conclusion: Low-dose Col provides similar max plasma concentrations to high-dose Col (standard dosing). These results suggest that peak colchicine blood levels of ≈6 ng/mL are adequate for pain reduction within the first 24 hrs following gout flare. Additional exposure from high-dose Col may only increase unwanted side effects. For early acute gout flare treatment, low-dose Col (1.2 mg + 0.6 mg after 1 hr) is recommended. The PK profile exhibited by the low-dose regimen should prove to be useful in predicting Col safety and efficacy in patients with compromised clearance or those concomitantly administered CYP3A4 or P-gp inhibitors.

Disclosure: R. Terkeltaub, NIH, 2, VA., 2, Takeda, 2, Altus, 5, Ardea, 5, BioCryst, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Proctor and Gamble, 5, Regeneron, 5, Savient, 5, EnzymeRx, 5, Takeda, 5, URL Pharma, 5, UCB, 5 ; **D. E. Furst**, Wyeth Pharmaceuticals, 5, UCB, 5, Novartis Pharmaceutical Corporation, 5, Nitec, 5, Merck Pharmaceuticals, 5, GlaxoSmithKline, 5, Genentech , 5, Gilead, 5, Centocor, Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Amgen, 5, Actelion Pharmaceuticals US, 5, Abbott Laboratories, 5, Xoma Corporation , 2, Wyeth Pharmaceuticals, 2, UCB, 2, Roche Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Nitec, 2, NIH, 2, GlaxoSmithKline, 2, Gilead, 2, Genentech , 2, Bristol-Myers Squibb, 2, Amgen, 2, Abbott Laboratories, 2, Actelion Pharmaceuticals US, 2, Xoma Corporation , 5, Abbott Laboratories, 8, Actelion, 8, UCB, 5, Abbott Laboratories, Actelion Pharmaceuticals US, Amgen, Bristol-Myers Squibb, Biogen Idec, Centocor, Inc., Genentech , Gilead, Merck Pharmaceuticals, Nitec ; **K. Kook**, URL Pharma ; **K. Bennett**, URL Pharma ; **K. Arnold**, URL Pharma, 3 ; **M. W. Davis**, URL Pharma, 1, URL Pharma, 3 .

1109

Assessment of a Gout Education Session. Timothy A. Lonesky[1] and L. Brown[2], [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]Hitchcock Clinic Inc, Lebanon, NH

Purpose: Gout is a growing health problem affecting 7% of men and 3% of women over 65 years of age. There is scant literature about patient understanding of gout or educational programs in management of the disease although there is abundant research about poor or mismanagement with emphasis on patient education repeatedly discussed. Also,both ACR and EULAR list efficacy of educational programs as future research agenda. This study was developed to educate our local gout population about their disease and correct various knowledge gaps with secondary goals of assessing patient characteristics, evaluating an education session with emphasis on the "match-fire" analogy adapted from Dr. Robert Wortmann's article in the Dec issue of Am J Med 1998 via a pre and post session questionairre, and evaluating any correlation between patient characteristics and gout knowledge.

Method: ICD 9 code diagnosis of gout in Department of Rheumatology at DHMC from 2007-2008 were recruited to participate. 374 patients were sent an invitation, inviting them and family members to attend an evening education session at the medical center. 10 sessions were lead by a rheumatology fellow with a powerpoint presentation followed by question and answers. Patients were given a 20 true or false questionairre at the beginning and conclusion of the session.

Results: Responders were 75% male with all of them finishing highschool and 60% attending some college. 42% had gout > 10 years. 58% had care via rheumatologist vs 42% via PCP (with 80% of these via non-physician primary). 64% felt their understanding of gout was "average." 27% knew their current uric acid level with a range of 3-5.4 mg/dL (all under care of rheumatologist and all answered medication questions correctly). The average pre-session correct score on the questionairre was 52% and the average post-session score was 75%. Questions with the greatest improvement in score included gouts relationship to obesity (+40%), dairy products (+59%), vitamin C (67%) along with gout being a "curable" disease with proper medical management (+53% with all patients believing this to be true by the end of the session). Participants thought the sessions were useful with a grading of 8.2 on a visual analogue scale. All participants improved their score but despite intervention, some areas continued with poor performance (<50% of participants correctly answering). These included questions about NSAID and steroid use in chronic gout treatment along with expectations of 300mg of daily allopurinol improving uric acid to < 6mg/dL.

Conclusion: In a highly educated population of gout patients, an intervention to improve knowledge gaps via a interactive educational session was successful however even immediately after a session, based on a true and false questionnaire, some areas of knowledge remained poor. Based on this, the visual aid "match-fire" analogy adaption, may be able to give patients a proper and easily understandable reference to the use of their medications. Future studies need to be done to see which educational interventions will improve gout management.

Disclosure: T. A. Lonesky, None; **L. Brown**, None.

1110

Gout Management in Primary Care Vs. Rheumatology: Evidence for Suboptimal Treatment. Robert T. Keenan[1], Robert A. Lehman[2], William R. O'Brien[3], Daria B. Crittenden[1], Kristen H. Lee[1] and Michael H. Pillinger[4], [1]NYU-HJD, New York, NY, [2]NYU Hospital for Joint Diseases, New York, NY, [3]New York University, New York, NY, [4]NYU Langone Medical Center/NYU Hospital for Joint Diseases, New York, NY

Purpose: Primary care physicians (PCPs) manage most gout patients, but several studies suggest that the quality of PCP gout management may differ from that of rheumatologists. To prevent acute gouty attacks, a serum uric acid (UA) of ≤ 6 is the consensus UA lowering target. We compared the achievement of UA ≤ 6 in patients managed by PCPs vs. rheumatologists.

Methods: Gout patients were identified, from among all NY Harbor VAMC patients ages 18-100 (n-33,000) as having any 1 of 7 ICD codes for gout. Gout patients were defined as managed by their PCP if they had not seen a rheumatologist during the study period (7/07-6/09), or treated by a rheumatologist if they had seen a rheumatologist ≥3 times during the interval. Patients with 1-2 rheumatology visits were excluded. Mean serum UA for the two groups were compared using R statistical software (version 2.8.1).

Results: Prevalence of gout in the overall population was 2.5% (34% African-American, 49% White, 8% Hispanic, 2.5% South East Asian, 1% Pacific Islander, 0.5% Native American and 5% unknown). All subjects were male; average age was 72 years. Among 575 patients meeting ICD-9 diagnosis for gout, 474 had been treated for gout only in primary care, whereas 85 had been managed by a rheumatologist. 5.3% in the PCP cohort vs. 14.1% in the rheumatology cohort had a crystal confirmation of their disease. Patients receiving allopurinol achieved UA ≤6 in the rheumatology- but not the PCP-treated group. Among 191 patients prescribed allopurinol in the PCP cohort, 25.7% had no UA measurement during the study period; in contrast, 100% of the 57 rheumatology patients receiving allopurinol had ≥1 UA measurement. Average allopurinol dose in the PCP and rheumatology cohorts were 196 mg and 182 mg, respectively. Among patients with gout and hypertension, 16.7% were prescribed hydrochlorothiazide (HCTZ) in the PCP cohort vs. 11.8% in the rheumatology cohort.

Uric acid outcomes in gout subjects by treatment setting

	PCP	**Rheumatology**	**P-value** α=0.05
Mean UA among all patients	7.85 (7.65,8.01) (n=474)	6.54 (6.12,6.97) (n=85)	<0.0001
Mean UA among patients prescribed allopurinol	6.94 (6.56,7.31) (n=142)	5.94 (5.49,6.39) (n=57)	0.0004
Mean UA among patients prescribed HCTZ	7.85 (7.33,8.37) (n=63)	6.22 (4.84,7.60) (n=10)	0.0218

Conclusion: Our analyses suggest that gout patients cared for by PCPs may be undertreated. Compared with rheumatologists, PCPs are more likely to under dose, and/or inadequately monitor the results of, UA-lowering therapy. PCPs may also be more likely than rheumatologists to eschew crystal diagnosis, and to fail to account for the UA-raising properties of anti-hypertensive diuretics. To ensure proper clinical care, rheumatologists may need to assume a greater role in treating gout patients, and/or better educate PCPs in appropriate gout management.

Disclosure: R. T. Keenan, None; **R. A. Lehman**, None; **W. R. O'Brien**, None; **D. B. Crittenden**, None; **K. H. Lee**, None; **M. H. Pillinger**, None.

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First Application of Computer-Assisted Analysis of Digital Photographs for Assessing Tophus Response: Phase 3 Studies of Pegloticase in Treatment Failure Gout. A. N. Maroli[1], R. Waltrip[1], M. Alton[1], Herbert S. B. Baraf[2], B. Huang[1], C. Rehrig[1] and R. Ford[3], [1]Savient Pharmaceuticals, Inc., East. Brunswick, NJ, [2]Arthritis & Rheumatism Associates, P.C., Wheaton, MD, [3]RadPharm, Princeton, NJ

Purpose: Based upon anecdotal investigator-generated digital photographs that identified tophus elimination with pegloticase treatment in Phase 2, a standardized photographic and analytic process was developed to assess tophus response in 6-month, double-blind, placebo-controlled Phase 3 studies of pegloticase.

Method: An approach to quantitation of tophus elimination was jointly developed by Savient and RadPharm. This used serial photography and a method of categorizing skin lesions similar to Response Evaluation Criteria in Solid Tumors (RECIST). As RECIST has been used by FDA/EMEA for oncologic drug approvals, the principles of RECIST were used to categorize the response of tophaceous mass lesions to a novel therapy. Specialized software for clinical trials was used to standardize image viewing, measurement, and annotation in an audit-tracked environment for integrity of the central reading process. Method manual and site-based training programs were used to ensure standardization of equipment, image acquisition and quality assurance. Analysis and measurement of tophi were performed by an independent blinded Central Reader (rheumatologist). Investigational sites (n=56: US, Mexico, Canada) were trained using identical equipment and standard view templates for hands and feet. Quality procedures were used to assure that digital media were properly labeled, processed and delivered for image analysis. Assessment was blinded to and independent of any Sponsor or trial site input. From each

subject's baseline views, Central Reader selected target tophi to follow utilizing a "Sequential Locked Read" paradigm; post-baseline photographs were read and compared with baseline image with no knowledge of intervening or future assessments. Calibrated electronic calipers were used to measure the tophus area. Complete response (CR) of an individual target tophus was defined as 100% decrease in area. Overall tophus response per subject was the complete resolution of at least one tophus without appearance of a new tophus or progression of an existing tophus.

Results: Method captured tophus response and was successfully operationalized in a multicenter clinical trial. Treatment with intravenous pegloticase 8 mg q2 weeks led to reduction in tophus burden compared to placebo: 22% of subjects experienced CR of a target within first 3 months (p=0.011) and 45% within 6 months (p=0.002).

Conclusion: Computer-assisted analysis of digital photographs, used for skin lesions in oncology, has been successfully applied to assessment of tophus treatment response in rheumatology. Standardized photographic data recording and computer-aided analysis in a Central Reader paradigm, successfully documented outcomes, with findings consistent with clinical observations.

Disclosure: A. N. Maroli, Savient Pharmaceuticals, Inc., 3 ; **R. Waltrip**, Savient Pharmaceuticals, Inc., 3 ; **M. Alton**, Savient Pharmaceuticals, Inc., 3 ; **H. S. B. Baraf**, Savient Pharmaceuticals, Inc., 9 ; **B. Huang**, Savient Pharmaceuticals, Inc., 3 ; **C. Rehrig**, Savient Pharmaceuticals, Inc., 3 ; **R. Ford**, RadPharm, 9

1112

The Costs of Treatment Failure Gout: A Claims-Based Analysis. E.Q. Wu[1], A.P. Yu[1], A. Guérin[2], D. Latremouille-Viau[3], M. Tsaneva[2] and A. Forsythe[4], [1]Analysis Group, Inc., Boston, MA, [2]Analysis Group, Inc., Montréal, QC, [3]Analysis Group, Inc., Montreal, QC, [4]Savient Pharmaceuticals, Inc.,, East Brunswick

Purpose: Gout is a chronic disease characterized by severe pain and swelling of joints due to deposition of monosodium urate crystals in joints, tendons and surrounding tissues. Patients who are refractory to conventional urate-lowering therapy i.e., unable to reduce SUA below 6.0mg/dL, have higher rates of flares and incidence of tophi which impose a significant disease and economic burden. This study estimated the cost of treatment failure gout from a payer perspective.

Method: As a surrogate to broadly represent the treatment failure gout population, the following metrics were used: in the MarketScan commercial claims database (2003/10-2008/09), patients diagnosed with gout (ICD-9-CM: 274) with ≥3 flares within a 12-month period were selected, with the first flare occurrence date as the index date. A gout flare was defined as an episode with gout diagnosis followed by a claim for NSAIDs, colchicine, corticosteroids, ACTH, or intra-articular aspiration or injection within 7 days, or a diagnosis for joint pain (ICD-9-CM: 719.4) followed by a claim for colchicine within 7 days. Patients were considered if they received allopurinol prescriptions and had tophus diagnoses (ICD-9-CM: 274.8x) by the end of one year. For each gout patient aged ≥ 18, a gout-free control with the same age, sex, and region of residence was selected and was assigned the same index date as his matched counterpart. Included patients needed to have at least 12 months of continuous enrollment following the index date. One year costs were compared between gout and gout-free patients. GLM models with log link and gamma distribution and two-part models were used, and controlled for age, sex, region of residence, and type of insurance. All costs were inflated to 2008 US dollars using the medical care component of the Consumer Price Index. A subgroup analysis among more severe gout patients with ≥6 flares was performed.

Results: A total of 373,186 enrollees received a diagnosis of gout, 679 of which met the criteria of treatment failure gout. The average age was 50 years, and 82% were male. Mean total annual cost was estimated at $17,603 for treatment failure gout patients, compared to $6,891 for the control group. After adjusting for confounding factors, incremental total cost of treatment failure gout was $10,222 (p<0.01), which was largely attributable to higher adjusted outpatient costs ($3,814; p=0.01), inpatient costs ($3,056; p<0.01), and drug costs ($879; p<0.01). A subgroup of 195 gout patients with ≥6 flares had even higher total healthcare costs, with adjusted incremental costs at $22,237 (p<0.01).

Conclusion: Treatment failure gout in patients on conventional urate lowering therapy whose SUA is not normalized presents substantial economic burden to the payers. Patients with more flares incurred even greater costs. This study, however, is limited by the lack of specific diagnostic codes in gout.

Disclosure: E. Q. Wu, None; **A. P. Yu**, None; **A. Guérin**, None; **D. Latremouille-Viau**, None; **M. Tsaneva**, None; **A. Forsythe**, Savient Pharmaceuticals Inc., 3 .

1113

Chronic Use of Pegloticase: Safety and Efficacy Update. J. S. Sundy[1], Herbert S. B. Baraf[2], SR Gutierrez-Urena[3], R. A. Yood[4], B. Huang[5], A. N. Maroli[5], R. Waltrip[5], Z. Horowitz[6] and M. A. Becker[7], [1]Duke Univ Medical Ctr, Durham, NC, [2]Arthritis & Rheumatism Associates, P.C., Wheaton, MD, [3]Hospital Civil De Guadelajara, Guadalajara, [4]Fallon Clinic, Worcester, MA, [5]Savient Pharmaceuticals, Inc., East. Brunswick, NJ, [6]Savient Pharmaceuticals Inc, East Brunswick, NJ, [7]University of Chicago, Chicago, IL

Purpose: To assess safety and durability of treatment response to intravenous (IV) pegloticase (PGL) 8mg every 2 weeks (q2wks) or q4wks during an open label extension (OLE) study in subjects with treatment failure gout who completed one of two replicate randomized double-blind, placebo-controlled trials (RCTs).

Method: Subjects completing 6 month Phase 3 RCTs of pegloticase, a PEGylated recombinant mammalian uricase, were eligible for OLE study. Data for first 6 months of OLE are presented. Subjects/investigators chose q2wk or q4wk PGL 8mg dosing schedule without knowledge of RCT group or response. Objectives of the OLE were assessment of safety and maintenance of RCT primary and secondary efficacy outcomes.

Results: 151/212 (71%) of RCT subjects and 151/157 (96%) of RCT completers enrolled in the OLE (82 PGL q2wks, 67 PGL q4wks, 2 observation). Adverse event (AE) patterns were similar between RCT and OLE, with exception of the continued decrease in incidence and frequency of gout flares observed for PGL after the first 3 months of the RCTs. The frequency of infusion reactions (IRs) or serious AE (SAE) IRs in OLE and RCTs were similar.

	PGL regimen (RCT to OLE)					
	q2 to q2 wks	**q2 to q4 wks**	**q4 to q2 wks**	**q4 to q4 wks**	**Pbo to q2wks**	**Pbo to q4wks**
N	34	23	25	28	23	16
IR, n(%)	6(18)	4(17)	7(28)	13(46)	12(52)	12(75)
SAE, n(%)	2(5)	0	1(4)	0	4(17)	3(19)
SAE IRs leading to discontinuation, n(%)	0	0	1(4)	0	2(9)	3(19)
IRs leading to discontinuation, n(%)	1(3)	1(4)	2(8)	2(7)	2(9)	3(19)

Three deaths occurred in the OLE (3/151); none was considered to be related to study drug. Cardiovascular (CV) event pattern and frequency of CV events was not different than that found in the RCT.

Forty-three of 48 subjects whose SUA was consistently <6 mg/dL on PGL in RCTs maintained SUA <6 mg/dL in OLE. While 32 subjects had complete resolution (CR) of at least 1 tophus on PGL in RCT, 20 additional subjects (12 of whom received PGL in the RCT) demonstrated their first CR in the OLE. Tophi progressed in 3 pts in OLE (who received PGL q2wks in RCT and OLE) whose SUA response was transient, but not maintained < 6mg/dL. Reductions in tender or swollen joint counts attained in RCTs continued or were maintained in OLE. Improvements in patient global assessment of disease activity, pain, and disability scores observed in RCTs improved or were maintained in OLE

Conclusion: In subjects with treatment failure gout, chronic pegloticase therapy is well tolerated with no suggestion of increased risk with treatment extending up to 1 year. Efficacy in reduction of SUA concentration and symptomatic endpoints was maintained.

Disclosure: J. S. Sundy, Savient Pharmaceuticals, 2 ; **H. S. B. Baraf**, Savient Pharmaceuticals, 2 ; **S. Gutierrez-Urena**, Savient Pharmaceuticals, 2 ; **R. A. Yood**, Savient Pharmaceuticals, 2 ; **B. Huang**, Savient Pharmaceuticals, Inc., 3 ; **A. N. Maroli**, Savient Pharmaceuticals, Inc., 3 ; **R. Waltrip**, Savient Pharmaceuticals, Inc., 3 ; **Z. Horowitz**, Savient Pharmaceuticals, 1 ; **M. A. Becker**, Savient Pharmaceuticals, Inc, 5 .

ACR/ARHP Poster Session B

ARHP Abstracts - B

Monday, October 19, 2009, 9:00 AM - 6:00 PM

1114

Balance Ability in Polyarticular Juvenile Idiopathic Arthritis. Vanessa Bueno[1], Claudio A. Len[2], Maria T. Terreri[3], Jamil Natour[4] and Maria O. Hilário[2], [1]Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo,, Brazil, [3]Universidade Federal de Sao Paulo, Brazil, [4]Federal University of Sao Paulo, Sao Paulo, Brazil

Purpose: To evaluate balance ability in children and adolescents with poliarticular juvenile idiopathic arthritis (JIA) and its correlation with joint limitation, functional capacity, pain VAS and Berg Balance Scale (BBS) score.

Methods: JIA patients with lower limbs involvement were consecutively selected from our outpatient Pediatric Rheumatology clinic. Inclusion criteria were age between 10 years-old and 16 years-old, minimum height of 130 centimeters and normal visual acuity. The control group comprised "healthy" children and adolescents matched for age and gender. Balance was measured by a Biodex stability System (Inc, Shirley NY). The patients protocol included Childhood Health Assessment Questionnaire (CHAQ), Pediatric Escola Paulista de Medicina - Range of Motion scale (Pediatric EPM-ROM) and a pain VAS. The Biodex test included two adaptation periods with an interval time of one minute each one and three consecutive 20 minutes test in level 8 (lower instability) and 2 (higher stability). We measured anterior-posterior (AP), medial-lateral (ML) and overall dislocation (OD).

Results: JIA group comprised 50 patients (35 girls, mean age 13,5 ± 2,19 years-old) and control group included 50 children and adolescents (35 girls, mean age 13,5 ± 2.18 years-old. In the patients group mean CHAQ score, Pediatric EPM-ROM and pain VAS were 0.83, 0.70 and 3.04, respectively. BBS score was 51 for patients and 55 for controls. We did not observed difference between JIA patients and controls in Biodex test level 8 ($p = 0,907$); in Biodex test level 2 the difference was statistically significant in all 3 variables: AP ($p = 0.007$), ML ($p = 0.004$ and OD ($p = 0.001$) We did not find any correlation among this variables and CHAQ, Pediatric EPM-ROM and pain (Spearman correlation coefficient).

Conclusion: Our polyarticular JIA patients have worse balance ability than healthy children; we must be alert to this problem in our daily routine.

Disclosure: V. Bueno, None; **C. A. Len**, None; **M. T. Terreri**, None; **J. Natour**, None; **M. O. Hilário**, None.

1115

Does the School Dimension Determine Impairment of Health-Related Quality of Life in Patients with Juvenile Idiopathic Arthritis?

Tania M.S. Mendonça[1], C.A. Len[2], Carlos H. M. Silva[1], Rogerio M.C. Pinto[3] and M.O.E. Hilário[4], [1]UNIVERSIDADE FEDERAL DE UBERLANDIA, Uberlandia, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil, [3]Brazil, [4]Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Purpose: To evaluate health-related quality of life (HRQL) of children and adolescents with juvenile idiopathic arthritis according to age group and arthritis subtypes using the Brazilian version of PedsQL™ 4.0

Methods: Patients with JIA and their respective caregivers were recruited in August 2008, from the Pediatric Rheumatology outpatient clinic at the Medical School of the Federal University of Uberlândia (Brazil). These patients were classified according to the ILAR criteria and, with their respective caregivers, answered the Brazilian version of PedsQL™ 4.0 and a sociodemographic evaluation questionnaire. The descriptive statistics characterized the population. The Kruskal-Wallis test was used to compare the medians of the PedsQL™ 4.0 domains scores of the patients and their caregiver, according to the subtypes of arthritis in the 2-4, 5-7, 8-12 and 13-18 year old age groups. Cronbach's alpha coefficient was used to confirm instrument reliability for this population.

Results: 52 children and adolescents with JIA (mean 11 ± 4.02 years) and their caregivers (mean 39.1 ± 9.19 years) participated in the study. The patients were predominantly oligoarticular (46.2%), attending basic education (82.7%), equivalent gender and with a low family income (75%). The Cronbach's alpha coefficient was adequate, with a variation of 0.7 to 0.9 for the PedsQL™ 4.0 domains of the groups evaluated.

Patients aged 8-12 years, of the oligoarticular subtype presented lower scores in the school dimension ($p<0.05$) of the Pedsql™ 4.0. According to the caregivers' perception, the same result was found, but for the polyarticular subtype ($p<0.05$).

Conclusion: JIA impaired the HRQL of patients as detected by the Brazilian version of PedsQL™ 4.0. The disease, therapy and side effects of the medications interfere in attendance at school and in concentration, diminishing the children's motivation in the 8-12 age group and making it difficult for them to adapt at school, independent of arthritis subtype. The family, school and interdisciplinary team should take steps to keep schooling from being more than minimally impaired.

Disclosure: T. M. S. Mendonça, None; **C. A. Len**, None; **C. H. M. Silva**, None; **R. M. C. Pinto**, None; **M. O. E. Hilário**, None.

1116

MACTAR, a Patient Perspective Outcome for Polymyositis and Dermatomyositis, Reveals Disease Aspects Not Covered by Traditional Outcomes. Li Alemo Munters[1], R.F. Van Vollenhoven[2] and Helene Alexanderson[1], [1]Rheumatology Unit, Department of Medicine and Department of Physical Therapy, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicin, Karolinska University Hospital, Karolinska Institutet., Stockholm, Sweden

Purpose: The objective of this study was to evaluate patient perspective on disease impact using the MacMaster Toronto Arthritis patient preference questionnaire (MACTAR) and to evaluate measurement properties of the MACTAR for patients with polymyositis (PM) and dermatomyositis (DM) in Sweden.

Method: The MACTAR is a semi-structured interview asking questions on different aspects of disease impact and their importance to the patient to improve. Twenty-eight patients with PM and DM (15 women and 13 men) were included. Eleven patients were diagnosed with PM and 17 with DM and they had a median age of 57 (range 28-74) years. Their median diagnosis duration was 9 (1-32) years; 9 worked full-time, 9 part-time, 7 were retired and 3 patients were on sick-leave. We analyzed measurements recommended by International Myositis Assessment Clinical Study Group (IMACS) and myositis specific outcomes including measures of disease activity (six-item core set), Myositis Damage Index, muscle strength (Manual Muscle Test), muscle endurance (Functional Index 2), activity limitation (Myositis Activities Profile and Health Assessment Questionnaire), participation restriction (Disease impact on well-being on a Visual Analogue Scale) and health related quality of life (SF-36) as well as the MACTAR, which was performed twice.

Results: Sexual activity, walking and social activities constituted the predominating problems selected by patients with chronic PM/DM as important to improve. The majority of activities captured by the MACTAR as important to improve were represented in the International Classification of Functioning Disability and Health (ICF) component Activity/Participation. Moderate to high correlations were revealed between the MACTAR and three domains of health related quality of life (r_s=-0.67- -0.73), a moderate correlation with measurements of activity limitation and participation restriction (r_s= 0. 51-0.60) and lower correlations for disease activity and disease damage. A good to excellent reliability of the MACTAR total score was revealed with weighted Kappa (K_w = 0.68) and intra-class correlation (ICC = 0.83) without signs of systematic variations, $p>0.05$.

Conclusion: The MACTAR identified aspects of disease impact of high importance to the patients not covered by IMACS recommended and myositis specific outcomes. The MACTAR seems to have promising measurement properties assessing patient perspective of activity limitation/ participation restriction and health related quality of life in patients with PM and DM in a Swedish context. The MACTAR might therefore be considered as a patient perspective outcome in clinical trials and other research settings.

Disclosure: L. Alemo Munters, None; **R. F. Van Vollenhoven**, None; **H. Alexanderson**, None.

1117

Perceived Home Demands of Women with Fibromyalgia: Five-Year Study. Susan T. Reisine V[1], Deborah Dauser[2], Judith A. Fifield[3] and Stephen Walsh[4], [1]Univ of CT Health Center, Farmington, CT, [2]University of Connecticut, Farmington, CT, [3]Univ of Connecticut Health Ctr, Farmington, CT, [4]University of Connecticut, Storrs, CT

Purpose: To assess changes in perceptions about the psychological demands of family work among women with fibromyalgia (FM) and assess the effects of demographic factors, employment, neuroticism, social support, hours of family work, fatigue and pain on perceived demands.

Methods: 287 female FMS patients were recruited from a national sample of rheumatologists. Participants were interviewed by phone at baseline and annually for four years. Data were collected on demographic characteristics, disease duration, pain and fatigue on 100 point visual analogue scales, neuroticism, social support, total number of hours in family work per week and perceived psychological demands of family work (range=7-35). 228 participants remained at the end of the study for a 79% retention rate. A slope for each person with at least two observations (N = 241) for the perceived home demands measure was estimated and then the overall slope was calculated. An unconditional means model was fit using multilevel modeling with SAS PROC MIXED to determine if a multilevel model would provide substantial benefit over a standard fixed effects model. Variables were entered sequentially into the model; non-significant terms were removed from the final model.

Results: At baseline, the mean age of participants was 47.3 (sd=11), had 14.3 (sd=2) yrs education, 90% were White, 50% employed, 63% were married with median household incomes of $40-49,999; mean score on pain was 57 (sd=24); on social support was 59 (sd=8) , on neuroticism was 57.8 (sd=13); on hours of nurturant work per week was 26 (sd=23), and on hours of instrumental work per week was 26 (sd=16), on fatigue score was 75 (sd=22); and on perceived demands was 28.5 (sd=7). The rate of change at study year one was -2.4. The rate of change in the growth slope was 1.4 and there was a deceleration of -.26. By year 5, home demands among women with FM were significantly lower by about 8 points. There was no difference in home demands between those who were employed versus those who were not employed after adjusting for age, race, neuroticism, social support and fatigue. There was a significant within-person association between fatigue and home demands such that those with higher fatigue also had higher perceived home demands and those with lower fatigue levels also had lower perceived home demands. Pain was not significantly associated with perceived demands.

Conclusion: Women with FM perceive high psychological demands from family work; employment does not affect perceived demands; fatigue and perceived demands move together through time, although it is unclear whether fatigue shapes perceptions or demands affect level of fatigue; the significant reduction in perceived demands may reflect a process of adaptation to family demands over time.

Disclosure: S. T. Reisine, None; **D. Dauser**, None; **J. A. Fifield**, None; **S. Walsh**, None.

1118

A New Plantar Tender Point in Fibromyalgia: A Worthy Candidate for the ACR Classification Criteria? A. Spindler[1], W. Spindler[1], V. Bellomio[1], A. Berman[1], E. Lucero[1], H. Berman[1], R. Sueldo[1], L. Gonzalez[1], M.V Gandur[1], M. Guardia[1], A.L Barbaglia[1], M. Santana[2], C. Waimann[3], K. Kyrmair[3], R. Chaparro del Moral[4], O. Rillo[5] and J. Moreno[6], [1]Hospital Padilla, Tucuman, Argentina, [2]Facultad de Medicina, Tucuman, Argentina, [3]IREP, Buenos Aires, Argentina, [4]Hospital Tornu, Buenos Aires, Argentina, [5]Hospital Tornu, [6]CER, San Juan

Purpose: Fibromyalgia (FM) is a complex, chronic condition which causes widespread pain accompanied by tenderness at 11 or more of 18 predetermined tender point sites, ACR Classification Criteria (1990 FMACRCC). Because 10 of these sites are in the neck and shoulder areas, which are major target areas for rheumatic and musculoskeletal conditions, diagnostic dilemmas often arise. Because of this reason reproducible tender points placed elsewhere would be advantageous in diagnosis of FM. The objective of this study was to assess sensitivity and specificity of a tender point placed infero-medially in the distal third of the longitudinal plantar arch in FM patients and controls

Method: A multicenter study was carried out in consecutive patients with FM (1990 FMACRCC) and concurrent healthy controls matched by sex and age (± 3 years). The proposed site, the accepted ACR sites (pairs) and control sites (pairs) biceps, quadriceps, and external aspect of the foot were evaluated by digital pressure averaging 4 kg/cm^2 exerted by a previous trained rheumatologist. Sensitivity and specificity of the new, the ACR accepted and the control tender points were compared by unpaired t-test and the McNemar test.

Results: There was a total of 55 FM female patients with an average age of 47 ± 9.8 years. Healthy controls comprised 48 females with a similar age distribution (44 ± 11 years). The new plantar site was tender in 48/55 FM patients (87%) vs. 2/48 controls (4%) giving a sensitivity of 87%, specificity of 96%, positive LR of 20.9 (CI 95%=6.2-76.1) and negative LR of 0.13 (CI 95%=0.06-0.25). Some of the ACR tender sites had lower sensitivity and specificity than the new plantar site i.e, occiput was tender in 15% of controls (sensitivity 71%, specificity 85%), trapezius was positive in 33% of controls (sensitivity 87%, specificity 67%) and low cervical was positive in 35% of controls (sensitivity 78%, specificity 65%).Control sites were negative in 34/48 (71%) FM patients with the plantar site positive. The plantar site had good concordance in FM patients with tender sites such as the lateral epicondyle (73%) and the occiput (65%)

Conclusion: Our findings indicate that a tender site located infero-medially in the distal third of the longitudinal plantar arch has a high sensitivity and specificity in patients with FM as defined by the FMACRCC. Furthermore, it had a greater specificity than cephalad sites such as occiput, trapezium and low cervical sites. Further investigations on this novel site appear warranted.

Disclosure: A. Spindler, None; **W. Spindler**, None; **V. Bellomio**, None; **A. Berman**, None; **E. Lucero**, None; **H. Berman**, None; **R. Sueldo**, None; **L. Gonzalez**, None; **M. V. Gandur**, None; **M. Guardia**, None; **A. L. Barbaglia**, None; **M. Santana**, None; **C. Waimann**, None; **K. Kyrmair**, None; **R. Chaparro del Moral**, None; **O. Rillo**, None; **J. Moreno**, None.

1119

Impact of Chronic Gout On Foot Function: Case-Control Study. Keith Rome[1], David Survepalli[1], Alex Sanders[1], Maria Lobo[2], Fiona M. McQueen[3], Peter McNair[1] and Nicola Dalbeth[4], [1]AUT University, Auckland, New Zealand, [2]Auckland District Health Board, Auckland, New Zealand, [3]University of Auckland, Auckland, [4]University of Auckland, Auckland, New Zealand

Purpose: Despite the predilection of gout to the foot, the impact of this disease on foot function is currently unknown. The aim of this case-control study was to analyse the impact of chronic gout on foot function and measures of foot disability.

Method: Cases with gout (n=25) were recruited from rheumatology outpatient clinics. All cases had a history of acute gout according to ACR diagnostic criteria (median disease duration 21 years, flare frequency 2.92/year, 44% with tophi). Cases were excluded if they were experiencing an acute gout flare at the time of assessment, had lower limb amputation or diabetes mellitus. Age, sex and BMI-matched control participants (n=25) without arthritis, lower limb amputation or diabetes mellitus were also analysed. Plantar pressures were recorded using an in-shoe system to determine peak pressure and pressure-time integrals under ten regions of the foot. An instrumented walkway was used to capture spatial and temporal gait parameters. Disease impact was measured using the Leeds Foot Impact Scale. To preserve data independence, data from the right foot of each participant were analysed.

Results: Significant differences in all foot measures were observed between cases and controls (Table). In particular, significant differences were present in the pressure-time integrals across all foot regions except under the hallux and lesser toes, with higher pressures over time in the gout group. Gait parameters that included walking speed, cadence and double-support were also impaired in cases with gout. Patient reported scores of disease impact were significantly higher in the cases.

Conclusion: Chronic gout is associated with important changes in load-bearing function across the entire foot, which may contribute to the development of pain and disability in this disease.

Table: Foot function measures (median, IQR)

Variable	Control Group	Gout Group	P
Peak Pressures (kPa)			
Medial Heel	276 (230-362)	259 (190-316)	0.59
Lateral Heel	261 (205-317)	253 (180-292)	0.07
Midfoot	101 (85-117)	140 (99-189)	<0.01
Hallux	264 (142-326)	129 (74-224)	<0.01
2-5th Toes	176 (137-256)	130 (87-174)	<0.01
1 Metatarsophangeal Joint (MTPJ)	228 (176-314)	201 (128-284)	0.28
2 MTPJ	247 (195-315)	352 (172-389)	0.30
3 MTPJ	281 (205-341)	347 (178-431)	0.25
4 MTPJ	195 (174-392)	260 (154-321)	0.77

5 MTPJ	168 (117-300)	168 (137-253)	0.09
Pressure-Time Integrals (kPa.sec)			
Medial Heel	61 (46-72)	74 (65-78)	<0.01
Lateral Heel	61 (49-69)	71 (67-91)	<0.01
Midfoot	68 (58-79)	80 (67-91)	0.02
Hallux	56 (46-66)	59 (42-70)	0.09
2-5th Toes	61 (48-67)	66 (43-81)	0.23
1 MTPJ	74 (63-86)	78 (66-92)	0.01
2 MTPJ	74 (60-84)	78 (68-93)	0.04
3 MTPJ	76 (63-86)	80 (71-90)	0.03
4 MTPJ	84 (71-95)	84 (71-95)	0.05
5 MTPJ	80 (72-92)	80 (72-92)	0.03
Spatial and Temporal Gait Parameters			
Walking Speed (m/s)	1.1 (0.9-1.3)	0.9 (0.8-1.1)	<0.01
Cadence (steps/min)	104 (96-114)	95 (91-102)	<0.01
Double Support (s)	0.16 (0.13-0.18)	0.19 (0.16-0.22)	<0.01
Leeds Foot Impact Scale			
Impairment/ footwear	0 (0-2)	10 (5-15)	<0.01
Activity limitation/participation restriction	0 (0-0)	17 (5-25)	<0.01

Disclosure: K. Rome, None; **D. Survepalli**, None; **A. Sanders**, None; **M. Lobo**, None; **F. M. McQueen**, None; **P. McNair**, None; **N. Dalbeth**, None.

1120

Illness Perception in Patients with Gout. Nicola Dalbeth[1], William J. Taylor[2], Jimmy Chong[1], WingChi Leung[1], Rini Chegudi[1], Anne Horne[1], Fiona M. McQueen[1] and Keith Petrie[1], [1]University of Auckland, Auckland, New Zealand, [2]University of Otago Wellington, Wellington, New Zealand

Purpose: Illness perception is a key determinant of behaviour directed at managing disease. Although low adherence to both dietary advice and pharmacological therapy has been reported in patients with gout, patients' perception of the disease has not been systematically studied. The aim of this study was to examine illness perception in patients with gout.

Methods: 105 patients with gout for less than 10 years were recruited from primary and secondary care settings. Participants completed a gout-specific Brief Illness Perception Questionnaire (B-IPQ), pain visual analogue scale, work instability scale, and medication adherence questionnaire. Serum urate and flare frequency were also recorded.

Results: There was a large variation in patients' perception of the illness and perceived ability to control their symptoms (Table). Generally, patients viewed gout as a chronic condition that was responsive to treatment but not strongly influenced by personal actions. Most patients believed gout was caused by diet or alcohol use and the majority believed they had a good understanding of their illness. Overall gout was seen as having a moderate impact on their life. Patients who reported greater flare frequency and pain had higher B-IPQ consequence, identity, emotional impact scores and lower personal control scores (all $p<0.05$). No relationship was observed between medication adherence and B-IPQ scores. A more negative overall B-IPQ score correlated strongly with work instability ($r=0.598$, $p<0.0001$). Of the clinical features assessed, pain and serum urate were independently associated with negative illness perceptions, accounting for 28% of total variance in multiple linear regression analysis.

Conclusion: Negative illness perception is associated with poorly controlled disease and work disability in patients with gout. Longitudinal studies are now needed to determine the influence of illness perception on outcomes in this disease.

Table: Summary of illness perception measures based on components of the B-IPQ.

Brief Illness Perception Questionnaire	**Mean (SD)**
Consequences (10=severely affects life)	5.30 (3.48)
Timeline (10=will continue forever)	7.19 (3.40)
Personal control (10=extreme amount)	5.40 (3.19)
Treatment control (10=extremely helpful)	7.50 (3.03)
Identity (10= many severe symptoms)	5.85 (3.12)
Concern (10=extremely concerned)	7.14 (3.04)
Understanding (10=very clearly)	7.22 (2.70)
Emotional impact (10=extremely affected)	5.28 (3.58)
Average B-IPQ – questions 3, 4, 7 reversed (α=0.801)	5.15 (2.06)
Most important factor believed to cause gout	**n (%)**
Diet	36 (34)
Alcohol	15 (14)
Medications/therapy	9 (9)
Injury/trauma	6 (6)
Bodily illness	5 (5)
Genetics	5 (5)
Stress/lifestyle	4 (4)
Weight	2 (2)
No response/no idea	19 (18)

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1121

Reduced Quality of Life Is Associated with Impaired Functional Capacity and Higher Levels of Fatigue in Patients with Systemic Lupus Erythematosus. Annette M. Oeser, Young-Hee Rho and C. Michael Stein, Vanderbilt University, Nashville, TN

Purpose: Spitzer's Quality of Life Index (QL Index; Spitzer WO et al, J Chronic Dis 1981, 34(12):585-597) is a simple Apgar-like scale that measures the general well- being of patients and is easy to administer. It has been used in patients with cancer, congestive heart failure, and the frail elderly. However, there is no information about its performance in patients with systemic lupus erythematosus (SLE). Thus, we examined the hypothesis that QL Index is significantly associated with disease severity, fatigue, and functional capacity in patients with SLE.

Methods: We studied 162 subjects with SLE and 88 control subjects. Controls were frequency-matched based on age, sex, and race. Demographic and clinical data were obtained from patient interview, medical record review, physical examination, and patient questionnaires, including Spitzer's QL Index, Modified Health Assessment Questionnaire (MHAQ), Fatigue Severity Scale (FSS), and Rheumatology Attitudes Index (RAI), and visual analog scales (VAS) measuring pain, fatigue and disease activity. The QL Index is scored with a high number representing a better quality of life, while MHAQ, FSS, RAI, and the VAS scales are scored in the opposite direction. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Disease activity and damage were ascertained by SLEDAI and SLICC, respectively. Differences between patients and controls were determined by Wilcoxon rank sum test for continuous variables. Spearman's rank correlations were used to examine the association between QL Index and the MHAQ, FSS, RAI, pain VAS, fatigue VAS, disease activity VAS, CRP, ESR, SLEDAI and SLICC. Data are presented as median [interquartile range].

Results: QL was significantly lower in patients with SLE (8 [7-10]) than control subjects (10 [10-10]), $p < 0.001$). In SLE the QL Index was inversely correlated with MHAQ (rho= -0.69, $p < 0.001$), RAI (rho=-0.66, $p < 0.001$), fatigue severity scale (rho=-0.72, $p < 0.001$), pain VAS (rho=-0.61, $p < 0.001$), fatigue VAS (rho=-0.55, $p < 0.001$), and disease activity VAS (rho=-0.51, $p < 0.001$). The QL Index was also negatively correlated with CRP (rho=-0.24, $p = 0.002$), SLEDAI (rho=-0.29, $p < 0.001$) and SLICC (rho=-0.25, $p = 0.001$), but not ESR (rho =-0.06, $p=0.47$).

Conclusion: Quality of Life, as measured by the QL Index, is reduced in patients with SLE as compared to controls. This reduction is significantly associated with increased levels of fatigue, impaired functional capacity and markers of disease activity. Spitzer's Quality of Life Index is a simple test that captures components of many symptoms that contribute to decreased quality of life in SLE.

Disclosure: A. M. Oeser, None; **Y. H. Rho**, None; **C. M. Stein**, NIH, 2.

1122

The Interferon Signature Is Not Associated with Depression or Fatigue in Systemic Lupus Erythematosus. Erinn Kellner[1], Pui Lee[1], Yi Li[1], Mark S. Segal[2], Eric S. Sobel[1], Minoru Satoh[1] and Westley H. Reeves[1], [1]University of Florida, Gainesville, FL, [2]Dept. of Medicine, Univ. of Florida, Gainesville, FL

Purpose: Patients with SLE often suffer from depression and fatigue in addition to the physical manifestations of the autoimmune disease. Elevated production of type-I interferons (IFN-I) has been found in lupus patients and recombinant IFN-I therapy is known to trigger a variety of neuropsychiatric side effects including depression and fatigue. This study was conducted to evaluate the relationship between dysregulated IFN-I production and the manifestations of depression or fatigue in lupus patients.

Method: Depression and fatigue in patients with SLE (n = 58) were assessed by Beck's Depression Inventory and the Multidimensional Fatigue Index (MFI), respectively. Anxiety, pain and energy levels were evaluated by visual analog scales. Serum IFN-I levels were assessed using the expression of interferon-stimulated genes (ISGs) in peripheral blood mononuclear cells (quantitative PCR).

Results: Depression and fatigue were reported by more than half of SLE patients in our study but these neuropsychiatric findings were largely unexplained by disease-related factors such as clinical manifestations, complement levels, medication usage, or autoantibody profile. In line with previous findings, elevated ISG expression was present in about two-thirds of SLE patients. However, through both cross-sectional and longitudinal studies analysis we found no significant correlation between ISG expression and the levels of depression or fatigue.

Conclusion: Although recombinant IFN-I (IFN-alpha) therapy is associated with a wide-range of neuropsychiatric side effects including depressive illness, elevation of endogenous IFN-I levels is unlikely to be responsible for the depression and fatigue experienced by lupus patients.

Disclosure: E. Kellner, None; **P. Lee**, None; **Y. Li**, None; **M. S. Segal**, None; **E. S. Sobel**, None; **M. Satoh**, None; **W. H. Reeves**, None.

1123

Impact of Physical Activity Program in Systemic Lupus Erythematosus. Marcelo I. Abrahão[1], Rafael Montenegro-Rodrigues[2], Roberta G. Marangoni[3], Stella Peccin[1] and Virginia F.M. Trevisani[1], [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Rodrigues Montenegro, São Paulo, Brazil, [3]Marangoni, São Paulo, Brazil

Purpose: To verify the impact of physical activity in quality of life, and physiological capabilities in patients with Systemic Lupus Erythematosus (SLE).

Method: Sixty-three SLE patients, according to 1997 ACR criteria, not practitioners of physical activity were selected. Their mean age were 42.2± 15.2 years, mean BMI 28.3± 11.1 and mean disease duration of 3.83.8 ± 3.2 years. The patients were randomized and allocated into three groups; cardiovascular training (CT), endurance training (ET) and the control group (CG) to be executed three times a week during 50 minutes for twelve weeks . The group held training CT performed exercise with intensity of 65% to 75% of heart rate reserve. The group held training ET performed 8 exercises of 15 repetitions in a total of 3 series with intensity of 65% to 75% of maximum load. The CG group received orientations about SLE disease .To evaluate the effect of the program for physical activity, muscle strength and aerobic capacity were assessed by a blinded evaluator, using a dynamometer analog (IMF) and 12-minute walk test (T12), respectively, on the first visit and after twelve weeks of the program. The SF36 (Physical Aspect) questionnaire and visual analogue scale for pain, were also assessed on the first visit and twelve weeks afterward. Data analysis: This was ANOVA (analysis of variance) for numerical variables between groups. Chi - square for categorical variables between groups. Test - paired t for each group between the times.

Result: The results are described in the table below

	PA		Pain		IMF		T 12	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
CG	24.7 ±27.2	29.7±17	6.5±1,5	5.6±2	20.3±7.5	19.7±7.4	936±169	904±187
CT	33.3±34*	49.8±34*	5±2,1	4.6±2	23.9±9.7*	34.5±13.2*	1019±224*	1406±256*
ET	17.3±16*	27.7±15*	6.2±1,4	4.1±1.6*	25.7±10.6*	45.3±15.4*	911±171*	1148±172*

*p<0,05

PA: Physical Aspect

Conclusion: Endurence training showed to be more effective than cardiovascular training in patients with SLE. Physical activity program may be useful for improving quality of life and physiological capabilities future studies will be needed to determine the universal efficacy of this method.

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1124

Low Lean Mass: a Major Factor for Low Bone Mass in Pre-Menopausal Women with Systemic Lupus Erythematosus. Luciana P. Costa, Eloisa Bonfa, Valeria F. Caparbo, Eduardo F. Borba, Luciana F. Muniz, Juliane A. Paupitz and Rosa M.R. Pereira, Faculdade de Medicina da USP, São Paulo, Brazil

Purpose: To analyze the frequency of low bone mineral density and risk factors for bone loss in pre-menopausal women with SLE

Method: Ninety-three SLE patients, pre-menopausal women,≤11 years disease duration were evaluated and had the bone mineral density (lumbar spine and femur) analyzed by dual-energy X-ray absorptiometry (DXA). Low bone mass for chronological age was defined if Z-score was ≤ -2 SD. Body composition was also analyzed by DXA. Vertebral fractures were analyzed at entry by VFA (vertebral fracture assessment) using DXA software. Demographic, clinical and laboratorial data related to SLE and risk factors for OP/fractures (personal or familial history of fracture, age, smoking, glucocorticoid dose, physical activity and calcium intake) were obtained from an ongoing electronic database protocol and interview. Laboratory evaluation included calcium, phosphorus, alkaline phosphatase, parathormone and vitamin D. Statistical analysis was performed using Fisher's, *t* Student's tests and logistic regression analysis.

Results: Twenty nine (31.2%) patients presented low bone mass for chronological age (Z-score ≤ -2 SD) in any site evaluated (lumbar spine, femoral neck and total femur). The comparison of SLE patients with Z-score ≤ -2SD (Group 1) with patients with Z-score > -2SD (Group 2) revealed no difference regarding OP/fractures risk, such as age (29.17 ± 5.68 vs. 30.64 ± 8.59 years, p= 0.40), BMI (25.02 ± 5.36 vs. 26.33 ± 5.11 kg/m^2, p= 0.26), percentage of Caucasian (68.9 vs. 67.2%, p= 1.0), current smoking (6% vs. 10%, p=1.0), high physical activity (12.5 vs. 35%, p=0.11), daily calcium intake (518.13 ± 1.3 vs. 572.70 ± 370.89mg, p=0.75) or personal (18.8 vs. 10.8%, p=1.0) or familial history of fractures (6.3 vs. 10.8%, p=0.42). The analysis of disease and treatment factors revealed comparable findings for organ involvements (p>0.05), number of ACR criteria (5.58 ± 1.30 vs. 5.34 ± 1.18, p=0.38), disease duration (3.89 ± 3.04 vs. 3.89 ± 3.18 years, p= 0.99), last SLICC (0.38 ± 0.62 vs. 0.25 ± 0.50, p= 0.29), mean follow-up SLEDAI score (5.54 ± 2.91 vs. 4.97 ± 3.45, p=0.45), maximal glucocorticoid dose (50.35 ± 16.44 vs. 44.39 ± 21.93mg, p= 0.20), cumulative glucocorticoid dose (23.7 ± 9.59 vs. 17.6 ± 15.3g, p=0.28), number of methylprednisolone pulse therapy (1.96 ± 2.59 vs. 2.01 ± 2.85, p= 0.94) or immunossupressor use (93% vs. 84%, p=0.20). Biochemical bone parameters were also alike in both groups: serum calcium, phosphorus, alkaline phosphatase, parathormone and vitamin D (p>0.05). The frequency of vertebral fractures by VFA was low and comparable in Group 1 and 2 (0 vs. 1,6%, p=1.0). Body composition evaluation demonstrated that lean mass was significantly lower in the group with low bone density (37.8 ± 4.9 vs. 41.6 ± 6.2g, OR 1.14, CI 1.04 – 1.26, p 0.007) whereas fat mass (21.5 ± 8.2 vs. 24.3 ± 9.7, p=0.18) and % of fat (34.3 ± 6.5 vs. 34.6 ± 7.1, p=0.84) were similar in both groups.

Conclusion: Low lean mass is a major risk factor for low bone mineral density in pre-menopausal women with SLE reinforcing the relevance of a nutritional and exercise program for these patients.

Disclosure: L. P. Costa, None; **E. Bonfa**, CNPq # 305468/2006-5, 2 ; **V. F. Caparbo**, None; **E. F. Borba**, None; **L. F. Muniz**, None; **J. A. Paupitz**, None; **R. M. R. Pereira**, CNPq # 305691/2006-6, 2 .

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Measurement and Characteristics of Fatigue in Patients with Inflammatory Arthritis Prior to Anti-TNF Therapy. Patricia Minnock[1], Gabrielle McKee[2], Oliver M. FitzGerald[3], Anne Barbara Mongey[3], Douglas J. Veale[3] and Barry Bresnihan[3], [1]Our Lady's Hospice, Dublin 6, Ireland, [2]Trinity College Dublin, Dublin, Ireland, [3]St Vincent's University Hospital, Dublin, Ireland

Purpose: The unique contribution of fatigue to the assessment of patients with inflammatory arthritis has been demonstrated. The purpose of this study was 1) to compare the performance of two fatigue scales, and 2) to evaluate the relationship between fatigue and the core outcome measures in patients with inflammatory arthritis prescribed anti-TNF therapy.

Methods: Patients with rheumatoid arthritis (RA) and patients with psoriatic arthritis (PsA) prescribed anti-TNF therapy underwent standard clinical assessment of disease activity at baseline. Fatigue was measured using 2 validated scales: 1) the multidimensional assessment of fatigue scales (MAF) and 2) a one dimensional 5-point ordinal scale (OS). The clinical characteristics and the relationship between fatigue and 6 core outcome measures were evaluated across the two diseases.

Results: A total 188 patients were enrolled (RA, 135; PsA, 53). At baseline, the mean ages (SD) were 54.3 (12.8) years in RA, and 45.8 (12.5) in PsA. The mean (SD) MAF levels were 28.3 (11.2) and 26.6 (12.2) in RA and PsA, respectively. The 5-point OS measures of fatigue were as follows: none (RA, 6.3%; PsA, 10.0%), mild (RA, 16.2%; PsA, 17.5%), moderate (RA, 40.5%; PsA, 35.0%), severe (RA, 27.0%; PsA, 30.0 %), very severe (RA, 9.9%; PsA, 7.5%). The table summarises baseline clinical characteristics:

	RA		**PsA**	
	Mean	SD	Mean	SD
SJC28	7	5	5	6
TJC28	9	8	7	6
Pain	5	2	6	2
Patient Global Health	6	2	6	3
CRP	25	43	15	20

HAQ	1.0	0.679	0.653	.573
DAS28-CRP	5.01	1.20	4.49	1.14
Haemoglobin	12.9	1.7	13.4	1.6

Significant correlations ($p<0.01$) between both fatigue scales and the core outcome measures TJC (OS, r= 262; MAF, r= 307), Pain (OS, r= 477; MAF, r= 469), GH (OS, r= 546; MAF, r= 520), HAQ (OS, r= 436; MAF, r= 399), were observed across both disease groups. On multiple regression analysis (backward deletion technique) fatigue in RA was poorly explained by the core set variables (R^2= .324); while in the PsA model (R^2= .543) both HAQ (Beta .505; p=.000) and GH (Beta .364; p=.005) made significant contributions to assessment of fatigue.

Conclusion: This study demonstrated that the single item 5-point ordinal scale performed as well as the MAF with respect to correlations between fatigue and the core outcome measures of disease activity. Furthermore, these findings further confirm the independence of fatigue as an outcome measure in RA, and the association between fatigue and both function and global health in PsA.

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Creation of a Short Version of the Valued Life Activities Questionnaire (S-VLA). Patricia Katz[1], Diane D. Allen[1], Afton L. Hassett[2], Tracy Li[3] and R. Maclean[3], [1]UCSF, SF, CA, [2]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [3]Bristol-Myers Squibb, Princeton, NJ

Purpose: Disability in valued life activities (VLAs), defined as the wide range of activities that individuals may perform on a daily basis, has been strongly linked to psychological well-being, satisfaction with function, and quality of life among individuals with rheumatoid arthritis (RA). Need for accommodations (ACCs) in VLAs predicts progression of disability in RA. The current VLA disability questionnaire queries difficulty in 33 activities, with 4 follow-up questions for each activity regarding ACCs. Difficulty is rated on a 5-point scale from no difficulty (0) to unable to perform the activity (4). A scoring method incorporating use of ACCs has been developed. Our objective was to create a short version of the questionnaire, incorporating use of ACCs.

Methods: Data from 2 years' administration of the long form VLA questionnaire (L-VLA) in a longitudinal cohort of individuals with RA were used (n=449, 421). Analyses were first conducted with Year 1 data and then validated with Year 2 data. Item response analyses using ConQuest were performed. Items were deleted based on misfit (weighted mean square statistic <0.75 or >1.34 AND t-statistics <-2 or >+2), logit values that duplicated information provided by other items providing information at similar logit values, and substantive considerations. Psychometric properties of the short version (S-VLA) were compared to those of the L-VLA.

Results: Partial credit and rating scale models were both tested; the partial credit model had fewer item and step misfits (G^2 likelihood ratio = 623.881, $p<.0001$). The scoring range was expanded to 0-5 to account for use of ACCs (0=no difficulty, no ACCs; 1=no difficulty, with ACCs; other difficulty ratings increased by 1 to account for additional category). Deletions were progressive, resulting in a 21-item version, a 14-item version, and 4 12-item versions. A 14-activity version of the VLA questionnaire, with 1 follow-up question for each regarding ACCs, was selected. The S-VLA had 0 misfitting steps; 2 items had potential misfit but were retained for both substantive reasons and to provide logit spread. Correlation between L-VLA and S-VLA scores was .97; correlations of the L-VLA and S-VLA with other measures of functioning and RA impact were similar (Table). Analyses were confirmed in Year 2 data.

	EAP reliability	Cronbach's a	HAQ	Overall rating of RA impact 0-100	RA affects things you NEED to do	RA affects things you LIKE to do
L-VLA	.949	.97	.79	-.54	.74	.65
S-VLA	.932	.94	.83	-.56	.74	.66

Conclusion: A short form of the VLA disability questionnaire has been developed. The S-VLA appears to be reliable and valid, and can provide a brief assessment of disability in a broad range of life activities. Since it includes the broad range of activities, it may be more sensitive to change than other measures of functioning such as the HAQ and may appear more relevant to individuals with RA.

Disclosure: P. Katz, Bristol-Myers Squibb, 2 ; **D. D. Allen**, Bristol-Myers Squibb, 2 ; **A. L. Hassett**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5 ; **T. Li**, Bristol-Myers Squibb, 3 ; **R. Maclean**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 .

1127

The Accuracy of Self-Administered Rheumatoid Arthritis Activity Compared with Clinician Exam. Marlena Hyer Kern and Peter K. Gregersen, Feinstein Institute for Medical Research, Manhasset, NY

Purpose: The joint exam in Rheumatoid Arthritis (RA) is highly variable between patients and practitioners. This evaluation compares two aspects (presence and severity) of the self report of joint pain to the clinician exam for joint swelling and tenderness.

Method: Questionnaire Data was collected prospectively on patients diagnosed with RA during one-time research visit for the NARAC genetic study of RA. Study subjects (n= 1644) were seen individually by study personnel who performed a 28 count joint assessment of pain and swelling. At the same visit participants also completed the Rheumatoid Arthritis Disease Activity Index (RADAI) – a self administered questionnaire combining information on the presence of pain as well as pain severity in ten joint areas.

The examiners were trained by one board certified rheumatologist with return demonstration and analysis of assessments

Results: Both dichotomous and continuous measures of pain by self report show good correlation with clinician based assessment of joint tenderness and swelling. Continuous pain measures were marginally superior. The Spearman correlation coefficients were computed to determine the degree of correlation between the clinician joint count and both the patient's pain (yes/no – $r=0.484$ $p<0.0001$ $N=1644$) and intensity of pain (0=none, 1=mild, 2=moderate, 3=severe; $r=0.523$ $p<0.0001$ $N=1644$) in ten joint areas.

Conclusion: There was good correlation between the patient self report and the clinician assessment of rheumatoid arthritis disease activity. The data suggest that self report may be a cost effective substitute for clinician based joint assessment when conducting studies of rheumatoid arthritis. Further development of this analysis may permit large scale studies of disease activity in RA, including assessments of response to novel therapies, without the expense of clinician based evaluation Conclusion

Disclosure: M. H. Kern, None; **P. K. Gregersen**, None.

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A Computer Time Trade-off: A Good Alternative for the Interview Time Trade-off in Rheumatoid Arthritis. Laurien Buitinga[1], Louise Braakman-Jansen[1], Erik Taal[1] and M.A.F.J. van de Laar[2], [1]University of Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente & Universtiy Twente, Enschede

Purpose: The purpose was to evaluate the test-retest reliability of a computer Time Trade-Off (TTO) (an instrument that measures preferences for health states) in patients with Rheumatoid Arthritis (RA), and to compare the computer with the interview TTO regarding feasibility, agreement, and convergent validity.

Method: A cross-over design was used to compare the computer with the interview TTO. Fifty-nine RA patients participated. Thirty patients completed both TTO measures. Twenty-nine other patients completed the computer TTO twice to examine test-retest reliability. Feasibility was measured by comparing actual and experienced time duration of the TTOs and assessing general experience of the patient. Convergent validity was measured by calculating Spearman's correlation between both TTOs. Agreement between both TTOs was measured by using the Bland-Altman analysis.

Results: Both TTOs were feasible. The computer TTO showed high test-retest reliability (ICC=0.88, 95% CI: 0.75 to 0.94), and high convergent validity ($r=0.73$) with the interview TTO. Bland-Altman analysis showed a small mean difference (0.06, SD=0.14) between the computer and interview TTO. Limits of agreement were wide (-0.22 to 0.34).

Conclusion: Feasibility and reliability of the computer TTO were good. Convergent validity of the computer TTO was high when the interview was used as validation standard. Agreement between the interview and computer TTO was good at group level, indicated by the small mean difference in utilities between both methods. The computer TTO is a good alternative for measuring utilities in RA.

Disclosure: L. Buitinga, None; **L. Braakman-Jansen**, None; **E. Taal**, None; **M. A. F. J. van de Laar**, None.

1129

Analysis of Correlated Ordinal Data in a Self-Matched Study with Applications to Knee Pain Severity. Yanyan Zhu[1], Howard Cabral[2], Charles E. McCulloch[3], David T. Felson[4], Michael C. Nevitt[3] and Yuqing Zhang[1], [1]BUSM, Boston, MA, [2]BUSPH, Boston, MA, [3]UCSF, SF, CA, [4]Boston University School of Medicine, Boston, MA

Purpose: In longitudinal studies, pain severity is often measured on an ordinal scale. To minimize confounding from person-level factors we have proposed a self-matched study in which comparisons are made within a knee over time and one knee per person is studied. To date, no statistical method is available to analyze such ordinal data when persons provide data for two knees. We adapted amalgamating conditional logistic regression (ACLR) for self-matched studies and tested 4 modifications to account for the correlation between knees.

Method: We used 4 methods to account for between-knee correlation while applying ACLR: 1. Clustered: treat a person (cluster) as a stratum; 2. Pooled: obtain point estimates assuming independence but calculate proper robust variance estimates; 3. WEE: apply weighted estimating equations (WEE), the weighted version of the estimating equations used in the pooled method. Each knee was weighted by the inverse of the number of knees a person provided; 4. WCR: perform within-cluster resampling (WCR). Each time a knee was randomly selected from each person with replacement. We evaluated the performance of these methods by simulation and applied them to assess effusion in relation to knee pain severity in the Multicenter Osteoarthritis Study (MOST). Both simulated data and real data included 1349 persons. 188 persons had data for both knees, while the remainder contributed a single knee. Of the knees, 119 had observations from 3 time points and the rest had 2. A random-intercept proportional odds model was used in simulation. The simulated data (500 replicates) had a 4-level ordinal outcome variable and two covariates, one continuous from a N(0,1) distribution and the other binary (p=0.2). The regression coefficients were set at b_1=0.5 and b_2=1.0.

Results: The effect estimates from all methods were close to true value with bias less than 1% except for the clustered method, and the average model-based standard errors (SE) were close to the true SE (SD) (Table 1A). When these methods were used on the MOST data, all results suggested that increased severity of effusion was associated with higher severity of knee pain, but the magnitude from clustered method differed from others (Table 1B).

Conclusion: Pooled data, WEE and WCR methods generated very consistent results when the proportion of persons with data for two knees was small (18%). Further studies are required to assess the performance of these approaches when proportion of persons with data for two knees is relatively large.

1A. Simulation

	b_1=0.5			b_2=1.0		
Method	**Est**	**SD**	**SE**	**Est**	**SD**	**SE**
Clustered	0.481	0.048	0.050	0.950	0.170	0.168
Pooled	0.499	0.053	0.054	1.009	0.200	0.199
WEE	0.499	0.054	0.056	1.008	0.207	0.203
WCR	0.499	0.054	0.056	1.008	0.208	0.203

Est: mean estimated betas

SD: standard deviation of the estimated betas

SE: average of estimated standard errors		
1B. Effusion and Knee Pain Severity		
Effusion Score	**1 vs 0**	**2-3 vs 0**
Method	**OR_1 (95% CI)**	**OR_2 (95% CI)**
Clustered	1.30 (0.88, 1.91)	3.72 (2.32, 5.94)
Pooled	1.11 (0.72, 1.71)	2.70 (1.55, 4.70)
WEE	1.06 (0.68, 1.65)	2.52 (1.43, 4.43)
WCR	1.06 (0.69, 1.65)	2.52 (1.43, 4.43)

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The Chest Also Has a Spine. Bruce Rothschild[1] and Youssef Masharawi[2], [1]Arthritis Ctr, Baldwin, KS, [2]The Stanley Steyer School of Health Professions, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

Purpose: Bone alterations visible on chest x-rays are often overlooked or simply not reported. Radiation exposure concerns and artifacts have compromised use and interpretation of thoracic vertebral x-rays. Standards for recognition of compression fractures have been suggested, but are somewhat arbitrary. This study reports a new diagnostic technique for distinguishing osteoporotic fractures on routine lateral chest x-rays.

Method: The anterior, middle and posterior thoracic vertebral heights were measured on lateral chest x-ray in 3 groups: A control group of 120 individuals with unaffected vertebrae, 44 individuals with osteoporotic fractures and in 28 individuals with Scheuermann's disease. First and second derivatives were obtained of the relationships among the anterior height/posterior height (A/P), anterior height/mid height (A/M) and mid height/posterior height (M/P).

Results: The A/P indices (T6-T10) in all three groups were statistically indistinguishable. The M/P indices (T6-T10) were significantly smaller than the A/M indices in the osteoporosis group. The ratio of A/M to M/P first derivatives at thoracic vertebrae T6-T10 were significantly greater in the osteoporosis group than in the control and Scheuermann's groups ($p<0.05$). The intersection, on the superior aspect of the vertebral body, of the anterior-midpoint line and the posterior-midpoint line created an 'angle of depression' in the osteoporosis group, contrasted with an 'angle of elevation' in the Scheuermann's group.

Conclusion: Direct visualization of the intersection (described mathematically as the second derivative) of the A-M and M-P lines permits recognition of osteoporosis in the standing (weight-loaded) chest x-ray, in contrast to standard unloaded thoracic spine technique. Although most trabecular loss occurs subjacent to endplates, spine density testing focuses on more central vertebral regions. The technique reported herein identifies at least an often overlooked subset of individuals requiring bone-protective intervention.

Disclosure: B. Rothschild, None; **Y. Masharawi**, None.

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No Link Between C-Reactive Protein (CRP) and Bone Mineral Density (BMD) in Men, but Menopause Status Modifies the Relation in Women: The Framingham Osteoporosis Study. R.R. McLean[1], X. Zhang[1], E.J. Benjamin[2], L.A. Cupples[3], D.P. Kiel[1] and M.T. Hannan[1], [1]Hebrew SeniorLife & Harv Med Sch, Boston, MA, [2]Framingham Heart Study & Boston Univ, Boston, MA, [3]Biostat Dept, Boston Univ Sch of Pub Hlth, Boston, MA

Purpose: Laboratory studies suggest several pro-inflammatory cytokines influence bone resorption, which may partly mediate bone loss due to estrogen deficiency. Epidemiologic studies have not elucidated the interrelations of inflammatory biomarkers, menopause status and BMD in women, and few have examined men. We determined the cross-sectional association between elevated systemic inflammation, indicated by increased serum CRP concentration, and BMD among men and women in the Framingham Offspring Study. We hypothesized an inverse relation between CRP and BMD, which would be strongest in postmenopausal women not on estrogen.

Method: Fasting blood samples were obtained from 1,291 men and 1,614 women (1998-2001) and CRP (mg/L) was measured using a high-sensitivity assay (interassay CV=5.3%). Using clinical cut points, participants were categorized into CRP groups (<1, 1 to 3, >3 mg/L). Femoral neck BMD (g/cm^2) was measured with a Lunar DPX-L. Women were categorized as premenopausal (n=231), postmenopausal on estrogen (n=498), and postmenopausal not on estrogen (n=893). We used analysis of variance to compare crude mean BMD among CRP groups, separately for men and groups of women. Using analysis of covariance, we further adjusted for age (y), height (in), weight (lbs), physical activity (PASE) and current smoking (y/n).

Results: Mean age was 61 y (range 29-86). Due to a consistent threshold effect at 1 mg/L the upper 2 CRP groups were combined (≥1 mg/L). Crude mean BMD was similar between CRP groups for men and premenopausal women, yet was greater in the ≥1 mg/L group in postmenopausal women. After adjustment the lack of association in men remained, yet premenopausal women with CRP ≥1 mg/L tended to have 3.6% lower BMD (P=0.06). In postmenopausal women not on estrogen the ≥1 mg/L group had 2.3% higher BMD (P=0.04) but the difference was not significant for those on estrogen.

Crude and least-squares adjusted* mean (±SE) femoral neck BMD for CRP groups by sex, menopause status and estrogen use.

		CRP <1 mg/L	CRP ≥1 mg/L	P value
Men		(*n=341*)	(*n=950*)	
	Crude	0.974 (0.007)	0.972 (0.005)	0.82
	Adjusted	0.982 (0.007)	0.970 (0.004)	0.14
Premenopausal women		(*n=86*)	(*n=143*)	
	Crude	0.962 (0.014)	0.970 (0.011)	0.65
	Adjusted	0.985 (0.013)	0.952 (0.010)	0.06
Postmenopausal women on estrogen		(*n=71*)	(*n=426*)	
	Crude	0.866 (0.015)	0.899 (0.006)	0.05
	Adjusted	0.876 (0.014)	0.897 (0.006)	0.18
Postmenopausal women not on estrogen		(*n=206*)	(*n=682*)	
	Crude	0.799 (0.009)	0.838 (0.005)	<0.01
	Adjusted	0.815 (0.008)	0.834 (0.004)	0.04

*Adjusted for age, height, weight, physical activity, smoking

Conclusion: Our findings suggest increased systemic inflammation may be a risk factor for lower BMD among premenopausal women, but not for men or postmenopausal women on estrogen. Elevated inflammation was associated with higher BMD in postmenopausal women not on estrogen, contrary to our hypothesis. Future studies should examine the role of estrogen using biomarkers rather than crude estrogen status categories, and explore comorbidities that could explain our unexpected findings among postmenopausal women.

Disclosure: R. R. McLean, None; **X. Zhang**, None; **E. J. Benjamin**, None; **L. A. Cupples**, None; **D. P. Kiel**, None; **M. T. Hannan**, None.

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Efficacy and Safety of Concurrent Training in Systemic Sclerosis. Ana Lucia de Sa Pinto[1], Bruno Gualano[2], Romy B. C. de Souza[1], Vitor S. Painelli[2], Natalia C. Oliveira[1], Guilherme G. Artioli[2] and Fernanda R. Lima[1], [1]School of Medicine - University of Sao Paulo, Sao Paulo, Brazil, [2]School of Physical Education - University of Sao Paulo, SP, Brazil

Purpose: It has been demonstrated that exercise capacity is reduced in systemic sclerosis. Moreover, we recently showed that aerobic training is an effective and safe strategy to improve exercise tolerance, aerobic condition and oxygen saturation in these patients. However, the optimal training model for these patients remains to be determined. Therefore, we aimed to investigate the effects of 12-week concurrent training program in patients with systemic sclerosis.

Method: Nine patients without evidence of pulmonary involvement (pulmonary artery systolic pressure equal to or below 40 mmHg, forced vital capacity measured by spirometry and diffusion lung capacity of carbon monoxide (DLCO) higher than 75% of the predicted value) were engaged in a 12-week aerobic and resistance exercise program. Lower and upper limb dynamic strength (assessed by leg press and bench press one maximum repetition [1RM], respectively); isometric strength (assessed by trunk extension and handgrip test), balance and mobility (assessed by timed-up-and-go test), and muscle function (assessed by timed-stands test); Rodnan score, digital ulcers and Raynaud phenomenon; and inflammation and muscle (creatine kinase [CK] and aldolase) blood markers were assessed at baseline and after the 12-week program.

Results: Exercise training significantly enhanced 1RM leg press (41%) and 1RM bench press (12.9%) as well as trunk extension (23.6%) and handgrip strength (11.1%). Muscle function was also improved (14%, $p = 0.04$) but balance and mobility were not modified. Time-to-exhaustion was increased (46.5%, $p = 0.0004$) and the change in aerobic condition (VO2 peak and ventilatory thresholds) did not reach statistical significance ($p > 0.05$). Rodnan score was also not altered muscle enzyme remained within normal levels (CK: pre 113 ± 87.2 vs. post 122 ± 90.7 UI/l and aldolase: pre 5.23 ± 2.3 vs. post 5.47 ± 2.4 UI/l). No change was observed in digital ulcers and Raynaud phenomenon. There were no cardiac complains or muscle injury.

Conclusion: This is the first study to demonstrate that a 12-week concurrent program is safe and substantially improves muscle strength and function in patients with systemic sclerosis, but does not promote clinical benefits on aerobic condition.

Disclosure: A. L. D. S. Pinto, None; **B. Gualano**, None; **R. B. C. de Souza**, None; **V. S. Painelli**, None; **N. C. Oliveira**, None; **G. G. Artioli**, None; **F. R. Lima**, None.

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Effectiveness of Sensorimotor Training in Patients with Rheumatoid Arthritis. Kelson NG Silva Sr.[1], Lucas E.P.P Teixeira[1], Aline M. Imoto[1], Marcelo I. Abrahão[1], Alvaro N. Atallah[2], Stella Peccin[1] and Virginia F.M. Trevisani[1], [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Sao Paulo, Brazil

Purpose: The purpose of this study was to evaluate the effectiveness of sensorimotor training at improving functional capacity and pain relieve in patients with rheumatoid arthritis.

Methods: A randomized, controlled assessor blinded trial was conducted with assessments made before and after 04 months. The sample of 102 patients was statistically randomized into two groups: intervention group (balance training + medicine clinical treatment) and control group (only medicine clinical treatment). The duration of the sensorimotor training was 16 weeks with exercise frequency twice a week and duration of each exercise session of 40-50 minutes. The outcomes used were: Health Assessment Questionnaire (HAQ), Timed Up & Go Test (TUGT) and pain visual analogue scale (VAS). For statistical analysis, the team used Mann-Whitney Test to compare both groups (continuous outcomes), paired T-test for comparison between before and after intervention. For all tests an alpha=5% was used, being considered significant $p<0,05$.

Results: The baseline assessment demonstrates the homogeneity of the two groups (age, disease duration, height, weight, gender, HAQ, TUGT and VAS). Ninety-one patients had concluded the research. As observed in Table 1, there were statistically significant difference in the results of the HAQ, TUGT and VAS that it demonstrates improvement of the functional capacity and pain. No improvements were apparent in the control group.

Conclusion: Based on the findings of our study, we conclude that sensorimotor training is effective in improvement of functional capacity and pain relief.

Table 1

Variables	Control Group		Intervention Group		p-value
	Before	After	Before	After	
HAQ	1,30 ± 0,69	1,31 ± 0,72	1,41 ± 0,60	0,70 ± 0,42*†	p < 0,05
TUGT	10,05 ± 4,96	9,45 ± 5,31	9,82 ± 2,84	6,73 ± 1,17*†	p < 0,05
VAS	7,00 ± 2,79	6,35 ± 2,91	7,15 ± 2,12	4,61 ± 2,13*†	p < 0,05

* It indicates significant statistical difference in relation to the group has controlled the same for moment.

† It indicates significant statistical difference in relation to before experiment moment.

Disclosure: K. N. Silva, None; **L. E. P. P. Teixeira**, None; **A. M. Imoto**, None; **M. I. Abrahão**, None; **A. N. Atallah**, None; **S. Peccin**, None; **V. F. M. Trevisani**, None.

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Associates of Tolerance to Neuromuscular Electrical Stimulation in Rheumatoid Arthritis. Sara R. Piva[1], Nathan Strudle[1], Gustavo J. M. Almeida[1], M. C. Wasko[2], G. Kelley Fitzgerald[1] and Anthony Delitto[1], [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Purpose: Nearly two-thirds of patients with rheumatoid arthritis (RA) experience muscle weakness and atrophy. Neuromuscular electrical stimulation (NMES) is a viable intervention to treat muscle atrophy and weakness in RA. The therapeutic effect of NMES is dependent on the dose of electrical stimulation. Tolerance is a limiting factor of NMES effectiveness because patients must tolerate high doses of NMES to maximize gains in muscle function. Identifying factors associated with NMES tolerance may guide strategies to improve tolerance to this intervention. This study aimed to identify psychological factors associated with NMES tolerance in subjects with RA

Method: Thirty eight subjects with RA participated in this cross-sectional study, with age 60 ± 11 years, 63% female, BMI 27 ± 6. Measures of social and biomedical characteristics included age, gender, race, marital status, education, height, weight, disease duration, medication, and disability (HAQ). Psychological factors included pain coping strategies, pain acceptance, sense of control over life and environment, anxiety, depression, and the sensory and affective domains of pain. NMES procedure: Subjects sat on an isokinetic dynamometer. The maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscles strength was determined. Torque output during the MVIC was the reference to determine NMES dose (% of MVIC torque generated during electrically elicited muscle contraction). Then, 15 NMES contractions were administered to the quadriceps muscles (stimulus parameters 75Hz, 450 µsec, on/off time 14/46sec). Intensity of the NMES was increased as tolerated. NMES tolerance was defined as the highest NMES dose tolerated by each subject during the NMES procedure. NMES procedure was repeated during 2 visits to allow adaptation to the electrical stimulation. Analysis: We calculated bivariate correlations between NMES tolerance and all other variables. Variables significantly correlated were selected to build a linear regression model to predict NMES tolerance. The social and biomedical characteristics were first forced into the model. Then, psychological factors were added using a stepwise approach

Results: Bivariate correlations demonstrated that more years of education, less disability, lower anxiety, and higher scores in 2 coping strategies (coping self-statements and ignoring pain sensation) were associated with higher NMES tolerance. After controlling for education and disability, only ignoring pain sensation was a predictor. Education and disability explained 45% of variability in NMES tolerance and ignoring pain sensation explained additional 13%. Regression diagnostics revealed that the assumptions of linear regression models were not violated

Conclusion: RA subjects who ignore pain sensation tolerate higher doses of NMES. These results suggest that incorporating coping strategy techniques to help subjects ignore the sensation of pain will help to increase tolerance to the NMES

Disclosure: S. R. Piva, None; **N. Strudle**, None; **G. J. M. Almeida**, None; **M. C. Wasko**, None; **G. K. Fitzgerald**, None; **A. Delitto**, None.

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Post-Acute Physiotherapy for Primary Total Hip Arthroplasty: A Cochrane Systematic Review. MD Westby[1], S. Carr[1], D. Kennedy[2], V. Brander[3], M. Bell[2], MM Doyle-Waters[4] and C. Backman[5], [1]Mary Pack Arthritis Program, Vancouver, BC, [2]Sunnybrook Health Sciences Centre, Toronto, ON, [3]Northwestern Orthopaedic Institute, Chicago, IL, [4]Centre for Clinical Epidemiology & Evaluation, Vancouver, BC, [5]University of British Columbia, Vancouver, BC

Purpose: To determine the effects of post-acute physical therapy (PT) following primary total hip arthroplasty (THA) for osteoarthritis (OA) on pain, function and health-related quality of life (HRQoL).

Method: Randomized and clinical controlled trials published 1990 - 2008 were identified using electronic and secondary searches (no language restrictions).Included studies involved adults who underwent primary THA for OA and received PT treatment in any setting, after discharge from acute care and initiated within 12 months of surgery. Studies involving revision, hemi- or resurfacing surgery, inflammatory arthritis or recent fracture were excluded. Two reviewers screened papers for inclusion, extracted data using a standardized form and assessed methodological quality using an 11-item scale (van Tulder). Clinical heterogeneity, grades, weighted mean difference (WMD) and 95% confidence intervals for primary outcomes were determined. Effect sizes for trials with small samples and differing baseline values were calculated using mean change values for within and between group differences.

Results: Of 1,538 trials identified, 98 were retained for second level screening, and 8 for full review. Main reasons for exclusion were: timing, type of intervention and lack of THA subgroup data. Trial heterogeneity prevented meta-analysis. Overall quality was low to moderate. Only 3 trials reported adequate randomization, concealed allocation and blinded outcome assessors. While participants (N = 497) were similar across studies, interventions and comparators varied substantially. A ‘silver’ grade was given to all trials. Positive mean post-test values were found for: 1) surgeon-rated function with body weight (BW) supported treadmill walking (WMD 13.60, [7.58, 19.62]) compared to routine inpatient care; 2) Timed Up and Go with unsupervised home exercises (WMD 1.8, [0.15, 3.45]) versus outpatient PT; and 3) Sit-to-Stand test after outpatient resistance training (WMD -4.50, [-7.09, -1.91]) and daily home exercises with electrical stimulation (WMD -3.00, [-5,97, -0.03]) compared to standard care. No between-group differences for pain or HRQoL were found. Positive standardized effect sizes ranged from 0.87 to 1.50 (large effects).

Conclusion: There is limited evidence to support the use of inpatient BW supported treadmill training, outpatient resistance exercises and home-based exercise with and without electrical muscle stimulation for improving surgeon-rated and performance-based function after THA. High quality trials with larger samples and standardized outcome assessment methods are needed, however, to establish specific treatment recommendations for post-acute PT after THA.

Disclosure: M. Westby, None; **S. Carr**, None; **D. Kennedy**, None; **V. Brander**, None; **M. Bell**, None; **M. Doyle-Waters**, None; **C. Backman**, None.

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Post-Acute Physiotherapy for Primary Total Knee Arthroplasty: A Cochrane Systematic Review. MD Westby[1], D. Kennedy[2], DL Jones[3], A. Jones[4], MM Doyle-Waters[5] and Catherine L. Backman[6], [1]Mary Pack Arthritis Program, Vancouver, BC, [2]Sunnybrook Health Sciences Centre, Toronto, ON, [3]West Virginia University, Morgantown, WV, [4]Federal University of Sao Paulo, São Paulo, Brazil, [5]Centre for Clinical Epidemiology & Evaluation, Vancouver, BC, [6]University of British Columbia, Vancouver, BC

Purpose: To determine the effects of post-acute physical therapy (PT) following primary total knee arthroplasty (TKA) for osteoarthritis (OA) on pain, function and health-related quality of life (HRQoL).

Method: Randomized controlled trials published between 1990 and 2009 were identified using electronic and secondary searches (no language restrictions).

Included studies involved adults who underwent primary TKA for OA and received PT interventions in any setting, after discharge from acute care, and initiated within 12 months of surgery. Studies involving revision, unicompartmental surgery, inflammatory arthritis or recent trauma were excluded. Two reviewers screened papers for inclusion, extracted data using a standardized form and assessed methodological quality using an 11-item scale (van Tulder). Clinical heterogeneity, grades, weighted mean difference (WMD) and 95% confidence intervals were determined for primary outcomes. Effect sizes for trials with small samples and differing baseline values were calculated using mean change values for within and between group differences.

Results: Of 2,534 trials identified, 47 were retained for second level screening, and 7 for full review. Main reasons for exclusion were: timing, type of intervention and lack of TKA subgroup data. Trial heterogeneity prevented meta-analysis. Overall quality ranged from low to high. Six trials reported adequate randomization, concealed allocation and blinded outcome assessors. While participants (N = 779) were similar across studies, interventions and comparators varied substantially.

A 'gold' level grade was given to 3 trials and 'silver' to 4. Positive mean post-test values were found for: 1) pain (WMD -7.60, [-14.15, -1.05]) and the SF-36 Mental Component Summary (WMD -4.00, [-6.84, -1.16]) after out-patient intensive functional rehabilitation compared to standard home therapy; and 2) 3-minute walk test (WMD 24.40, [12.82, 35.98]) after daily electric muscle stimulation versus standard PT. No between-group differences were found for self-reported function, timed stair climb or 6-minute walk test. Positive standardized effect sizes ranged from 0.52 to 1.47 (medium to large).

Conclusion: There is limited evidence to support the use of outpatient functional exercises and electrical muscle stimulation for improving pain, mental health status and walking speed after TKA. High quality trials with larger samples and standardized outcome assessment methods are needed, however, to establish specific treatment recommendations for post-acute PT after TKA.

Disclosure: M. Westby, None; **D. Kennedy**, None; **D. Jones**, None; **A. Jones**, None; **M. Doyle-Waters**, None; **C. L. Backman**, None.

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Describing "Usual" Physical Therapy Practice Following Total Knee Replacement in Montgomery County, Pennsylvania. Carol A. Oatis[1], Jl Brennan[1], S. Kushman[1], A. Werner[1] and Patricia D. Franklin[2], [1]Arcadia Univ, Glenside, PA, [2]Univ of MA Med School, Worcester, MA

Purpose: Total knee replacement (TKR) is one of the most common surgeries performed in the United States at an approximate rate of 500,000 per year. Recovery from TKR requires physical therapy, yet research identifying "best" practice following this procedure is lacking. The purpose of this study was to describe "usual" therapy practices following TKR in the acute care (AC), home care or inpatient rehabilitation (HCIR), and outpatient settings (OP).

Methods: 145 physical therapists from 32 randomly selected facilities in Montgomery County, PA were provided with surveys for participation. 7 physical therapists considered "thought leaders" were also included to ensure representation of the full spectrum of care. Chief physical therapists at the selected sites were asked to provide surveys to all physical therapists in their facility who treat patients following TKR. The survey was made available online, using Survey Monkey™, or in hard copy. The survey assessed 105 exercise and therapeutic modalities that may be considered after TKR. "Usual" care was operationally defined as interventions used "always" or "often" by more than 50% of respondents. "Consensus" was defined as agreement exceeding 85%.

Results: 80 surveys were returned at a response rate of 53%. Consensus in all three settings included knee flexor/extensor stretching and strengthening, and gait training on indoor surfaces. Usual care in the three settings included ankle PF stretching. Although some form of strength and flexibility exercises for the hip, knee and ankle were utilized in all three settings, little agreement existed for frequency, intensity or mode of exercise in any setting. For example, active knee extension in standing and standing knee extension with resistance were uncommon in OP (<50%). Stabilization and abdominal exercises were rare in AC and OP (>50% rarely or never do) and variable in HCIR (42% rarely or never do and 11% often or always do). Neuromuscular electrical stimulation was very rare or variable in all settings (36-87% rarely or never do). Ice was usual care in AC but consensus in OP. Heat was usual care in OP. Patellar mobilizations were very uncommon in AC (<15%), variable in HCIR (38% often or always do, 32% rarely or never do) and usual care in OP (84%). OP gait training was usual care but < 32% reported gait training against resistance.

Conclusion: This study describes usual physical therapy intervention following TKR provided in Montgomery County, PA. While agreement exists in the general approach to treatment, wide variability in exercise intensity, frequency, and mode exists. Use of therapeutic

modalities also varies. An understanding of the existing variability in practice may help explain the disparity in patient outcomes, as well as help direct future research to determine "best practice."

Disclosure: C. A. Oatis, None; **J. Brennan**, None; **S. Kushman**, None; **A. Werner**, None; **P. D. Franklin**, None.

1138

Translating Physical Activity Guidelines Into Motivating Language for People with Arthritis. Teresa J.. Brady[1], K. Sammons[2], K. Grulikowski[2], M. Taylor[2] and K. Schermerhorn[2], [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Porter Novelli, Atlanta, GA

Purpose: In October 2008 the Department of Health and Human Services (HHS) released new guidelines recommending that all adults participate in at least 2.5 hours of moderate physical activity each week. The Centers for Disease Control and Prevention's Arthritis Program is revising a health communications campaign designed to promote physical activity (PA) among people with arthritis (PWA). The purpose of this qualitative study was to determine how best to describe the HHS guidelines in terms that motivate PWA to increase their PA.

Methods: 27 mall intercept interviews were conducted in Atlanta, Cleveland, and Houston in February 2009. Inclusion criteria were: self report of doctor diagnosis of arthritis, exercising less than three days/week, some limitations due to arthritis, belief that exercise can reduce arthritis pain, black or white, age 40-70, less than college education and income less than $75,000. Each respondent viewed 3 print ads, each using a different descriptor of the physical activity guideline (2.5 hours/week, 30 minutes 5 days/week, or 150 minutes/week). Order of ads was rotated for each interview. The three descriptors were then displayed together and respondents were asked to identify which would be most likely to motivate them to increase their physical activity. Respondents were also asked to comment on other elements of ads they found motivating.

Results: Sample was 52% female, 55% black, 63% income under $45,000. Despite the fact that most respondents recognized that all 3 descriptors represented the same amount of PA, the majority (78%) found 30 minutes 5 days/week to be the most motivating PA descriptor. Rationale included: time frame fit schedule, 30 minutes would be physically easier to do, smaller amount of time would pass quickly, and concrete schedule eliminated need for any calculations. For the majority, the other descriptors, described as total hours or minutes, appeared too large and unattainable; the need to track and total time was also unappealing.

No racial differences were found, but gender differences did exist. All women preferred the 30 minutes 5 days/week descriptor, 38% of men preferred the 2.5 hour descriptor. A slight majority of these men had some college or trade school. Their rationale was also related to scheduling: these men thought they did not have time to exercise 5 days/week, but could meet the recommendation in 1-2 long sessions, such as a weekend basketball game.

Other concepts in body copy identified as motivating included connecting PA to improved mood, seeing results in 4-6 weeks, describing PA as more than keeping busy, and encouraging a choice of activity.

Conclusion: To motivate PWA to increase their physical activity, the new HHS PA guidelines need to be translated into descriptions that seem attainable for PWA. The majority prefer 30 minutes 5 days/week as the descriptor, although some men prefer to think of the cumulative 2.5 hours/week. Clinician counseling and population based health messages should use terms motivating for PWA.

Disclosure: T. J. Brady, None; **K. Sammons**, None; **K. Grulikowski**, None; **M. Taylor**, None; **K. Schermerhorn**, None.

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Engaging Media to Help Shape and Promote Arthritis Management Messages. Teresa J.. Brady[1], K. Sammons[2], L. Ramsey[1] and K. Heumann[2], [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Porter Novelli, Atlanta, GA

Purpose: Media are critical in shaping the public dialogue on health. Understanding media perspectives can help us position health messages to garner both media and public attention. The Centers for disease control and Prevention's Arthritis Program convened a Media Roundtable with leading media opinion leaders to discuss what the media see as drivers and motivators for health behavior change related to general public health issues, and specifically arthritis.

Methods: Three months of media coverage by leading national media vehicles were reviewed to identify priority reporters to invite to the roundtable discussion. The roundtable format included 30 minutes of presentation on the urgent realities of chronic disease generally and arthritis specifically followed by ninety minutes of semi-structured discussion among the reporters and CDC experts. Note-takers captured the discussion and notes were analyzed to identify predominant themes and key insights from the discussion.

Results: Six reporters, representing 4 national print vehicles (Time, Good Housekeeping, Essence, Better Health and Living), one wire service (Health Day) and one Web outlet (WebMD) accepted the invitation to participate.

Key themes that emerged from the discussion included:
Consumer attention gravitates to the "sexy"; arthritis is not seen as sexy. Media see arthritis as "a nuisance to be tolerated"
Positioning arthritis as a threat to "the way you want to lead your life" may allow it to compete with more "sexy" (i.e. scary) conditions
A story needs to be "news"-- but anything that is new to them (such as the existence and benefits of packaged self management programs) is considered news.
prevention is a "tough sell" and at a minimum we will need new and more creative examples of healthy behaviors if we expect to break through the "white noise".
Personal success stories work, particularly in the weight loss and fitness arenas.
Concerns about food and medication safety are driving consumer interest in natural remedies and a "back to basics" trend.
The non-pharmacological arthritis management strategies can be positioned as natural approaches to chronic disease management (i.e. "natural solutions you don't know about").

Conclusion: The media in attendance were quite engaged in the discussion; most asked if another roundtable would be held. Most arthritis messages are not "sexy", but can be positioned as natural solutions to the threat arthritis poses to quality of life. New more creative examples are needed, and personal success stories can be advantageous to promote arthritis management messages.

Disclosure: T. J. Brady, None; **K. Sammons**, None; **L. Ramsey**, None; **K. Heumann**, None.

ARHP Concurrent Abstract Sessions

Cognitive Functioning in Fibromyalgia and Lupus
Monday, October 19, 2009, 7:45 AM - 8:45 AM

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Cognitive Impairments in Patients Diagnosed with Fibromyalgia, Systemic Lupus Erythematosus, and Rheumatoid Arthritis. Kati Thieme, Anique Thieme and Richard H. Gracely, University of North Carolina, Chapel Hill, NC

Purpose: To determine the presence of cognitive impairments in fibromyalgia syndrome (FM), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) patients, to compare these impairments among there three patient groups and to healthy controls (HCs), and to evaluate the contributions of demographic, physical, pain, stress, affective, and cognitive variables to these impairments.

Method: Thirty-seven FM, 27 SLE, 26 RA patients, and 20 HCs underwent a neuropsychological assessment to evaluate concentration, memory, psychomotor speed, cognitive interference, learning, and recall deficits. Pain intensity, fatigue, and sleep disorders were assessed and adrenocorticotropic hormone (ACTH) were collected.

Results: FM and SLE patients showed significantly more cognitive impairments than RA patients and HCs. FM patients demonstrated significantly greater concentration and SLE patients more memory deficits. There were no significant differences between FM and SLE patients in psychomotor speed and complex attention, however, both groups showed significantly worse cognitive abilities than RA patients on all measures except for psychomotor speed. The combination of impaired sleep quality and increased ACTH-production explained 52.4% of the variance of impaired short-term concentration. Fatigue and non-clinically significant depression explained 72.9% of variance of deficits of recognition memory in patients with SLE.

Conclusion: The results support the presence of significant cognitive deficits in FM and SLE patients compared to RA patients and HCs. The association of cognitive impairments and fatigue in SLE suggests immunological influences, whereas ACTH influenced sleep quality in non-depressed FM patients implicating endocrine influences on neuropsychological functioning.

Disclosure: K. Thieme, German Research Foundation Th 899/1-1 and Th899/1-2, 2 ; **A. Thieme**, None; **R. H. Gracely**, None.

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Subjective Cognitive Complaints and Cognitive Impairment in out-Patients with Systemic Lupus Erythematosus. Janni Lisander Larsen, Asmus Vogel and Soren Jacobsen, Copenhagen University Hospital, Copenhagen, Denmark

Purpose: A considerable proportion of SLE patients have cognitive deficits. The relationship between subjective cognitive complaints and objective cognitive impairment in SLE, is variable. It is suggested that even minor subjective complaints of disturbances in memory and attention can be an indicator of cognitive dysfunction. However, others have not found such an association. The purpose of this study was to investigate the prevalence of cognitive impairment; depression and self reported cognitive complaints in outpatients with SLE. Further, the study aimed to explore the relationship between cognitive impairment, affective status and perceived cognitive difficulties in this group.

Method: 57 female outpatients with SLE, according to the 1997 revised criteria, where included. Median age 41. Median SLEDAI and damage scores were 0 ranging from 0-14 and 0-7, respectively. Cognitive complaints were assessed with the patient administered Perceived Deficits Questionnaire (PDQ). The questionnaire was followed by a comprehensive 1 hour neuropsychological test battery. To assess affective symptoms the Major Depression Inventory was applied. Age and sex adjusted normative data derived from previously sampled data on healthy controls.

Results: 22 of 57 patients (38.5%) where classified as cognitively impaired. The most common cognitive deficits were found in executive functions and attention. A low proportion of the patients reported cognitive problems (17.5%) and even among those subjects who had cognitive impairments the proportion of cognitive complaints remained very low (18%). Cognitive impaiment was not associated with history of neuropsychiatric SLE. In the present study 22.5% had scores indicating possible depression. Self-rated depressive symptoms had a high correlation with subjective complaints whereas only four neuropsychological tests were moderately but significantly correlated with subjective cognitive complaints. When these four variables and the self-rated depression score were entered into a linear regression model only the depression ratings had a significant impact ($p < 0.001$) on the PDQ score.

Conclusion: Cognitive impairments (mostly in mild degree) are common in female outpatients with SLE. The level of subjective cognitive complaints was generally very low and many patients with cognitive deficits did not have more complaints of cognitive dysfunction than healthy controls. Subjective cognitive complaints were strongly correlated to self-rated affective symptoms indicating that affective status, and possibly other factors like personality traits, are more important, for the level of subjective experience of cognitive functions, than actual cognitive performance. In patients with SLE complaints of cognitive problems may indicate impairment or reflect other factors like emotional distress or depression. Importantly, absence of subjective cognitive complaints does not exclude the presence of cognitive problems.

Disclosure: J. L. Larsen, None; **A. Vogel**, None; **S. Jacobsen**, None.

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Positive Affect as a Resilience Factor in Fibromyalgia and Other Complex Symptom Disorders. Afton L. Hassett[1], Shantal V. Savage[1], Sarah E. Dihmes[1], Steven Buyske[2] and Naomi Schlesinger[1], [1]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Rutgers University, Piscataway, NJ

Purpose: Patients with fibromyalgia and other complex symptom disorders (CSD) such as chronic Lyme disease and chronic fatigue syndrome frequently present to rheumatology clinics. These conditions are characterized by multiple physical symptoms that are often comorbid with psychiatric disorders. A number of investigations have demonstrated that a subgroup of CSD patients display resiliency – possess protective psychosocial characteristics that result in less disability and greater life satisfaction. Herein, the role of positive affect (PA) was explored for its potential contribution to better outcomes in patients with CSD.

Methods: Sixty individuals with CSD were evaluated using the Composite International Diagnostic Interview for somatic symptoms and self-report questionnaires: Positive and Negative Affect Scale, Health Assessment Questionnaire, Quick Inventory of Depressive Symptomatology, Satisfaction with Life Scale, and Symptoms Checklist. Participants were categorized as having “High PA” (½ standard deviation [SD] above the mean) and “Low PA” (½ SD below the mean). The “Normal PA” group was comprised of participants who scored

within ½ SD from the mean. Differences in positive and negative affect, number of symptoms, disability, depression and life satisfaction were evaluated.

Results: Patients in the High PA group reported significantly fewer symptoms than those in the Normal PA (P = 0.003) or Low PA (P = 0.0001) groups. Further, those with High PA reported less disability and greater life satisfaction than those with Low PA (P = 0.004 and P = 0.001, respectively). Depression was more common in Low PA compared to Normal (P = 0.004) and High PA (P<0.0001). Patients in the High PA group were more likely to be Caucasian and have more years of education than patients in the Normal and Low PA groups. There were no significance differences among PA groups regarding level of negative affect. All significant differences for outcomes remain significant after applying a Bonferroni correction for multiple testing.

Conclusion: A subgroup of patients with complex symptom disorders like fibromyalgia who have high levels of positive affect experience fewer symptoms, less disability, and greater life satisfaction than those with lower levels of positive affect.

Disclosure: A. L. Hassett, None; **S. V. Savage**, None; **S. E. Dihmes**, None; **S. Buyske**, None; **N. Schlesinger**, None.

1143

Cortisol Awakening Response and Affective Factors in Fibromyalgia. Afton L. Hassett[1], Angela Clow[2], David A. Williams[3] and Daniel Clauw[3], [1]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]University of Westminster, London, England, [3]University of Michigan, Ann Arbor, MI

Purpose: Alterations in hypothalamic-pituitary-adrenal (HPA) axis functioning have been commonly observed in subgroups of patients with fibromyalgia (FM). The cortisol awakening response has been shown to be particularly sensitive to psychological variables. In general, positive affective factors have been associated with lower morning cortisol levels, while negative affective factors have been associated with higher levels. However, the role of affective factors in cortisol awakening response has not been well studied in FM. The objective of this study was to evaluate relationships between positive and negative affective factors and cortisol levels after awakening in patients with FM and healthy controls.

Methods: Composite scores based on data collected over three days were calculated for the initial awakening cortisol sample and for the second sample taken 60 minutes after awakening for 20 patients with FM and 26 healthy controls. The following variables were considered in light of their likely association with affect: Center for Epidemiological Studies–Depression Scale (CES-D); Short Form 36 Health Survey (SF-36) subscales: Mental Health, Role Emotional, and Social Functioning; and the anger and anxiety symptoms from the State-Trait Personality Inventory (STPI).

Results: We found that in the healthy controls, higher morning cortisol levels were related to the negative affective variables depression (CESD; $r = .372$; $p = 0.03$) and anxiety (STPI; $r = .41$; $p = .02$) and inversely related to the positive affective variables SF-36 Role Emotional ($r = -.35$; $p = .05$) and Mental Health ($r = -.41$; $p = .02$) subscales. Conversely, in patients with FM, higher morning cortisol levels were not related to the negative affective variables. Instead, higher morning cortisol scores were related the positive affective variables including: SF-36 Role Emotional subscale ($r = .49$; $p = .02$), SF-36 Mental Health ($r = .48$; $p = .02$) and SF-36 Social Functioning ($r = .45$; $p = .03$). Overall, the relationships between cortisol and affective variables were most prominent at initial awakening and few of these relationships existed in composite cortisol scores evaluated later in the day.

Conclusion: Evaluation of affective variables in morning cortisol levels suggests a paradoxical relationship in FM. Unlike what was observed in the healthy controls, in FM positive affective factors were associated with higher morning cortisol levels, while negative affective factors were not associated with lower morning cortisol levels. We hypothesize that because hypocortisolism is common in FM, perhaps the higher cortisol scores influenced by positive affective factors may be indicative of *better* HPA axis functioning. Future studies should explore this possibility.

Disclosure: A. L. Hassett, None; **A. Clow**, None; **D. A. Williams**, None; **D. Clauw**, None.

ARHP Concurrent Abstract Sessions

Physical and Behavioral Health in Scleroderma

Monday, October 19, 2009, 9:15 AM - 10:15 AM

1144

Yearly, Standardized, Comprehensive Assessment and Treatment Advice for Patients with Systemic Sclerosis (SSc): Feasibility of a Day Care Program. Annemie JM Schuerwegh[1], Anne A. Schouffoer[1], Liesbeth JJ Beaart- van de Voorde[1], Francisca J. M. Tromp[1], Maarten K. Ninaber[2], Tom WJ Huizinga[1], Zuzana de Jong[1] and Thea PM Vliet Vlieland[1], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Pulmonology, Leiden University Medical Center, Netherlands

Purpose: The significant morbidity associated with systemic sclerosis (SSc) requires the involvement of various medical specialists and health professionals in many patients. In general, the provision of health care for patients with SSc is characterized by a lack of standardization and co-ordination. The aim of the present study was to test the feasibility of a yearly, standardized, comprehensive assessment program in a day care setting for patients with SSc .

Method: The scleroderma day care program is a yearly recurrent, two day-program for SSc patients referred by non-academic or academic rheumatologists. The program consists of: a) an inventory of the patients problems and needs by means of a questionnaire, to be filled in; b) pulmonary function tests, High Resolution CT thorax, ECG, transthoracal echography of the heart, cardio-pulmonary exercise testing (CPET), 24h rhythm registration and blood analysis; c) clinical history taking and clinical evaluation by a specialized rheumatologist, pulmonologist, cardiologist, and health professionals (occupational therapist, physical therapist and/or social worker) according to the patients needs. Diagnostic outcome parameters are discussed in a multidisciplinary meeting and result into a treatment advice for the referring rheumatologist. Feasibility was evaluated according to the number of patients referred over a period of 3 months, the completion of the planned diagnostic procedures within two working days, the necessary period to report the treatment advice to the referring rheumatologist and the number of treatment advices other than continuation of current therapy.

Results: Over a period of 3 months, 44 patients were referred; twenty patients completed the day care program (n= 10 tertiary referral; n=10 secondary referral). In all patients, the diagnostic tests were completed during the two treatment days. The numbers of patients in whom evaluations by a health professional was requested were for occupational therapy: 12, physiotherapy: 9 and social worker: 5. Treatment advice resulted in further referral to another specialist (n=2 respectively cardiac electrophysiology and endocrinology), analysis of suggestive pulmonary arterial hypertension (n=3), change of supportive medical therapy (n=3) or immunosuppressive therapy (n=4). Health professional advice resulted into further intensive treatment by a peripheral physical therapist (n=9), referral to a psychotherapist (n=1). The required period between the program and reporting the advice to the referring rheumatologist was 3,5 weeks.

Conclusion: These preliminary results of a specialized SSc day care program indicate that a compact diagnostic and advising route is feasible. An outcome evaluation of satisfaction by referring doctors and patients is necessary. Collecting data in a systematic manner will provide more insight into the course of the disease.

Disclosure: A. J. Schuerwegh, None; **A. A. Schouffoer**, None; **L. J. Beaart- van de Voorde**, None; **F. J. M. Tromp**, None; **M. K. Ninaber**, None; **T. W. Huizinga**, None; **Z. de Jong**, None; **T. P. Vliet Vlieland**, None.

1145

Measuring Body Image Avoidance in Patients with Systemic Sclerosis. Lisa R. Jewett[1], Brett D. Thombs[2], Marie Hudson[2], Leslie Heinberg[3], Fredrick M. Wigley[4] and Jennifer A. Haythornthwaite[5], [1]McGill University, Montreal, QC, [2]McGill University and Jewish General Hospital, Montreal, QC, [3]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Clevland, OH, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]Johns Hopkins University, Baltimore, MD

Purpose: Patients with systemic sclerosis, or scleroderma, experience substantial disfigurement, often in visible and socially relevant areas of the body. Social avoidance related to body image distress is a significant problem for individuals with acquired disfigurement from medical illness or injury. However, body image avoidance has never been systematically studied in patients with scleroderma and existing measures are designed for non-disfigured individuals with body image and/or eating concerns. The objective of this study was to compare

the validity and reliability of a general Body Image Avoidance Questionnaire for Acquired Disfigurement (BIAQ-AD; N = 181) with a disease-specific measure for patients with acquired disfigurement from scleroderma (BIAQ-Scleroderma; N = 93).

Method: 203 female patients completed the BIAQ-AD, the BIAQ-Scleroderma, or both between 1997 and 2002. The BIAQ-AD was adapted from the Body Image Avoidance Questionnaire (Rosen et al., 1991) by removing weight and eating-related items, and the BIAQ-Scleroderma included items reflecting scleroderma-specific concerns (e.g., I wear long sleeves to hide skin changes). Confirmatory factor analysis and exploratory factor analysis were performed with MPLUS to determine the factor structure; internal consistency reliability was assessed using Cronbach's alpha; and concurrent validity was assessed by comparing BIAQ-AD and BIAQ-Scleroderma with the Adapted Satisfaction with Appearance Scale (ASWAP), Beck Depression Inventory (BDI) and the McGill Pain Questionnaire Short-Form (MPQ-SF).

Results: A 1-factor model provided the most parsimonious fit for both the BIAQ-AD ($\chi2(21) = 44.25$, CFI = .98, TLI = .99, RMSEA = .08), and the BIAQ-Scleroderma ($\chi2(19) = 53.28$, CFI = .92, TLI = .94, RMSEA = .14). The BIAQ-AD (Cronbach's alpha = 0.87) correlated 0.44 with the ASWAP, 0.72 with the BDI, and 0.25 with the MPQ-SF. The BIAQ-Scleroderma (Cronbach's alpha = 0.83) correlated 0.68 with the ASWAP, 0.59 with the BDI, and 0.27 with the MPQ-SF.

Conclusion: The high correlation of the general measure (BIAQ-AD) with the Beck Depression Inventory suggested it overlapped with general distress substantially more than the scleroderma-specific BIAQ-Scleroderma, which better addressed distress related to body image avoidance. Therefore, the BIAQ-Scleroderma is the preferred tool for assessment of body image avoidance in patients with scleroderma. The development and validation of the BIAQ-Scleroderma is a necessary initial step towards better assessment of body image avoidance in patients with scleroderma, however, further research is needed towards the development and testing of interventions to help these patients function better socially.

Disclosure: L. R. Jewett, None; **B. D. Thombs**, None; **M. Hudson**, None; **L. Heinberg**, None; **F. M. Wigley**, None; **J. A. Haythornthwaite**, None.

1146

The Longitudinal Trajectory of Depressive Symptoms in Systemic Sclerosis. Evan G. Newton, McGill University, Montreal, QC

Purpose: Studies find depression to be consistently elevated in chronic disease samples. A recent systematic review found 36-65% percent of scleroderma patients to have significant depressive symptoms. However, little is known about the course of depression over time among patients with chronic disease. The majority of studies in rheumatoid arthritis find depression to be stable over time. These studies, however, fail to account for patient drop-out and how change in depressive symptoms may reflect change in disease symptoms. When multiple imputation was used to account for missing data, we found that disability increased over time in the CSRG registry, and that much of this change in disability was explained by change in the symptoms of systemic sclerosis. The objective of this study was to determine the course of depressive symptoms in our sample, and to see what symptoms of disease might be related to depressive symptoms over time.

Method: The sample consisted of all patients in the CSRG registry who were assessed annually between 2004 and 2008. At the annual assessments, patients completed a standardized evaluation including a medical history, physical evaluation, of various measures of disease status, and the CES-D. Multiple imputation was used to account for missing data. Mixed-effects models were conducted to model the CES-D trend over time, taking into account symptoms of scleroderma.

Results: 741 patients presented a baseline, with a sample mean on the CES-D of 14.37 (10.4), 59% having limited disease, 41% having diffuse disease. Of the demographic variables, marital status =2.16, 95% CI = 0.18, 4.13) and greater than high schoolβ(unmarried) (=-1.39, 95% CI = -2.78, -0.00) were predictive of CES-Dβeducation (=0.83,βscores. Of the time varying disease covariates, breathlessness (=0.56, 95% CI =β95% CI = 0.60, 1.06) and gastrointestinal symptoms (0.37, 0.75) were the strongest predictors of CES-D scores. Visit number was not predictive of depressive symptoms.

Conclusion: Despite the increase in disability over time, depressive symptoms were stable. This finding suggests that a person with scleroderma may have already taken into account the uncertain future of living with a chronic disease, resulting in significant but stable depressive symptoms in the face of further reductions in physical health.

Disclosure: E. G. Newton, None.

1147

The Influence of Illness Perceptions On Physical and Mental Health in Scleroderma. S. Arat[1], P. Verschueren[1], E. De Langhe[1], M. Vanthuyne[2], V. Smith[3], K. Van den Heede[4], D. Blockmans[1], F. Houssiau[2], F. De Keyser[3] and R. Westhovens[1], [1]Rheumatology and Internal Medicine, University Hospitals KULeuven, Leuven, Belgium, [2]Université catholique de Louvain, Brussels, Belgium, [3]Ghent University Hospital, Ghent, Belgium, [4]Nursing Competence Center, University Hospitals KULeuven, Belgium

Purpose: To evaluate the contribution of illness perceptions and coping on physical and mental health in a large inception cohort of scleroderma patients.

Method: This is a cross-sectional study in a group of 217 scleroderma patients included in the Belgian Systemic Sclerosis Cohort (BSSC), evaluating patients at entry, month 6 and yearly thereafter. Patients completed the Revised Illness Perception Questionnaire (IPQ-R) as well as a coping questionnaire –COPE. Epidemiological data and disease specific data such as scleroderma subtypes and disease activity (according to the European Scleroderma Study Group) were collected as part of the BSSC registry. Physical and mental health were measured on each follow-up consultation by the Short Form 36 (SF-36). The relationship between illness perceptions and physical/mental health as well as between coping and physical/mental health, was analysed using multivariate linear regression analysis adjusted for age, gender, disease activity and scleroderma subtype.

Results: According to Leroy's classification**,** 49 patients had limited systemic sclerosis (lSSc), 129 limited cutaneous systemic sclerosis (lcSSc) and 39 diffuse cutaneous systemic sclerosis (dcSSc). The total sample consisted of 48 men and 169 women. The median age was 54 years, median disease duration 5 years and median Modified Rodnan Skin Score 4. Having lcSSc and disease activity were significantly ($p<0.05$) associated with physical health (beta standardized coefficients (bsc) respectively 0.182 and -0.119). The perception of "serious consequences" and "strong illness identity" was even more strongly associated with physical health ($p<0.001$) (bsc respectively -0.359 and -0.327). Disease activity was significantly ($p=0.005$) associated with mental health (bsc -0.166). "Strong illness identity" and "higher patients' emotional response to their condition" were associated with lower mental health ($p<0.001$) (bsc respectively -0.292 and -0.279). Coping variables were also associated with physical and mental health but resulted in less significant associations. Coping (in terms of behavioural disengagement, mental disengagement and positive reinterpretation and growth) mediated the link between "illness identity" and mental health. The coping style "substance use" mediated the link between "psychological attributions" and mental health. Coping did not interact in the relation between illness perception variables and physical health.

Conclusion: Illness representations are more significant contributors to physical and mental health than classical disease characteristics and therefore should be taken into account in the daily care of patients with scleroderma.

Disclosure: S. Arat, None; **P. Verschueren**, None; **E. De Langhe**, None; **M. Vanthuyne**, None; **V. Smith**, None; **K. Van den Heede**, None; **D. Blockmans**, None; **F. Houssiau**, None; **F. De Keyser**, None; **R. Westhovens**, None.

ACR Plenary Sessions

Plenary Session II: Discovery 2009

Monday, October 19, 2009, 11:00 AM - 12:30 PM

1149

Efficacy and Safety of Rituximab in Subjects with Active Proliferative Lupus Nephritis (LN): Results From the Randomized, Double-Blind Phase III LUNAR Study. R. Furie[1], R. J. Looney[2], B. Rovin[3], Kevin M. Latinis[4], G. Appel[5], J. Sanchez-Guerrero[6], F.C. Fervenza[7], R. Maciuca[8], P. Brunetta[9], D. Zhang[8] and J. Garg[8], [1]North Shore-LIJ Health System, Lake Success, NY, [2]University of Rochester, Rochester, NY, [3]Ohio State, Columbus, OH, [4]KS Univ Med Ctr, Kansas City, KS, [5]Columbia, New York, NY, [6]Inst Nacional, Mexico City DF, Mexico, [7]Mayo Clinic, Rochester, MN, [8]Genentech, South San Francisco, CA, [9]Genentech, Inc., South San Francisco, CA

Purpose: Small, uncontrolled LN studies have suggested that RTX may be efficacious. The efficacy and safety of RTX compared to placebo (PLA) added on to background therapy of mycophenolate mofetil (MMF) and corticosteroids in pts with proliferative LN was studied.

Methods: Pts with class III/IV LN and urine protein to creatinine ratio (UPCR) >1 were randomized 1:1 to receive RTX (1000mg) or PLA on days 1, 15, 168, and 182. Primary endpoint (EPS) was % pts with complete (CRR) or partial renal responses (PRR) at Wk 52 and was analyzed by a stratified Wilcoxon rank sum test.

Results: 72 pts were randomized to each arm and were similar at baseline (BL). Overall mean age at entry was ~30 yrs, ~90% were female, 28% were Black, 36% Hispanic, 31% White, and 67% had class IV LN. BL mean UPCR was 4.0 ±2.8 and serum creatinine was 1.0 ±0.5 mg/dL Mean daily MMF dose was 2.4±0.63g in PLA and 2.7±0.41g in RTX. There were no statistically significant differences in the primary or clinical secondary EPS. Blacks and Hispanics randomized to RTX had greater responses compared to PLA than Whites, but statistical significance was not achieved. RTX had a greater effect on levels of anti-dsDNA and complement at Wk 52. Peripheral CD19+ B cells were depleted in all RTX pts and maintained in most pts until Wk 52. Serious adverse events (SAEs) and infectious SAEs were similar between groups. Neutropenia (1 vs 4), leukopenia (3 vs 9), and hypotension (3 vs 9) occurred more frequently in RTX. Two deaths (sepsis and pneumonitis) occurred in the RTX group.

Conclusion: To date, LUNAR is the largest randomized, placebo-controlled trial to evaluate RTX as an intervention in LN. Although there were numerically more responders in the RTX group (57% vs 46%), the study did not show a statistically significant difference in primary or clinical secondary EPS. RTX had a significantly greater effect on levels of anti-dsDNA and complement, although the clinical significance of this is unclear. AEs and SAEs were similar in frequency between groups, with no new or unexpected safety signals.

Table: Efficacy EPS and Safety

	PLA (N=72) N (%)	RTX (N=72) N (%)	p-value*
Primary			
CRR PRR	22 (30.6) 11 (15.3)	19 (26.4) 22 (30.6)	0.55
Key Secondary			
Pts with BL UPCR>3 to UPCR<1	53.7	47.4	0.51
% change from BL in anti-dsDNA	50	69	<0.01
Mean Change from BL in C3 (mg/dL)	25.9	37.5	<0.03
Exploratory			
Pts with BILAG Renal Domain Score C at Wk52	28 (38.9)	39 (54.2)	0.07
Overall response (CRR+PRR)	33 (45.8)	41 (56.9)	0.18
Black	9/20 (45)	14/20 (70)	0.20
Hispanic	11/23 (48)	16/29 (55)	0.78
White	13/26 (50)	10/19 (53)	1.00
Pts with new immunosuppressant prior to Wk52	8 (11.1)	1 (1.4)	0.03

Safety	(N=71)	(N=73)	
SAE	25 (35.2)	22 (30.1)	
Infusion-related SAE	2 (2.8)	1 (1.4)	
Infection AE	61 (85.9)	61 (83.6)	
Infection SAE	12 (16.9)	12 (16.4)	
HACA+	4 (5.6)	8 (11.1)	
Deaths	0 (0)	2 (2.7)	

**P-values are 2-sided and not adjusted for multiplicity*

Disclosure: R. Furie, Genentech, Biogenidec, Roche, 5, Genentech, Biogenidec, Roche, 2 ; **R. J. Looney**, Biogen Idec, 5 ; **B. Rovin**, Genentech ., 5 ; **K. M. Latinis**, Genentech , 5 ; **G. Appel**, Genentech, 2 ; **J. Sanchez-Guerrero**, Genentech , 5 ; **F. C. Fervenza**, Genentech , 2 ; **R. Maciuca**, Genentech , 3 ; **P. Brunetta**, Genentech , 3 ; **D. Zhang**, Genentech ., 3 ; **J. Garg**, Genentech , 3 .

1150

Azathioprine Versus Mycophenolate Mofetil for Maintenance Immunosuppression of Proliferative Lupus Nephritis: Results of a Randomized Trial (MAINTAIN). Frederic A. Houssiau[1], David P. D'Cruz[2], Shirish R. Sangle[2], Philippe Remy[3], Carlos Vasconcelos[4], Enrique de Ramon Garrido[5], Inge-Margrethe Gilboe Sr.[6], Isabelle Ravelingien[7], Maria Tektonidou[8], Genevieve Depresseux[1], Loic P. Guillevin[9] and Ricard Cervera[10], [1]Universite catholique Louvain, Brussels, Belgium, [2]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [3]Hôpital Henri Mondor, Créteil, France, [4]Unidade de Imunologia Clínica - Hospital Santo António, Oporto, Portugal, [5]Hospital del SAS de Malaga, Malaga, Spain, [6]Rikshospitalet, Oslo, Norway, [7]Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium, [8]University of Athens, Athens, Greece, [9]Hopital Cochin, Paris, France, [10]Autoimmune Diseases. Hospital Clínic, Barcelona, Spain

Purpose: To demonstrate the superiority of mycophenolate mofetil (MMF) over azathioprine (AZA) as maintenance therapy of proliferative lupus nephritis in a randomized investigator-initiated open trial.

Method: 105 (mainly Caucasians) lupus patients from 29 European centers, with WHO Class III, IV, Vc or Vd nephritis and with a 24-hour proteinuria ≥ 0.5 gram were included. The number of patients was calculated to obtain a power of 0.80 with an α level of 0.05, on the basis of an anticipated 35% renal flare rate in the AZA group and a 10% flare rate in the MMF group, this difference being considered as clinically meaningful. All patients received 3 daily intravenous (IV) pulses of 750 mg methylprednisolone, followed by oral glucocorticoids (0.5 mg/kg/d equivalent prednisolone; per protocol tapering), and 6 fortnightly cyclophosphamide IV pulses of 500 mg (Euro-Lupus regimen). Based on randomization performed at baseline, AZA (target dose: 2 mg/kg/d) or MMF (target dose: 2 g/d) was started at week 12 for a total period of 60 months. Time to renal flare was the primary endpoint. Survival curves were derived using the Kaplan-Meier method and statistically tested with the Log rank test. All patients had a theoretical followup of ≥ 3 years. Analyses were by intention-to-treat.

Results: 52 and 53 patients were randomized in the AZA and MMF groups, respectively. Their baseline clinical, biological and pathological characteristics did not differ. After a median (range) followup of 53 (15-65) months, 24 patients had been dropped (mainly for pregnancy wish [n = 10; 2 AZA and 8 MMF, p = 0.05] and toxicity [n = 7; 5 AZA and 2 MMF], NS). A renal flare was observed in 13 AZA patients and 9 MMF patients. Time to renal flare, to severe systemic flare, to benign flare and to renal remission did not statistically differ. Doubling of serum creatinine occured in 4 AZA and 3 MMF patients. Infectious side-effects did not differ between the groups but drug-related hematological cytopenias were statistically more frequent in the AZA group (p = 0.03).

Conclusion: After a median followup of 53 months, MMF was not superior to AZA to prevent renal relapses of lupus nephritis.

Disclosure: F. A. Houssiau, Aspreva, 5 ; **D. P. D'Cruz**, Aspreva, 5 ; **S. R. Sangle**, None; **P. Remy**, None; **C. Vasconcelos**, Aspreva, 5 ; **E. de Ramon Garrido**, None; **I. M. Gilboe**, None; **I. Ravelingien**, None; **M. Tektonidou**, None; **G. Depresseux**, None; **L. P. Guillevin**, Aspreva, 5 ; **R. Cervera**, Aspreva, 5 .

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A Novel Autoantibody against 200/100 Kd Proteins Is Associated with Necrotizing Myopathy. Lisa Christopher-Stine, Grace Hong, Livia Casciola-Rosen, Andrea M. Corse and Andrew Mammen, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: The inflammatory myopathies are a family of conditions characterized by proximal muscle weakness, elevated serum muscle enzymes, and inflammatory infiltrates on muscle biopsy. However, ~20% of patients with clinical features of myositis do not have a significant degree of inflammation on muscle biopsy. Instead, biopsies from these patients demonstrate numerous degenerating, necrotic, and regenerating myofibers. Necrosis may be seen in patients with muscular dystrophies or toxic exposure as well as in those patients with myositis specific autoantibodies (MSAs). Nevertheless, a substantial proportion of patients with necrotizing myopathies have none of these known associations. We sought to determine novel autoantibody associations in patients with predominately necrotic features in the absence of substantial inflammatory infiltrates on muscle biopsy.

Method: 225 patients in the Johns Hopkins Myositis Cohort had both a muscle biopsy available for review at our institution and banked serum. Biopsies were evaluated for the presence of inflammation, regeneration, degeneration, necrosis, and vacuolar change. Antibody specificities in patient sera were assessed by performing immunoprecipitations from 35S-methionine labeled HeLa cell lysates.

Results: 38 patients in the JHU Myositis Cohort had predominant necrosis on muscle biopsy without histologic findings of perifascicular atrophy or red-rimmed vacuoles. Sera from these patients were screened by immunoprecipitation for the presence of novel autoantibodies. 12 patients had known autoantibody association or other diagnoses [SRP (6), anti-Jo-1(1), 1 anti-PL12 (2), anti-PL-7 (1), profound hypothyroidism(1), and dysferlinopathy(1)]. The remaining 26 patients had no known MSAs or other diagnosis to explain the necrotizing myopathy. A novel autoantibody specificity was found in 16 of these 26 patients (62%). These sera immunoprecipitated a pair of proteins with molecular weights of 100 kDa and 200 kDa. In contrast, control human sera did not precipitate these or other proteins. Only one additional patient with this autoantibody specificity was identified among 197 patients without prominent features of necrosis on muscle biopsy.

Conclusion: We have identified a novel autoantibody specificity which is associated with characteristic muscle biopsy findings and a variable clinical phenotype. Since we have not found instances of sera which precipitated only one of these proteins, we hypothesize that these may be subunits of a protein complex. Our findings show that patients with anti-200/100 represent a distinct subgroup of necrotizing myopathy patients that were previously considered to be “autoantibody negative.” Future studies will be directed towards identifying the autoantigens recognized by these autoantibodies.

Disclosure: L. Christopher-Stine, None; **G. Hong**, None; **L. Casciola-Rosen**, None; **A. M. Corse**, None; **A. Mammen**, None.

1152

Combination Antibiotics as a Treatment for Chronic Chlamydia-Induced Reactive Arthritis. John D. Carter[1], Luis R. Espinoza[2], R.D. Inman[3], K.B. Sneed[1], Louis Ricca[1], Frank B. Vasey[1], Joanne Valeriano[1], J.A. Stanich[4], C. Oszust[4], H.C. Gerard[4] and Alan P. Hudson[4], [1]University of South Florida, Tampa, FL, [2]LSU Medical Center, New Orleans, LA, [3]Toronto Western Hospital, Toronto, ON, [4]Wayne State University, Detroit, MI

Purpose: *Chlamydia trachomatis* (Ct) and *Chlamydophila (Chlamydia) pneumoniae* (Cpn) are known triggers of reactive arthritis (ReA). These chlamydial species exist in a persistent metabolically active infection state in the synovium suggesting that persistent chlamydiae may be susceptible to antimicrobial agents. The goal of this study was to investigate whether a six-month course of combination antibiotics is an effective therapy for patients with chronic *Chlamydia*-induced ReA.

Methods: This study was a 9-month, double-blind, triple-dummy prospective trial assessing a 6-month course of combination antibiotics as a treatment for *Chlamydia*-induced ReA. Eligible patients were age 18 to 70 years, fulfilled a modified European Spondyloarthropathy Study Group (ESSG) Criteria, and had disease duration equal to or longer than 6 months. Subjects had to be polymerase chain reaction (PCR)-positive for Ct or Cpn in order to be randomized to therapy; randomization was performed in a 1:1:1 fashion. Treatment was for 6

months; the 3 groups included doxycycline 100mg twice daily and rifampin 300mg daily, azithromycin 500mg daily x 5 days then twice weekly and rifampin 300mg daily, or matching placebos. The primary efficacy endpoint was to assess the number of responders in the combination antibiotic group vs. placebo at month 6 compared to baseline. Responders were defined as those subjects who improved 20% or more in at least 4 of 6 predefined validated variables without worsening in any one variable.

Results: 80 subjects were screened and 42 were randomized to treatment (27 to combination antibiotics and 15 to placebo). Subjects in each group had similar demographics and baseline characteristics. At month 6, 17/27 subjects (63%) randomized to combination antibiotics were responders compared to 3/15 (20%) on placebo (P-value = 0.01). Secondary efficacy endpoints showed similar results with significant improvement in the modified swollen joint count, tender joint count, physician global assessment (P-values 0.0007, 0.002, and 0.0009, respectively), and a trend with the erythrocyte sedimentation rate (P-value = 0.07) in those patients on combination antibiotics compared to placebo. 6/27 (22%) subjects on combination antibiotics experienced complete resolution of their symptoms whereas 0/15 subjects on placebo achieved this endpoint. There were significantly more subjects who became PCR negative at month 6 in the active therapy group than in the placebo group (P-Value = 0.03). Adverse events (AE's) were mild; there were no significant differences between the groups.

Conclusion: These data suggest that a 6-month course of combination antibiotics are an effective therapy for chronic *Chlamydia*-induced ReA and that chlamydial organisms in a persistent infection state are susceptible to this treatment approach.

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1153

Serial Re-Screening in High Risk Patients On Anti-TNF-α Therapy Validate CDC Recommendations for Monitoring TB Risk. D. Cooray[1], R. Moran[1], A. Broumand[1], S. Bagheri[1], J.S. Louie[2], DE Furst[2] and GA Karpouzas[1], [1]Harbor UCLA Med Ctr, Torrance, CA, [2]University of California Los Angeles, Los Angeles, CA

Purpose: *Mycobacterium tuberculosis* (MTB) and non-tuberculous mycobacteria (NTM) have been reported in patients (pts) receiving anti-Tumor Necrosis Factor-α (aTNF) agents, either as a result of reactivation of latent disease (LTB) or as new infections. Pts considered for aTNF therapy should undergo tuberculin skin testing (TST) and/or ex vivo cellular responses to mycobacterial antigens (Quantiferon) and chest x-ray (CXR). Asymptomatic pts with mycobacterial reactivity [TST or Quantiferon positive (+)] and a negative (-) CXR are typically treated with Isoniazid (INH) for 9 mos. In symptomatic pts, CDC suggests obtaining sputum cultures and chest Computed Tomography (CT). We report our extended follow-up of re-screens and subsequent conversion rates in aTNF exposed pts, and propose a comprehensive algorithm for dissemination in all new converters.

Methods: We reviewed 411 pts treated with aTNF agents between 11/1/2000 and 6/16/2009 at a county hospital. Pts were included for analysis if they had received at least one month (mo) of adalimumab (ADA), etanercept (ETN), or loading dose of infliximab (IFX) 3mg/kg at 0,2, and 6 weeks. Screening TST and CXR were obtained and (-) pts were serially re-screened while continuing aTNF therapy. Since this population is considered high risk, induration of ≥ 5mm was considered to be (+) on TST. Those who were asymptomatic with a new (+) TST were tested with cultures and polymerase chain reaction (PCR) assessment of sputum, urine, and stool for MTB or NTM, along with CXR or chest CT.

Results: Of 411 pts exposed to aTNF therapies, 382 received baseline TST and 100 tested (+). Seventeen of 100 TST (+) pts had evidence of old granulomatous disease but were asymptomatic. All 100 pts with TST (+) were given INH for 9 mos. Of the remaining 282 TST (-) pts, 174 had 1 re-screen at least 1 year later, 46 had 2 re-screens, and 10 had at least 3-4 re-screens. Eighteen of 230 (7.8%) rescreened pts developed a (+) TST (induration size 15.05±5.9 mm) while treated with aTNF agent: 3 pts were on ETN (50mg qw), 13 pts on ADA (5 on 40mg qow and 8 on 40mg qw), 2 pts on IFX . All were asymptomatic and had (-) CXR. Two of the 18 converters (11%) had (+) sputum cultures: 1 for MTB and 1 for M.chelonae respectively and were committed to 4 drug regimen for 6 months. Urine, stool cultures and PCR were (-). The remaining 16 pts with TST conversions were treated with INH for 9 mos continued their aTNF and did not develop active TB over a median of 13 months.

Conclusion: Our expanded cohort reveals a high prevalence of LTB on baseline screening as well as TST conversions with 3 aTNF agents at varying time points. Despite the fact that pts may be clinically asymptomatic, we were able to uncover active disease by obtaining cultures

on all pts that seroconvert. We validate the CDC recommendations that all pts on aTNF agents should have yearly TST. If new LTB becomes evident, prompt therapy with INH prevents active infection. Cultures and PCR of sputum, urine, and stool in addition to chest CT may be prudent adjuncts for monitoring.

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ACR Concurrent Abstract Sessions

Angiogenesis, Cell Trafficking, and Cell Retention: The Dynamics of Inflammation

Monday, October 19, 2009, 2:30 PM - 4:00 PM

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IL-17 Upregulates Expression of Proangiogenic Mediators, and Vascularity Is Elevated in the IL-17-Induced Arthritis Model. Shiva Shahrara[1], Sarah R. Pickens[1], Michael V. Volin[2], Chiang-Ching Huang[1] and Richard M. Pope[1], [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Midwestern University, Downers Grove, IL

Introduction: IL-17 is a proinflammatory cytokine that plays a crucial role in animal models of rheumatoid arthritis (RA). However the role of IL-17 in the angiogenesis of RA has not been determined.

Purpose: These studies were performed to identify the role of IL-17 in mediating proangiogenic factors in cells present in the RA synovial tissue and whether local expression of IL-17 in murine ankles affected vascularity within the joint.

Methods: Microarray studies were performed using synovial tissue (ST) fibroblasts from 6 patients with RA that were treated or untreated with IL-17 for 5h. The data were quantile normalized, and IL-17-activated genes were determined by Student's t test. Expression of the proangiogenic factors was confirmed in RA fibroblasts by real-time RT-PCR. Additionally, human microvascular endothelial cells (HMVECs) were examined for IL-17-induced proangiogenic factors. Finally, ankles harvested from adenovirally expressed IL-17 (Ad-IL-17) or the control group (Ad-CMV) were stained with von Willebrand factor.

Results: IL-17-induced proangiogenic factors identified in RA fibroblasts by microarray analysis included fibroblast growth factor (FGF2), heparin-binding EGF-like growth factor (HBEGF), CXCL1, CXCL5, CXCL8 and CCL2. Employing real-time RT-PCR, we confirmed that IL-17 induced the expression of FGF2, CXCL1, CXCL5 and CCL2 ($p<0.05$) in RA ST fibroblasts. Although not detected in the microarray results, we also demonstrated that 4 to 8h of IL-17 induced the expression of vascular endothelial growth factor (VEGF) by RA fibroblasts ($p<0.05$). We also examined HMVECs for IL-17-induced proangiogenic factors and found that IL-17 markedly increased the expression of VEGF and CXCL1 starting at 2h ($p<0.05$). Given that IL-17 induced proangiogenic factors from RA ST fibroblasts and HMVECs, we asked whether intra-articular injection of IL-17 into mice ankles had any effect on synovial tissue vascularity. The Ad-IL-17 treated group demonstrated significantly greater ankle circumference on days 4 and 10 post injection compared to the Ad-CMV control group. Von Willebrand staining of ankles harvested from day 10 post injection demonstrated that Ad-IL-17 treated mice have significantly ($p<0.05$) increased endothelial staining compared with Ad-CMV control group.

Conclusion: These results suggest that IL-17 mediates angiogenesis in RA by inducing proangiogenic factors from RA ST fibroblasts and HMVECs. Therefore, IL-17 and its downstream proangiogenic factors may be potential targets in RA.

Disclosure: S. Shahrara, None; **S. R. Pickens**, None; **M. V. Volin**, None; **C. C. Huang**, None; **R. M. Pope**, None.

1155

Soluble Junctional Adhesion Molecule-C Promotes Mononuclear Cell Recruitment in Rheumatoid Arthritis. Bradley J. Rabquer[1], Nanditha Teegala[1], Charles A. Lesch[1], M. Asif Amin[1], Jeffrey H. Ruth[1], Matthew K. Shaheen[1], Phillip L. Campbell[1], Beat A. Imhof[2] and Alisa E. Koch[3], [1]University of Michigan, Ann Arbor, MI, [2]Centre Medical Universitaire, Geneva, Switzerland, [3]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Rheumatoid arthritis (RA) is characterized by synovial hyperplasia, neovascularization, and inflammatory cell infiltration. We have shown that junctional adhesion molecule-C (JAM-C) is overexpressed on endothelial cells (ECs) and fibroblasts in the RA synovium, mediates myeloid cell adhesion to the RA synovium, and that soluble JAM-C (sJAM-C) is elevated in RA synovial fluid (SF) compared to osteoarthritis SF or normal serum. The aim of this study was to determine which cells produce sJAM-C and if sJAM-C is a mononuclear cell (MNC) chemoattractant.

Methods: We performed ELISAs to detect sJAM-C in the culture supernatant of ECs and RA synovial fibroblasts. *In vitro* monocyte (MN) chemotaxis assays were used to determine if sJAM-C is chemotatic for MNs and if sJAM-C contributes to the RA SF chemotatic potential for MNs. The ability of sJAM-C to induce leukocyte migration *in vivo* was assessed using a mouse peritoneal leukocyte recruitment model.

Results: sJAM-C was present in the culture supernatant of human microvascular endothelial cells (HMVECs, n=3 experiments, mean 16 pg/ml), immortalized human microvascular endothelial cells (HMEC-1s, n=4 experiments, 80 pg/ml), and RA synovial fibroblasts (n=7 patients, 78 pg/ml). Stimulation of HMVECs (n=3), HMEC-1s (n=4), or RA synovial fibroblasts (n=7) with tumor necrosis factor-α (TNF-α) resulted in increased sJAM-C production compared to nonstimulated cells (6.9 fold increase, 2.1 fold increase, and 1.4 fold increase, respectively, $p<0.05$). *In vitro*, sJAM-C stimulated MN migration in a dose dependent manner that was significantly greater than PBS from 1 to 250 nM (n=4 experiments, $p<0.05$). In an *in vivo* mouse peritoneal recruitment model, sJAM-C induced significantly more macrophage and lymphocyte migration than PBS (n=10 mice, $p<0.05$). When sJAM-C was depleted from RA SFs, the ability to chemoattract MNs *in vitro* decreased by a mean of 25% (n=3 patients, $p<0.05$)

Conclusion: Our results indicate that: 1) sJAM-C is secreted by ECs and RA synovial fibroblasts, and TNF-α stimulates this secretion; 2) sJAM-C promotes MN migration *in vitro* and MNC migration *in vivo;* and 3) sJAM-C is a significant contributor to the RA SF chemotatic potential for MNs. These results suggest that modulation of sJAM-C may provide a novel route for controlling synovial MNC infiltration in RA.

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Macrophage Migration Inhibitory Factor and CD74 Regulate Leukocyte Chemotactic Responses Via Facilitation of MAPK and RhoAGTPase Activation. Leilani Santos, Huapeng Fan, Pam Hall, Julia Gregory, Michael J. Hickey and Eric F. Morand, Monash University, Clayton, Australia

Purpose: Macrophage migration inhibitory factor (MIF) contributes to the pathogenesis of rheumatoid arthritis, lupus, and atherosclerosis, via mechanisms including facilitation of leukocyte recruitment. The mechanisms whereby MIF affects leukocyte recruitment are unknown. We therefore investigated the contribution of MIF, and its receptor CD74, to leukocyte responses to chemokines in vivo and in vitro.

Methods: Intravital microscopy, in vitro migration assays, immunoblotting, confocal microscopy and activated Rho GTPase protein assays were used to examine the role of MIF and CD74 in responses to CXCL1 (KC) and CCL2 (MCP-1), which are classical neutrophil and monocyte chemokines respectively.

Results: Intravital microscopy of muscle postcapillary venules demonstrated that leukocyte rolling and adhesion induced by recombinant MIF were significantly reduced in CD74-/- mice, consistent with CD74 acting as the receptor for MIF-mediated leukocyte recruitment events in vivo. Significant increases in leukocyte adhesion and emigration were observed in vivo in response to injection of CXCL1, and both parameters were significantly reduced in either MIF-/- or CD74-/- mice.

CXCR2 (CXCL1 receptor) expression was intact in MIF-/- neutrophils, but both MIF-/- and CD74-/- neutrophils exhibited reduced chemotactic responses to CXCL1 in in vitro migration assays. CXCL1 induced phosphorylation of p38 but not ERK MAP kinase in WT neutrophils, and this was significantly impaired in both MIF-/- and CD74-/- neutrophils.

Similarly, CCL2-induced leukocyte adhesion and emigration were significantly reduced in both MIF-/- and CD74-/- mice. MIF-/- and CD74-/- macrophages exhibited normal CCR2 expression but reduced CCL2-induced phosphorylation of ERK MAP kinase. MIF signalling through CD74 has been suggested to depend on F-actin stress fiber formation and RhoAGTPase. CCL2-induced F-actin stress fiber formation and RhoAGTPase activity were significantly reduced in both MIF-/- and CD74-/- macrophages.

Conclusion: These data suggest that MIF, through CD74, promotes chemokine-dependent leukocyte recruitment via facilitation of intracellular signal transduction responses. These findings suggest a new mechanism for the actions of MIF, and suggest that MIF inhibition could impact on chemokine-dependent leukocyte recruitment in inflammatory diseases.

Disclosure: L. Santos, None; **H. Fan**, None; **P. Hall**, None; **J. Gregory**, None; **M. J. Hickey**, None; **E. F. Morand**, Cortical Pty Ltd, 5 .

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IL-17A Upregulates Angiogenesis, Cytoskeletal Rearrangement and Cell Migration in a Chemokine Dependent Manner. Ellen Margaret Moran[1], Jennifer McCormick[1], Mary Connolly[1], Aisling Kennedy[1], Ursula Fearon[2] and Douglas J. Veale[1], [1]Dublin Academic Medical Centre, St.Vincent's University Hospital, Dublin, Ireland, [2]Dublin Academic Medical Centre, St.Vincent's University Hospital, Dublin 4, Ireland

Purpose: IL-17A is a pivotal cytokine implicated in the pathogenesis of RA. The aim of this study was to examine the functional effect of IL-17A on angiogenesis, cytoskeletal architecture and cell migration.

Method: IL-17A, VEGF and Ang1/2 were measured by ELISA in paired serum/synovial fluid (SF) from inflammatory arthritis patients. Synovial α-SMA expression was quantified by immunohistochemistry in the same patients. RA synovial explants, RASFCS and human dermal endothelial cells (HDECs) were stimulated with IL-17A (10-50ng/ml). Angiogenesis was assessed by HDEC Matrigel tubule formation assays. Cytokine and chemokine expression in the culture supernatants was measured using protein arrays and ELISA. RASFC and HDEC actin cytoskeleton integrity, invasion and cell migration was assessed by dual immunofluorescence staining, invasion and wound repair assays. RASFC integrin expression was examined using integrin binding assays.

Results: HDEC tubule formation was upregulated by 270% compared to basal following IL-17A stimulation ($p<0.05$). IL-17A SF levels correlated with VEGF SF ($r2=.747$) and Ang2 SF ($r2=.843$) levels (all $p<0.01$). IL-17A serum levels correlated with aSMA expression ($r2=.451$, $p<0.05$) a marker of blood vessel maturity. GROα, IL-6, IL-8 and MCP-1 production by RA explants and RASFCs was significantly increased by IL-17A stimulation ($p<0.05$). IL-17A induced HDEC and RASFC migration and invasion as visualized by wound repair and invasion assay an effect that was inhibited by the presence of neutralizing antibodies against GROα and MCP-1. IL-17A significantly increased RASFC β1 integrin expression ($p<0.05$) but downregulated αv β3 expression. Examination of the IL-17A amino acid sequence revealed two integrin binding domains. IL-17A induced disassembly of the actin cytoskeleton and loss of FA, showing dramatic filopodia formation compared to unstimulated cells. This effect was blocked by incubation with a pharmacological inhibitor of Rac1 a member of the Rho GTPases family. Rac1 inhibition also blocked IL-17A induced RASFC wound closure.

Conclusion: These data suggest IL-17A expression within the RA joint is associated with angiogenic growth factors and vascular stability. IL-17A upregulates angiogenesis and induced chemokine dependent cell migration. Finally, IL-17A induces cytoskeletal rearrangement possibly via a β1 integrin-Rac1 dependent pathway.

Disclosure: E. M. Moran, None; **J. McCormick**, None; **M. Connolly**, None; **A. Kennedy**, None; **U. Fearon**, None; **D. J. Veale**, Wyeth Pharmaceuticals, 2, GlaxoSmithKline, 2, Schering-Plough, 5, Wyeth Pharmaceuticals, 8 .

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Alterations in the Hypoxic Joint Environment and Blood Vessel Maturity Pre/Post Anti-Tnfα Therapy. Aisling Kennedy, Chin Teck Ng, Monika Biniecka, Jacintha O'Sullivan, Douglas J. Veale and Ursula Fearon, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Purpose: Angiogenesis is an early event in inflammatory arthritis. Persistent mature blood vessels within the synovial tissue following treatment of arthritis may be re-activated to induce a pro-inflammatory response. The aim of this study is to assess blood vessel maturity and stability pre/post anti-TNFα therapy and examine their relationship to *in vivo* tissue oxygen pO_2, disease activity scores and angiogenic growth factor expression.

Method: Twenty IA patients were assessed at baseline and three months post anti-TNFα therapy. Response to treatment was assessed using DAS28 and CRP scores. Using a specialist pO_2 probe (Licox), pO_2 levels in synovial tissue (ST) *in vivo* under direct visualisation at arthroscopy were assessed at baseline and 3 months post therapy. Matched serum, synovial fluid (SF) and ST were collected. Blood vessel (BV) maturity was assessed by dual immuno-fluorescent staining using Factor VIII (endothelial cell marker) and αSMA (pericyte marker). 8 dihydro 2'-deoxyguanosine (8-oxo-dG), a marker of pro-mutagenic lesions, was used to assess oxidative DNA damage *in situ* in ST by IHC. VEGF and Ang2 were measured by ELISA.

Results: Seventy-five % of patients responded to anti-TNFα therapy, which reduced DAS from 4.49 (2.76-6.52) (median (range)) to 3.17 (1.54-4.48) (median (range)) ($p<0.05$). At baseline a significant number of immature vessels (showing no pericyte recruitment, indicating a loss of endothelial/pericyte cell-cell contact) was demonstrated in patients with inflammatory arthritis ($p<0.01$), in contrast to OA and normal tissue where all vessels had acquired pericytes and were mature. A significant reduction in number of synovial blood vessels (Factor VIII) was demonstrated post therapy ($p<0.05$), in contrast to αSMA, where there was no significant change. This resulted in a significant increase in BV maturity in responders ($p<0.01$) suggesting blood vessel stability and quiescence. This was coupled with a decrease in SF VEGF and Ang2. BV nuclear 8-oxo-dG expression was decreased post-therapy with a lower levels demonstrated in responders vs non-responders ($p<0.05$). pO_2 levels in responders increased from 2.4% (median) at baseline to 3.4% (median) with the pO_2 levels in non-responders decreasing from 3.7% to 2.5%. Significant inverse correlations were observed between DAS28-CRP and pO_2 (r-0.36, p=0.009), ΔDAS28 and ΔBV-maturity (r=-0.606, p=0.008), 8-oxo-dG nuclear % and pO_2 (r=-0.391, p=.007). ΔVEGF and ΔAng2 correlated with ΔDAS28 (r=0.39, $p<0.05$ and r=0.4, $p<0.05$ respectively).

Conclusion: Blood vessel maturity, stability and DNA damage are reduced post anti-TNFα therapy and associated with disease activity and *in vivo* pO_2 levels. Blood vessel maturity may perpetuate a hypoxic environment within the synovial tissue, driving oxidative damage and maintaining angiogenic growth factor levels.

Disclosure: A. Kennedy, None; **C. T. Ng**, None; **M. Biniecka**, None; **J. O'Sullivan**, None; **D. J. Veale**, Wyeth, Schering Plough, 8, Wyeth, Schering Plough, 5, Wyeth, Schering Plough, GlaxoSmithKline, 2 ; **U. Fearon**, None.

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Chemokine Receptors CCR7 and CXCR5 and the TNF:TNF Receptor System Are Important for the Retention of CD4+ T Cells From RA Patients in the Synovial Membrane. Manuela Rossol[1], Undine Meusch[1], Anett Schulz[1], Christoph G. Baerwald[2] and Ulf Wagner[2], [1]University of Leipzig, Leipzig, Germany, [2]University Hospital, Leipzig, Germany

Purpose: Infiltration of the synovial membrane with lymphocytes is a hallmark of rheumatoid arthritis (RA). We previously described an in vitro system to study this process. CD4+ T cells from the blood of RA patients invaded tissue sections of RA synovial membrane in higher numbers than CD4+ T cells from healthy controls. Goal of the present study was to analyze underlying mechanisms.

Methods: Using a horizontally oscillating microtome, vital tissue sections of 30-40µm thickness were prepared from synovial tissue of RA patients. The tissue sections were co-cultured with fluorescence-labelled CD4+ T-cells from RA patients. After 24 hours, the tissue sections were vigorously washed and analyzed by inverse fluorescence microscopy.

Results: Both naive and memory CD4+ T cells from RA patients were equally able to infiltrate the synovial tissue sections. Blockade of the chemokine receptors CCR7 or CXCR5 significantly inhibited the retention of RA CD4+ T cells in the synovial membrane. Recovery of the tissue invading CD4+ T cells by enzymatic digestion of the tissue and subsequent FACS analysis of CD4+ T cells revealed the presence of TNF-receptor 1, while non-infiltrating CD4+ T cells from the culture supernatant did not express TNF-receptor 1. In addition, TNF producing CD4+ T cells from synovial tissue which were isolated by immunomagentic separation, did infiltrate the tissue in high numbers, whereas isolated TNF non-producing CD4+ T cells did not. Accordingly, an anti-TNF antibody blocked the tissue infiltration by CD4+ T cells.

Conclusion: Both naive and memory CD4+ T cells of RA patients have the intrinsic capability to migrate and persist in the synovial tissue. The process depends on chemokine receptors and the TNF:TNF receptor system.

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ACR Concurrent Abstract Sessions

Anti-Citrullinated Protein Antibodies in Rheumatoid Arthritis

Monday, October 19, 2009, 2:30 PM - 4:00 PM

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Moderate to Severe Adult Periodontitis Increases Risk of Rheumatoid Arthritis in Non-Smokers and Is Associated with Elevated ACPA Titers: The ARIC Study. J. A. Molitor[1], A. Alonso[1], M.H. Wener[2], B.S. Michalowicz[3], J. Beck[4], V. H. Gersuk[5], J.H. Buckner[5] and A.R. Folsom[1], [1]Univ of MN, Minneapolis, MN, [2]Univ of WA, Seattle, WA, [3]Univ of MN, Minneapolis, [4]Univ of NC, Chapel Hill, [5]Benaroya Rsch Ini., Seattle, WA

Purpose: Genetic risks for the development of anti-citrullinated peptide antibodies (ACPA) have been established, but the only environmental exposure consistently associated with ACPA+ Rheumatoid Arthritis (RA) risk is tobacco exposure (TE).

Objectives**:** 1. Establish the risk for development of incident (new) RA cases in a large cohort characterized for periodontitis severity and smoking status. 2. Assess ACPA and RF seropositivity of RA cases.

Method: We studied 6616 participants in the Atherosclerosis Risk in Communities (ARIC) study who were examined 4 times during the period 1987-1998 and for whom a detailed periodontal assessment was made in 1996-1998. Periodontitis status (no, mild, moderate or severe disease) was determined using published criteria. Subjects hospitalized with a discharge code of RA in the 9 years before their periodontal exam were designated as having “prevalent” RA; those with a first-time RA discharge code up to 8 years following their periodontal assessment were designated as having “incident” RA. Hazard ratios (HR) were determined using the Cox proportional hazards model adjusting for age, sex, and race. Available sera from 1990-92 and 1996-98 from both the incident and prevalent RA cases were examined with a second-generation ACPA ELISA and ELISA for IgG-RF, IgA-RF, and IgM-RF. HLA- DR4 alleles were determined by quantitative real-time PCR.

Results: Incidence rates of RA in the ARIC cohort were comparable to those in Olmsted County, MN. The HR of developing RA in subjects with moderate to severe periodontitis (n= 27) was 2.6 (95% CI=1.0-6.4, p=0.04), compared to those with no to mild periodontitis (n= 6). Among lifetime non-smokers, the HR was 8.8 (95% CI=1.1-68.9, p=0.04). In adjusted analyses, periodontitis severity was not associated with RA incidence among current and former smokers. ACPA levels were significantly higher in participants with moderate-severe periodontitis than in those with no-mild periodontitis (222.5 U vs. 8.4 U, p=0.04). Of 13 cases with ACPA+ at either sampled visit, 11 were both smokers and had moderate-severe periodontitis (85%, vs 47% predicted, chi-square, P=0.007), indicating a possible interaction between smoking and periodontitis in the production of ACPA. Of 12 DR4+ participants, 6/7 ACPA+ were both smokers and had moderate-severe periodontitis, whereas only 1/5 ACPA-/DR4+ individuals was both a smoker and had moderate-severe periodontitis (p=0.07, Fisher’s exact test).

Conclusion: Moderate to severe periodontitis may be a risk factor for the development of RA in non-smokers. Individuals with moderate to severe periodontitis have higher ACPA titers than those with no or mild periodontitis. There is evidence of an interaction between smoking and periodontitis increasing the likelihood of high-titer ACPA.

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The Mechanisms Underlying Arthritogenicity of Human Anti-Citrulline Antibodies. William Brintnell[1], David A. Bell[2] and Ewa Cairns[3], [1]Univ Western Ontario, London, ON, [2]SJHC, London, [3]Univ Western Ontario, London

Purpose: Determine the mechanisms responsible for the arthritogenic effects of human anti-citrulline antibody.

Background: We previously reported that intra-peritoneally (ip) administered affinity purified human RA IgG anti-citrulline antibody (ACA) to FcγRIIb deficient mice induced inflammatory arthritis. This was not seen with human RA IgG devoid of ACA (CCP_2) or serum IgG purified from normal donors.

Methods: Human RA IgG ACA (vs. CCP_2) was affinity purified with a proprietary citrullinated peptide (JED) from ten patients with RA. 45 U of anti-CCP_2 or equal concentration of purified human IgG without anti-CCP_2 activity (4-20 μg of IgG) was administered ip to pre-autoimmune FcγRIIb deficient or wild type B6129SF2/J or DR4 tg mice. The joints were examined by H&E staining. Intra-articular (ia) citrulline was detected by the AMC reagent and C3 deposition by goat $F(ab')_2$ anti-mouse C3 antibody.

Results: Inflammatory arthritis developed and peaked 12 days following ip injection of purified human RA IgG ACA but not equal concentration of RA IgG lacking ACA in the FcγRIIb deficient mice. Control wild type mice or DR4 tg mice did not develop arthritis unless they were also administered ia citrullinated human fibrinogen. The ia deposition of citrulline and C3 was seen in all arthritic mice. Naïve FcγRIIb deficient mice but not wild type mice also had significant deposition of citrulline. Purified ACA lacked C1q binding.

Conclusion: The arthritis in these mice is due to ia binding of affinity purified human RA ACA to ia citrulline leading to complement activation and arthritis. Ia citrulline in FcγRIIb deficient mice may result from the spontaneous apoptotic release of citrulline from synoviocytes while in control wild type and DR4 tg mice citrulline must be administered exogenously. These studies indicate that: 1) human IgG anti-citrulline antibody is arthritogenic and 2) the inflammatory arthritis resulting from anti-citrulline antibody is dependent on ia citrulline release. These studies have important implications for understanding the mechanisms of arthritis induction by ACA in human RA.

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Smoking and Anti-CCP Antibodies Predict Rheumatoid Arthritis. Carl Turesson[1], Ulf GB Bergström[1], Lennart Truedsson[2], Olle Melander[3], Tore Saxne[4] and Lennart TH Jacobsson[1], [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Section of MIG, Department of Laboratory Medicine, Lund, Lund University, Lund, Sweden, [3]Section of Medicine, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [4]Section of Rheumatology, Department of Clinical Sciences, Lund, Lund University, Lund, Sweden

Purpose: Previous studies indicate that smoking is a predictor of rheumatoid arthritis (RA) and that anti-CCP antibodies may be detected in individuals who develop RA years before onset. Our purpose was to investigate circulating autoantibodies and their relation to smoking before the onset of RA.

Method: The study design was a nested case-control study. Between 1991 and 1996, subjects (n=30447; 12121 men and 18326 women) from a defined catchment area were included in a community based health survey. Information on life style factors was obtained using a self-administered questionnaire, and blood samples were stored from all participants. From this population, individuals who developed RA *after* inclusion were identified by linking the health survey database to a community based RA register and to local and national patient administrative registers. One control for each case, matched for sex, year of birth and year of screening, who was alive and free of RA when the index person was diagnosed with RA, was selected from the health survey. Anti-CCP antibodies, antibodies to mutated citrullinated vimentin (anti-MCV) and IgM RF were determined by ELISA.

Results: One hundred and seventy two patients (36 men/136 women, mean age at RA diagnosis 63 years, 67 % RF positive at diagnosis or later) were diagnosed with RA after inclusion in the health survey. The median time from inclusion to RA onset was 5 years (range 1-13). Current smoking was a predictor of RA ($p<0.001$). Serum was available from 169 cases and 168 controls. Pre-RA cases were more likely to be anti-CCP positive (>20 U/mL; 21.9 % vs 0.6 %; $p<0.001$), with similar patterns for anti-MCV and IgM RF, and among men and women when studied separately. All three antibodies were detected up to 10 years before disease onset. The median anti-CCP level for positive cases

was 82 U/mL (interquartile range 36-170). Pre-RA cases screened 1-4 years before disease onset were more likely to be anti-CCP positive compared to those included 5 or more years before disease onset (28% vs 17%). There was no major difference in current smoking habits between anti-CCP positive and anti-CCP negative pre-RA individuals (38% vs 36% current smokers), but anti-CCP positive pre-RA cases were more likely to have a history of ever smoking (85% vs 61%; p=0.009). Current smoking was a predictor of RA in analysis restricted to anti-CCP negative subjects (odds ratio 1.88; 95 % CI 1.13-3.12).

Conclusion: Current smoking was not associated with anti-CCP antibodies occurring before the onset of RA, but previous smoking may have played a role in their development. Current smoking predicted RA in the absence of anti-CCP antibodies. This suggests that smoking may influence several distinct mechanisms in the pre-clinical phase of RA.

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Citrullinated Fibrinogen Stimulates TNF Release Via TLR-4 and Citrulinated Fibrinogen Immune Complexes Co-Stimulate through TLR-4 and Fc Gamma Receptor. Jeremy Sokolove[1], Xiaoyan Zhao[2] and William Robinson[3], [1]Stanford University Medical Center, Mountain View, CA, [2]Stanford University Medical Center, Palo Alto, CA, [3]Stanford School of Med, Stanford, CA

Purpose: Extravasation of fibrin(ogen) is ubiquitous in RA synovium and inflammation in general. Citrullinated proteins have been demonstrated within the inflamed synovium in RA and other forms of inflammatory arthritis and molecular characterization has consistently identified citrullinated fibrin(ogen) specifically. The presence of anti-citrullinated protein antibodies characterizes RA and has been associated with increased RA severity. The innate immune receptor TLR-4 is critical in murine models of RA and has been implicated in human RA. In addition to it's role in bacterial defense, several studies have demonstrated TLR-4 dependent signaling by damage associated non-microbial molecules including fibrin(ogen). We sought to determine whether citrullinated fibrinogen could stimulate through TLR-4 and whether citrullinated fibrinogen immune complexes could co-stimulate via TLR-4 and the Fc gamma receptor.

Methods: Murine peritoneal macrophages from wild-type or TLR-4 deficient mice or the murine macrophage cell line RAW 264.7 were used for in-vitro stimulation assays. Fibrinogen was citrullinated in-vitro at 37°C using rabbit PAD enzyme in the presence of 10mM CaCl and 5mM DTT. Native fibrinogen was treated identically except for the sham addition of PAD. Macrophages were treated with escalating doses of native fibrinogen (25-500 ug/ml), citrullinated fibrinogen (3.25-100 ug/ml), LPS, or citrullination buffer alone for 16 hours and supernatants subjected to ELISA to determine TNF secretion. Native or citrullinated fibrinogen immune complexes were formed by combination with rabbit anti-human fibrinogen polyclonal antibody and used to stimulate macrophages as above.

Results: Both native and citrullinated fibrinogen caused a dose dependent release of TNF from cultured murine macrophages and this effect was TLR-4 dependent. Citrullinated fibrinogen displayed significantly increased potency over native fibrinogen. Citrullinated fibrinogen immune complexes stimulated TNF release at levels significantly above that seen with citrullinated fibrinogen alone and this was attenuated in TLR-4 deficient macrophages. Further studies in human and animal systems including characterization of signaling pathways responsible for co-stimulation are currently under investigation.

Conclusion: This study demonstrates that citrullination of fibrinogen dramatically increases it's potency on TLR-4 mediated TNF release and that citrullinated fibrinogen immune complexes can co-stimulate through TLR-4 and Fc gamma receptor. Given that citrullinated fibrinogen, as well as several other RA associated autoantigens, are potential TLR-4 agonists, these observations suggest a novel pathogenic mechanism for RA associated autoantibodies in the initiation and propagation of synovial inflammation.

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Dosage of the HLA Shared Epitope Alleles in Relationship to Anti-Citrullinated Protein Antibodies and Radiological Damage in Rheumatoid Arthritis. H. Ulrich Scherer[1], Diane van der Woude[2], Silje W. Syversen[3], Michael van der Linden[2], Benedicte A. Lie[4], Tom W.J. Huizinga[2], Désirée M.F.M. van der Heijde[2], Annette H.M. van der Helm-van Mil[2], Tore Kvien[3] and René E.M. Toes[2], [1]Charité University Medicine, Berlin, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Oslo University Hospital, Oslo, Norway

Purpose: HLA shared epitope (SE) alleles are associated with the presence of anti-citrullinated protein antibodies (ACPA), the epitope recognition pattern of ACPA, and with radiological damage in patients with rheumatoid arthritis (RA). The aim of the present study was to elucidate the relationship between the dosage of HLA SE alleles and ACPA fine specificity, and to investigate their independent effects on disease outcome.

Method: Antibodies recognizing five distinct citrullinated antigens were determined by enzyme-linked immunosorbent assay in sera from 150 ACPA-positive RA patients who had been genotyped for HLA SE alleles. Annual radiographs were scored according to the Sharp-van der Heijde method, and the association between ACPA fine specificity and radiological damage after 5 years was investigated by Mann-Whitney U-tests and a linear mixed model. To investigate if there was an ACPA-independent effect of the HLA SE alleles on radiographic damage in RA, the relationship between the dosage of HLA SE alleles, ACPA status and radiological damage was assessed. A second cohort of 238 RA patients with 5- and 10-year radiographic follow-up was used for replication.

Results: HLA SE alleles predisposed in a gene-dose dependent manner to the recognition of certain citrullinated peptides such as vimentin 59-74 (chi-square p-value <0.001) and enolase 5-20 (p=0.006), but not to others such as fibrinogen β 36-52 (p=0.5). None of the ACPA fine specificities studied was associated with progression of radiological joint damage. In both RA cohorts, the initial relationship between HLA SE alleles and radiological damage was no longer present after stratification for ACPA-status, demonstrating that there is no ACPA-independent effect of HLA SE alleles on disease outcome.

Conclusion: Our results indicate that there is no association between the fine specificity of the ACPA response and radiological joint damage. Neither the presence of HLA SE alleles, as a surrogate marker for the constitution of the ACPA response, nor any of the citrullinated epitopes analyzed, was associated with progression of joint damage. These findings are compatible with the hypothesis that HLA SE alleles are instrumental in the priming of naive T cells which subsequently provide help to ACPA-producing B cells.

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The Periodontium Contains Citrullinated Proteins, PAD-2 Enzymes and HC Gp-39. W. Nesse, J. Westra, J. E. van der Wal, J. Balsma, F. Abbas, E. Brouwer and A. Vissink, University of Groningen and University Medical Center Groningen, Groningen, Netherlands

Purpose: Periodontitis is a chronic inflammation of the tissues anchoring the teeth within the jaws that is accompanied by loss of this anchoring tissue. Periodontitis is more common among rheumatoid arthritis (RA) patients and vice versa. The severity of RA is related to the severity of periodontitis, and treatment of periodontitis has been shown to lower the erythrocyte sedimentation rate and disease activity score of RA patients.

One hypothesis is that periodontitis might exacerbate or even induce auto-immunity. Anti-Cyclic Citrullinated Protein Antibodies (ACPAs) and human cartilage glycoprotein $39^{263\text{-}275}$/HLA-DRαβ1*0401 complexes (HC gp-39/HLAc), are highly specific for RA and are suspected of being involved in the etiology of RA. ACPAs target citrullinated proteins. Citrullination is catalyzed by Peptidyl Arginine Deiminase (PAD) enzymes. The present study was aimed at establishing the presence of citrullinated proteins, PAD-2 enzymes and HC gp-39/HLAc in periodontal tissue of periodontitis patients and in gingival crevicular fluid (GCF) samples of healthy controls.

Method: Periodontal tissue samples of 15 randomly selected periodontitis patients were stained for the presence of PAD-2 (Abcam, ab16478), citrulline (Chemicon, Ab5612) and HC gp-39/HLAc (Moab 12A, Organon). Synovial tissue samples of RA patients were used as a control for staining of PAD-2, citrulline and HC gp-39/HLAc. GCF samples were obtained from 8 healthy volunteers at sites exhibiting signs of gingival inflammation. They were tested for the presence of citrullinated proteins by Western Blotting (Anti-citrulline modification kit, Millipore). Synovial fluid of RA patients was used as positive control.

Results: Citrullined proteins and HC pg-39 were present in periodontitis tissue of respectively 6 and 7 out of 15 periodontitis patients. PAD-2 presence could not yet be ascertained in periodontitis tissue, possibly due to technical matters. Citrullinated proteins and PAD-2 were present in GCF samples of respectively 4 and 6 out of 8 healthy controls, at sites exhibiting gingival inflammation. Citrullinated proteins were present in synovial fluid of 5 out of 6 RA patients.

Conclusion: This is to our knowledge the first study showing that citrullination occurs *in vivo* in the periodontium, lending support to the hypothesis that periodontitis may exacerbate or even initiate ACPA formation. Furthermore, this study is the first to show that HC gp-

39/HLAc are present in periodontitis tissue. HC gp-39/HLAc presence was (up to now) thought to be highly specific for RA. In "healthy" controls**,** preliminary results also show presence of citrullinated proteins and PAD-2 enzymes in GCF taken from sites exhibiting gingival inflammation. Thus, the periodontium contains citrullinated proteins, PAD-2 enzymes and HC gp-39.

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ACR Concurrent Abstract Sessions

Etiology and Pathogenesis of Spondyloarthritis
Monday, October 19, 2009, 2:30 PM - 4:00 PM

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Dysregulation of Wnt/Beta-Catenin Signaling in Ank/Ank Mice Is Associated with Hypertrophic Chondrocyte Differentiation and New Osteoid Deposition in Articular Cartilage: a Novel Insight in a Mouse Model of Joint Ankylosis. F. Las Heras[1], K.P.H. Pritzker[2], H.W. Tsui[3], B. Chiu[3], F.W.L. Tsui[4] and R.D. Inman[4], [1]Mount Sinai Hospital. Institute of Medical Science. University of Toronto, Toronto, ON, [2]Mount Sinai Hospital. University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON, [4]Toronto Western Research Institute. University of Toronto, Toronto, ON

Purpose: The cellular basis of pathologic joint ankylosis remains unresolved. Wnt/β-catenin signaling activation has been associated with chondrocyte hypertrophy in animal models relating to osteoarthritis and joint ankylosis. To address the relation between the Wnt signaling pathway and the ankylosing process seen in *ank/ank* mice, we studied the pathology and β-catenin protein expression in articular chondrocytes from *ank/ank* mice.

Method: *ank/ank* mice and wild-type littermates at ages 8, 12 and 18 weeks (4 animals per time point) were used for this study. Sections from fixed, decalcified, paraffin-embedded knee joints were stained with hematoxylin and eosin. Chondrocyte size was determined using morphometric methods for articular cartilage in predetermined areas of the tibial plateau. Immunohistochemical staining with anti-collagen X, anti-tissue non-specific alkaline phosphatase (TNAP) and anti-β-catenin antibodies were performed on the fixed tissues.

Results: *ank/ank* chondrocytes in uncalcified cartilage were significantly larger than controls, in all age groups studied. *ank* mouse average chondrocyte area was 93.9 $\pm$ 36.0, 92.8 $\pm$ 30.4 and 100.0 $\pm$ 40.4 μm at 8, 12 and 18 weeks of age respectively, compared to an average chondrocyte area of 72.2 $\pm$ 29.2, 70.9 $\pm$ 25.0 and 64.8 $\pm$ 22.9 μm in wild-type mice. Two hypertrophic chondrocyte markers, collagen X and TNAP showed high expression in the articular chondrocytes of *ank/ank* mice. Immunohistochemistry for β-catenin expression revealed intense staining in *ank/ank* articular cartilage, with nuclear translocation. This strong cartilage staining was present in each age group studied. β-catenin was also expressed in *ank/ank* subchondral bone, primarily in osteoblasts and areas of new osteoid deposition. In contrast, β-catenin signal was only present in control mice at 8 weeks, with cytoplasmic but no nuclear staining.

Conclusion: The nuclear localization of b-catenin in the articular hypertrophic chondrocytes of *ank/ank* mice suggests that Wnt/b-catenin signaling plays a central role in these mice in the pathogenesis of joint ankylosis.

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Genome-Wide Screening Newly Discovers That the Tnfα- and IL17- Inducible RGS1 Is the Most Highly Differentially Expressed Gene in Undifferentiated Spondyloarthritis (USpA). David T. Y. Yu[1], Yu-ling Wei[2], James C. Wei[3], Feng Huang[4], Ming-Shiou Jan[5], Mark B. Frank[6], Micheal Centola[7] and Jieruo Gu[8], [1]UCLA Med Schl/35-36 Rehab Ctr, Los Angeles, CA, [2]UCLA, Los Angeles, CA, [3]Chung Shan Med Univ Hospital, Taichung, [4]Chinese PLA General Hospital, Beijing, China, [5]Chung Shan Medical University, Taichung, [6]Oklahoma Med Research Fdn, Oklahoma City, OK, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK, [8]3rd Affiliated Sun Yat-Sen Uni, Guangzhou

Purpose: Axial USpA is frequently considered to be an early form of ankylosing spondylitis (AS). Identifying the most highly differentially expressed PBMC gene will be useful in generating new diagnostic test and new experimental approach to pathogenesis of USpA and AS.

Method: Genome-wide microarray analyses followed by Realtime PCR validation of 25 promising candidates were carried out on PBMC from 20 healthy subjects, 21 AS and 28 axial USpA patients. 11 of the validated candidates were assessed again by PCR using a second cohort of 18 USpA, 23 AS, 12 RA, 8 mechanical low back pain patients and 26 healthy control subjects.

Results: Both microarray and PCR assays of the first cohort showed that the number of differentially expressed genes in USpA was > 6X more numerous compared to AS, which was surprisingly much less different from healthy subjects. Proinflammatory IL-1A, IL-1B, IL-6, IL-8 and several chemokines were differentially expressed only in USpA but not in AS. PCR results of the second cohort were in agreement. In both cohorts, RGS1 (regular of G-protein signaling-1) was identified as the most outstanding being 20.9 and 11.1 fold higher in USpA and AS compared to healthy subjects (p=0.000004 and 0.0002 after Bonferroni correction). RGS1 was not enhanced in RA or in those with mechanical low back pain. For distinguishing the combined USpA and AS group, the diagnostic potential was: sensitivity 84.2%, specificity 87.5%, +LR 6.7, PPV 97, NPV53.8. Evaluation of the specificity of RGS1 in the RGS family was carried out by comparing it to other members of the RGS family. PCR of the following common RGS members showed that only RGS1 carried diagnostic value: RGS -2, -3, -4, -5, -8. Next, to identify the responsible variant, we tested for RGS1 using 2 other pairs of primers spanning 2 different segments of the gene. The diagnostic potential was the same with all 3 pairs of primers. They also showed that the RGS1 isoform which was responsible was the Sp1 isoform. Although RGS1 has already been identified as candidate gene for diabetes and celiac disease, how it might cause pathology is unclear. Here, we tested 25 potentially arthritis-causing cytokines/chemokines with a cell line. TNFa and IL17 were discovered to be the strongest inducers of RGS1.

Conclusion: (1) The PBMC of USpA is different from AS in having many more highly expressed genes, including several which are proinflammatory. (2) The TNFa- and IL-17- inducible RGS1 is the most highly differentially expressed gene in USpA. (3) The role of RGS1 in SpA and other RGS1-related diseases is a new area of research.

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Spondyloarthritis in HLA-B27 Transgenic Rats Is Prevented by Epididymo-Orchiectomy Even After Onset of Epididymo-Orchitis.

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Purpose: In lines of rats transgenic (TG) for HLA-B27 and human β2m that develop spondyloarthritis (SpA), epididymo-orchitis (EO) develops in nearly all males. In the B27/hβ2m 21-3x283-2 F1 rats (*A&R* 54:1317, 2006), in which only males develop arthritis and spondylitis, EO is evident as scrotal swelling at a median age of 100 d, about 50 and 90 d before the median onset of arthritis and spondylitis, respectively. Here, we asked whether EO is a prerequisite for SpA in these rats.

Method: B27/hβ2m TG 21-3x283-2 F1 males underwent castration (bilateral resection of testis and epididymis), hemicastration (unilateral resection), or sham castration (scrotal incision only) between ages 36 d and 125 d. Castrated rats were given testosterone (T) replacement by either SQ implantation of T pellets or by twice-weekly SQ injections of T-17β-cypionate in sesame oil. Some sham castrated rats were given sesame oil alone. Rats were weighed, bled for serum, and observed for > 300 d for EO (in the sham and hemi- groups), arthritis, and spondylitis. Resected tissue was examined histologically.

Results: The earliest histologic inflammation was in the epididymis after 50 d of age, coinciding with the emergence of mature sperm. Histologic orchitis lagged epididymitis by several wks. The earliest age of arthritis onset was 112 d. As shown in the Table, no arthritis or spondylitis developed in the TG rats castrated before age 92 d (p=0.015 vs. sham castration, p=0.00004 vs. hemicastration), and these rats remained completely healthy. The arthritis that occurred in the rats castrated after 91 d of age had a later onset than in the control groups (p=0.034 compared with all controls). Only one rat of 8 castrated between 92 and 99 d developed arthritis, and this consisted only of dactylitis in a single digit that began at age 296 d. The other 2 rats that developed arthritis were castrated at 115 and 125 d.

Procedure	Age at procedure (d)	Total #	# arthritis	Age onset arthritis (median, d)	Maximum arthritis score (mean ± SD)	# spondylitis
Castration	43-91	18	0	—	—	0

Castration	92-125	11	3	296	2.3 ± 2.3	1
Sham castration	43-91	14	5	152	3.9 ± 2.5	1
Sham castration	92-115	7	5	158	5.4 ± 1.8	5
Hemicastration	36-91	21	13	148	4.8 ± 1.5	6

T pellet implantation resulted in serum T levels that tended to be below normal but were not significantly different from those found in the two control 21-3x283-2 groups. T ester SQ resulted in supraphysiologic serum T levels, but the growth curve was identical to that of the sham castrated rats.

Conclusion: Bilateral resection of testis and epididymis prevented subsequent development of SpA if carried out before the age of onset of arthritis, even if EO was already present. The data suggest that prolonged epididymitis and/or orchitis is an essential precursor of SpA in 21-3x283-2 F1 rats. Loss of physiologic androgen secretion is a formally possible, but much less likely, alternative explanation. The role of HLA-B27 in triggering EO in rats, and the role of genital tract inflammation in human SpA, are worthwhile topics for continued investigation.

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Mast Cells Contribute to Synovial Inflammation in Non-Psoriatic and Psoriatic Spondyloarthritis. Troy Noordenbos[1], Nataliya Yeremenko[1], Tineke Cantaert[1], Christine Teitsma[1], Marleen van de Sande[1], Paul P. Tak[2], Juan D. Canete[3] and Dominique Baeten[4], [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [3]Hospital Clinic de Barcelona and IDIBAPS, Barcelona, Spain, [4]Academic Medical Centrum, Amsterdam, Netherlands

Purpose: We recently observed a striking synovial infiltration with cells positive for C-kit, a marker for mast cells and hematopoietic stem cells, in psoriatic arthritis (PsA). As mast cells have potent inflammatory functions, including the production of TNF, we performed a systematic analysis of C-kit positive cells in different forms of chronic inflammatory arthritis.

Method: Synovial tissue biopsies from active rheumatoid arthritis (RA)(n=21), non-psoriatic spondyloarthritis (SpA)(n=16), and PsA (n=23) were stained by immunohistochemistry and double immunofluorescence. Synovial fluid (SF) from RA (n=18), SpA (n=19), and PsA (n=16) was analyzed by ImmunoCap and ELISA. The effect of C-kit inhibition by imatinib mesylate on proinflammatory cytokine production was tested in vitro on fresh SpA synovial biopsies.

Results: C-kit positive mononuclear cells were found in the synovial sublining in all disease groups but were significantly increased in SpA (p=0.010) and PsA (p=0.001) versus RA despite similar levels of global inflammation as reflected by CD3, CD20, and CD68 staining. Double stainings confirmed that C-kit positive cells were not hematopoietic stem cells but mast cells. SF levels of SCF, IL-3, and IL-33, all factors involved in chemotaxis and differentiation of mast cells, as well as sST2, the soluble decoy receptor for IL-33, were similar in all groups. Most C-kit positive mast cells in SpA synovium were degranulated as indicated by double staining with toluidine blue and anti-tryptase and by SF analysis for mast cell products. Interestingly, the synovial infiltration with C-kit positive cells in SpA persisted despite successful treatment with TNF blockers. However, C-kit inhibition in vitro strongly reduced the production (mRNA by qPCR) and secretion (protein by ELISA) of IL-6 and IL-8 by synovial biopsies, suggesting that mast cells contribute to the ongoing inflammatory process.

Conclusion: There is an increased synovial infiltration with and degranulation of C-kit positive mast cells in non-psoriatic and psoriatic SpA. Inhibition of C-kit in vitro leads to a reduction of proinflammatory cytokine production by synovial biopsies. These data suggest a role for mast cells in driving and/or sustaining the synovial inflammation in SpA.

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High-Density Genome-Wide Linkage Study in Spondyloarthritis (SpA) Families Identifies Three New Significant Susceptibility Chromosomal Regions. Maxime Breban[1], Félicie Costantino[2], Elena Zinovieva[2], Patrick Nitschke[3], Jean Philippe Jais[3], Emma Walton[2], Roula Said Nahal[1], Ivo Gut[4], Diana Zelenika[4], Gilles Chiocchia[2] and Henri Jean Garchon[2], [1]Ambroise Paré Hospital, Boulogne-Billancourt, France, [2]Institut Cochin, INSERM U567, Paris, France, [3]Université Paris-Descartes, Paris, France, [4]CNG, Evry, France

Purpose: The HLA-B27 allele is the major genetic susceptibility factor for SpA. However, the MHC region accounts for only half of the genetic predisposition to SpA. Previous linkage analyses have identified very few significantly linked non-MHC loci, of which a single locus called SPA2 on 9q31-q34 was replicated. More recent genome-wide association study spotted two highly relevant genes, ERAP1/ARTS1 and IL23R. Nonetheless, a significant fraction of the genetic predisposition to SpA remains to be explained. One major interest of linkage studies using large families is their potential to capture loci with low-prevalence disease alleles. Here, we report on a new genome-wide linkage scan using a large set of multiplex SpA families and a high-density panel of biallelic markers.

Method: 906 subjects from 144 families with multiple cases (range: 2-8 per family), comprising 334 affected-pairs were genotyped using Affymetrix® 250K single-nucleotide polymorphisms (SNPs) array. Genotypes were called using Chiamo. After removal of Mendelian errors, pedigrees were submitted to further cycles of error checking with MERLIN program. Multipoint non-parametric linkage analysis was then conducted with MERLIN using the Kong and Cox statistics and either a linear or an exponential model. Thresholds for significance and suggestiveness of linkage were computed as recommended by Lander and Kruglyak (Nature Genet 1995;11:241). Family-based association analyses of significantly linked regions were done using UNPHASED and FBAT.

Results: Besides the MHC that reached a maximum LOD score of 22.3 ($p < 10^{-10}$), 4 regions displayed significant evidence of linkage (LOD score ≥ 3.65; ≤ 0.05 false-positive region expected by chance): Xqter, 6p11-q11, 13q13 and 9q33 with maximum LOD scores of 5.94, 5.21, 4.38 and 4.06 respectively. Three of these regions are reported here for the first time. In addition, 12 regions were linked at a suggestive level (LOD score ≥ 2.23; ≤ 1 false-positive region expected by chance). Significantly linked regions were not affected by linkage disequilibrium modelling using the rsq option of MERLIN set at 0.1. Using this same data set, we initiated an association analysis of the 6p11-q11 region to pursue the linkage finding and detected 11 SNPs associated with P values ranging from $3x10^{-5}$ to $1x10^{-3}$. None of these SNPs was in linkage disequilibrium with the HLA-B27 allele located some 30 cM away ($D' < 0.1$ and $r^2 < 0.002$). Association analysis of other linked regions is underway. This will be followed by a replication study in independent trios and case-control sets.

Conclusion: In addition to the MHC and SPA2 locus, we identified several new chromosomal regions likely to influence SpA segregation in families. Our study emphasizes the interest of linkage studies using dense marker panels to elucidate the complex genetics of SpA.

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HLA Class I and II Associations of Ankylosing Spondylitis. Matthew A. Brown[1], Rui Jin[2], B. Paul Wordsworth[3], Millicent Stone[4], M. M. Ward[5], Michael H. Weisman[6] and John D. Reveille[7], [1]Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Woolloongabba, Queensland, 4102., Australia, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]NDORMS, Univ of Oxford, UK, Oxford, England, [4]University of Toronto, Toronto, ON, [5]NIH/NIAMS, Bethesda, MD, [6]Cedars-Sinai Med Ctr, LA, CA, [7]University of Texas Medical School at Houston, Houston, TX

Purpose: Whilst HLA-B27 is known to be the major MHC gene associated with AS, there is substantial evidence that other MHC genes, including other alleles of HLA-B and non-HLA-B loci, are also AS-associated. Association has been reported with HLA-B60 in many studies, but the subtype of B60 that is primarily involved is not known. Similarly, associations with HLA-DRB1 alleles, particularly HLA-DR1, have been reported in many series. Whether these are direct associations or reflect linkage disequilibrium with other MHC genes is unknown. We sought to investigate the MHC associations in AS in a large ethnically matched case-control cohort.

Method: 1376 Australian, British and North American AS cases of white European descent were typed for HLA-B, - C, -DRB1 and -DQB1 to 4 digit resolution. Control genotypes were available from 3610 controls from the 1958 British Birth Cohort (BC). Case-control comparisons were made by contingency table analysis for individual loci, and relative pre-dispositional effects analysis was performed to analyse the association of non-B27 HLA-B loci.

Results: In addition to association of HLA-B27 with AS, strong association was seen with non-B27 HLA-B alleles, (global association $P=10^{-15}$). This was due to associations with HLA-B38 ($P=2.7x10^{-6}$, OR=2.72), B40 ($P=1.5x10^{-5}$, OR=1.54), and B52 ($P=5.7x10^{-4}$, OR=2.53). These associations were confirmed in comparisons of both the UK and US cases independently, compared with the 1958 BC controls. The HLA-B40 association was mainly due to association of the B*4001 allele (P=0.0033, OR=1.39), with no significant association seen with the other major B40-split, B*4002 (P=0.1). Considering only B27-positive cases and controls, association was seen at HLA-DRB1 ($P=1.9x10^{-3}$) and DQB1 ($P=1.2x10^{-4}$), but not at HLA-C (P=0.3).

Conclusion: This study confirms that non-B27 HLA-B alleles including B38, B40 and B52 are significantly associated with AS. Association was also seen at HLA-DRB1 comparing B27-positive haplotypes, supporting the existence of non-HLA-B MHC associations with AS. Further SNP mapping in this dataset is being performed to refine these MHC associations.

Disclosure: M. A. Brown, None; **R. Jin**, None; **B. P. Wordsworth**, None; **M. Stone**, None; **M. M. Ward**, None; **M. H. Weisman**, None; **J. D. Reveille**, None.

ACR Concurrent Abstract Sessions

Health Services/Epidemiology: Osteoarthritis and Rheumatoid Arthritis

Monday, October 19, 2009, 2:30 PM - 4:00 PM

1172

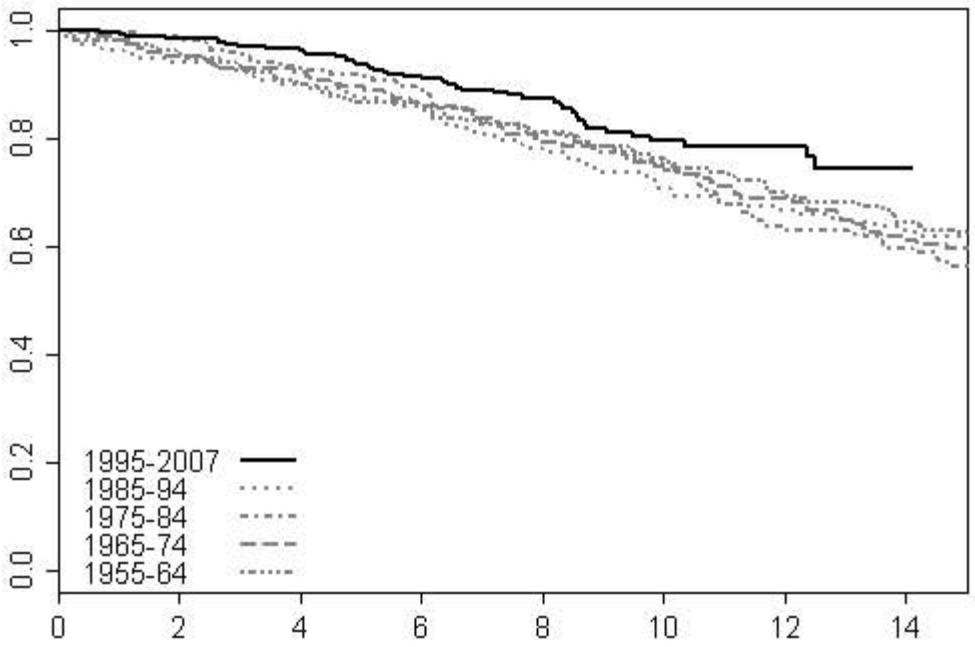
Has Survival Improved in Patients Recently Diagnosed with Rheumatoid Arthritis? Cynthia S. Crowson, Elena Myasoedova, Eric L. Matteson, Hilal Maradit Kremers, Terry M. Therneau and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: It is known that rheumatoid arthritis (RA) is associated with increased premature mortality, which does not seem to have substantially improved in recent decades. We examined whether survival has improved for patients who developed RA since 1995.

Method: A population-based inception cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1-1-1995 and 1-1-2008 was assembled and followed until death, migration, or 1-1-2009 for vital status. This cohort augmented our previous population-based cohort of RA patients who met criteria for RA between 1-1-1955 and 1-1-1995. Kaplan-Meier methods were used to estimate mortality rates. Cox proportional hazards models were used to compare survival by decade after adjusting for age and sex.

Results: The study population included a total of 1066 RA patients (mean age of 57.0 years, 71% women). Of these, 463 had incident RA in 1995-2007 (66% rheumatoid factor [RF] positive) with a mean follow-up of 6.3 years (total of 2956 person-years) during which 53 patients died. The remaining 603 patients (65% RF positive) had incident RA in 1955-1994 with a mean follow-up of 17.0 years (total of 10241 person-years) during which 419 patients died. In the 1995-2007 period, the 10 year survival was 79.5% (95% confidence interval [CI]: 74.0%, 85.4%). In comparison, the 10 year survival in the 1985-1994 decade was 70.7% (95% CI: 63.6%, 78.6%), which did not differ from the 3 decades prior to 1985 (p=0.87; see Figure). This represents a significant improvement in survival in RA patients diagnosed during the 1995-2007 period compared to the 1985-1994 decade (hazard ratio: 0.67; 95% CI: 0.45, 0.99; p=0.047) adjusting for age and sex. Further adjustment for RF positivity did not alter this difference. There was no evidence that this improvement in survival differed for RF positive compared to RF negative patients (interaction p=0.72).

Conclusion: Our findings suggest that survival in RA patients diagnosed since 1995 has significantly improved as compared to RA patients diagnosed in previous decades. Further study is needed to determine whether this improvement is related to more aggressive treatment strategies, the use of biologics, or other factors.



Disclosure: C. S. Crowson, None; **E. Myasoedova**, None; **E. L. Matteson**, None; **H. Maradit Kremers**, None; **T. M. Therneau**, None; **S. E. Gabriel**, None.

1173

The Relationship Between Use and Availability of Rheumatology Services. Crystal MacKay, Mayilee Canizares, Aileen Davis and Elizabeth M. Badley, Toronto Western Research Institute, Toronto, ON

Purpose: Access to rheumatology services is an ongoing challenge. Little is known about the patterns of use of rheumatology services and the relationship between use and availability of services. The objective was to examine health care visits to rheumatologists and availability of rheumatology services in a geographically defined region with universal health care coverage.

Method: Administrative data on physician billings from the regional health insurance plan database were used to examine ambulatory (outpatient) physician visits to rheumatologists in 2006/07. Person visit rates (number of people with visits per 100,000 population), visit rates (number of visits per 100,000 population), and age and sex distributions to rheumatologists were calculated. Availability of rheumatology services was examined using data from a survey of rheumatologists (2007). The relationship between rheumatology visits and availability of rheumatologists was examined using Poisson regression.

Results: Person visit rates to rheumatologists per 100,000 population were highest for osteoarthritis (OA) (311.9), followed by rheumatoid arthritis (RA) (305.8), and ill-defined conditions (e.g. pain in the leg) (155.4). Visit rates per 100,000 population were highest for RA (778.9) ill-defined conditions (616.2) and OA (361.3). The mean number of visits to rheumatologists for all arthritis was 2.0. Overall, person visit rates to rheumatologists increased with age for arthritis and related conditions. The female: male ratio was 2.6:1.

There were 1.2 rheumatologists per 100,000 population with geographic variation across the region. Overall, in areas with greater availability of rheumatologists, people with arthritis and related conditions were more likely to visit a rheumatologist ($p=0.01$). There was variation by specific condition. In areas with more availability, people with OA and other arthritis (e.g. soft tissue disorders) were more likely to visit a rheumatologist ($p=0.01$ and <0.0001, respectively). In contrast, visits for RA remained relatively consistent across regions, with no significant association between availability and use of rheumatologic services. This is consistent with results from the rheumatology

survey, in which rheumatologists reported shorter waiting times for likely inflammatory arthritis (mean =3.6 weeks) compared to non-urgent patients (mean=13.4 weeks).

Conclusion: Rheumatologists play a key role in the management of arthritis. While these findings suggest that availability influences utilization of rheumatologic services, it appears that rheumatologists may be prioritizing consultation with patients with inflammatory arthritis and seeing patients with non-inflammatory conditions if capacity is available. New models of care and strategies to enhance access to a full range of rheumatologic services are warranted in areas of low provision.

Disclosure: C. MacKay, None; **M. Canizares**, None; **A. Davis**, None; **E. M. Badley**, None.

1174

HMG-CoA Reductase Inhibitors (statins) Provides Primary Prevention for Rheumatoid Arthritis. Howard Amital[1], Gabriel Chodick[2], Yoav Shalem[2] and Varda Shalev[2], [1]Meir Medical Ctr, Kfar-Saba, Israel, [2]Department of Medical Informatics, Maccabi Healthcare Services,, Tel-Aviv, Israel

Purpose: The beneficial effects of statins on cardiovascular morbidity and mortality are unequivocally established. Recent findings indicate that statins also enhance anti-inflammatory effects in patients with various rheumatic conditions. Recent publications underline the presumptive role statins may have on treatment of rheumatic conditions; nevertheless data dealing with primary prevention of these disorders by statins are absent.

This study evaluated the effect of statin therapy in subjects with no indication of existing clinical or laboratory rheumatoid arthritis (RA) or osteoarthritis (OA)using the database of a one of the largest health maintenance organization (HMO) in Israel.

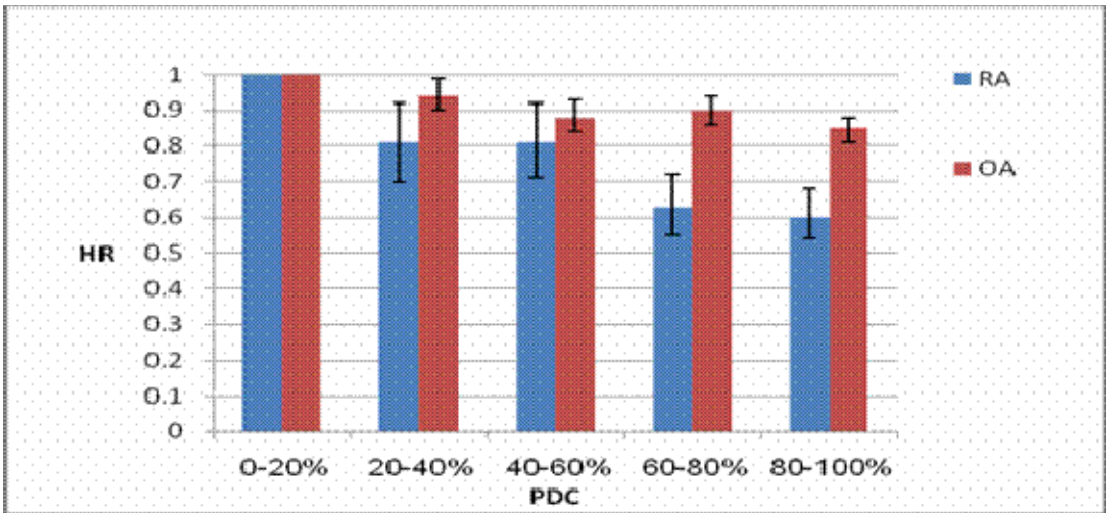
Method: This retrospective cohort study included all adults that were medically insured by the Maccabi Health services that had at least one dispensed monthly pack of statins between the 1.1.1998 through 31.12.2008. Patients who had precedent diagnosis of RA or OA prior to first purchase of statins (index date), were excluded. Patients that had a laboratory finding compatible with RA or were treated by a either a DMARD or a biological agent were excluded as well. The patients were followed throughout this period for the diagnosis of either RA or OA. These findings were validated by recording consequent relevant medications of laboratory tests.

In this study the population was sorted according to proportion of days covered (PDC) with statins subdivided by quintiles. The lowest quintile of PDC with statins served also as the control group.

Results: The study encompassed 211,627 patients (841,067 patient's years) who were treated. The percentage of females was 50.9% and of males 49.1%. During this period 2,578 new cases of RA were diagnosed (an incidence rate of 3.1 per 1,000 patient's year). During the same period among 193,699 patients (an overall 734,415 patient's years) 17,878 new cases of OA were diagnosed (an incidence rate of 24.3 per 1,000 patient's year). Analysis by quintiles revealed a clear and significant dose dependent decrease of RA incidence according to PDC quintiles (Fig. 1) whereas a significantly milder trend was demonstrated with OA. Patients in the highest PDC quintiles had a 40% decrease in the incidence rate of RA compared to 10% in patients with OA ($p<0.001$). Interestingly, the younger the age of which statin therapy was initiated, the higher the protective value it conferred (hazard ratio of 0.44, 0.56 and 0.62 in subjects who started by the age ranges of 18-55, 56-65 and 66-75 respectively, $p<0.001$).

Conclusion: In a "real life" database of a large HMO in Israel statin therapy may prevent future development of RA. A dose dependent manner was observed between the statin PDC and the prevention rate.

Figure 1 – A histogram demonstrating hazard ratios of the incidence of RA and OA in population without these diagnoses as function of statin proportion of days covered (PDC), $p<0.001$.



Disclosure: H. Amital, None; **G. Chodick**, None; **Y. Shalem**, None; **V. Shalev**, None.

1175

Rheumatoid Arthritis Susceptibility Variant at the CCL21 Locus Is Associated with Premature Mortality in Patients with Inflammatory Polyarthritis. T. Farragher[1], D. Plant[1], E. Flynn[1], S. Eyre[1], D. Bunn[2], W. Thomson[1], D. Symmons[1] and A. Barton[1], [1]arc Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Norfolk Arthritis Register, Norwich, United Kingdom

Purpose: Genome-wide association and subsequent replication studies have identified a number of confirmed rheumatoid arthritis (RA) loci in recent years. These findings have largely been established in cohorts with long-standing, severe disease and, as such, the identified variants could be markers of disease severity. RA is associated with premature mortality; indeed, this could be viewed as the ultimate marker of severe disease. Therefore, we aimed to establish whether any of the recently identified RA susceptibility loci are also associated with all-cause or cardiovascular disease (CVD) mortality in patients with inflammatory polyarthritis (IP).

Method: 17 single nucleotide polymorphism (SNPs) were selected for genotyping and tested using Sequenom® MassArray™ iPLEX chemistry in adults with recent onset IP recruited to a primary care-based inception cohort from 1989 to 2005. These SNPs were previously found in more than one well-powered study, to be markers associated with RA susceptibility and consisted of: rs1160542 (*AFF3*), rs2812378 (*CCL21*), rs763361 (*CD226*), rs4810485 (*CD40*), rs3087243 and rs231775 (*CTLA4*), rs6822844 (*IL2/IL21*), rs2104286 (*IL2RA*), rs743777 (*IL2RB*), rs6897932 (*IL7R*), rs1678542 (*KIF5A*), rs7574865 (*STAT4*), rs13207033, rs5029937 and rs6920220 (*OILG3/TNFAIP3*), rs10760130 and rs2900180 (*TRAF1/C5*). Vital status was ascertained from central records. The association of SNP marker allele carriage with mortality risk was assessed using Cox proportional hazard regression models after adjusting by gender. The mortality risks of those SNP marker alleles found to be associated were then stratified by anti-citrullinated protein/peptides antibody (ACPA) at baseline and shared epitope (SE).

Results: All 17 SNPs were successfully genotyped in 2,324 IP subjects. Carriage of 2 copies of the risk allele of rs2812378 mapping to the *CCL21* gene predicted increased all-cause mortality (hazard ratio (HR) 1.40; 95% confidence intervals (CI) 1.04, 1.87), while carriage of one or 2 copies also predicted increased CVD mortality (HR 1.33; 95% CI 1.01, 1.75). Although carriage of the *CCL21* risk allele was associated with mortality in those who were ACPA negative, the highest mortality risk was seen in subjects who had 2 copies of the *CCL21* risk alleles, 2 copies of SE and were ACPA positive (all-cause HR 3.20; 95% CI 1.52, 6.72: CVD HR 3.73; 95% CI 1.30, 10.72). The other 16 SNPs were not associated with increased mortality.

Conclusion: In this large study, we have found that carriage of the *CCL21* risk alleles was also associated with premature mortality in RA, independently of ACPA and SE status. Interestingly, CCL21 and its receptor CCR7 have previously been reported to play a role in the development of atherosclerosis. Therefore, the association between the risk allele at this gene and mortality, particularly CVD, highlights the potential inflammatory processes involved in the increased CVD risk experienced by RA patients.

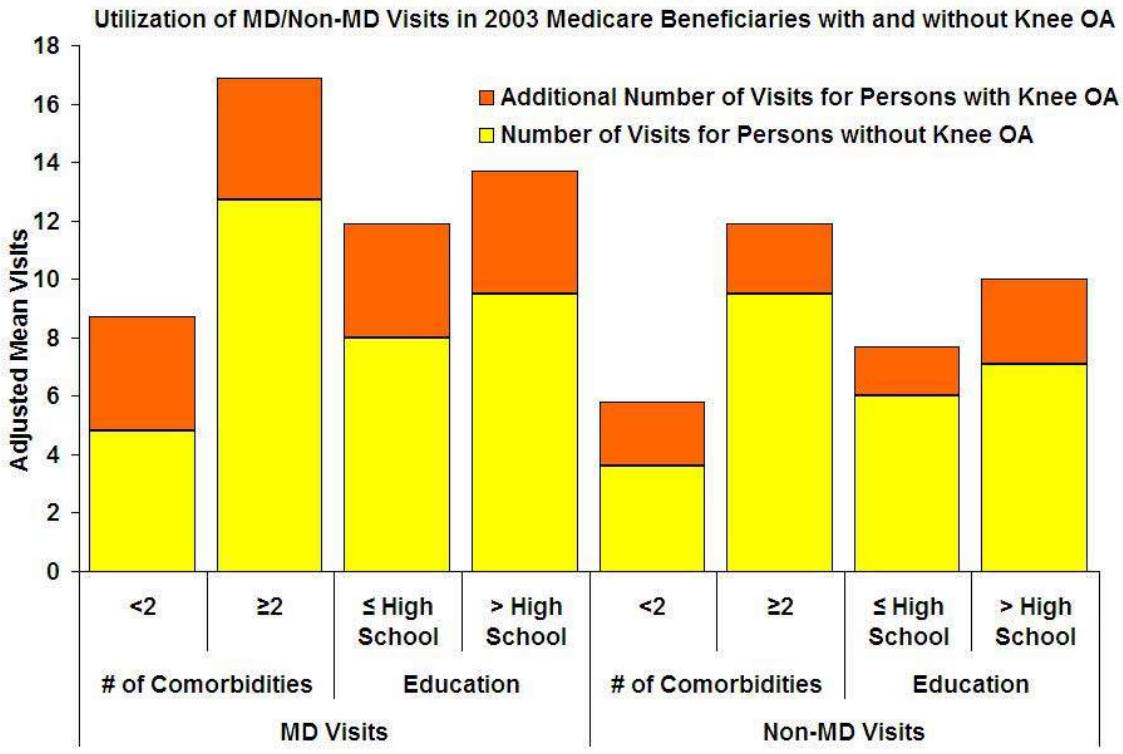
Disclosure: T. Farragher, None; **D. Plant**, None; **E. Flynn**, None; **S. Eyre**, None; **D. Bunn**, None; **W. Thomson**, None; **D. Symmons**, None; **A. Barton**, Arthritis Research Campaign, 2 .

1176

Effect of Knee Osteoarthritis On Outpatient Visits in a Population-Based National Sample. E.A. Wright[1], J.N. Katz[2], M.G. Cisternas[3], C.L. Kessler[1], A.G. Wagenseller[1] and E. Losina[4], [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]MGC Data Services, Carlsbad, CA, [4]Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA

Purpose: The impact of osteoarthritis (OA) on outpatient health care utilization in population-based samples has been rarely studied. Accurate estimates of resource usage are critical for informed health care policy development.

Method: Using the 2003 Medicare Beneficiary Study (MCBS), we selected a national cohort of persons with primarily knee OA, based on ICD-9 codes (715.x6, 715.x9, 715.x0), and a randomly selected cohort of sex and age-matched OA-free persons. MCBS is a population-based survey of a stratified random sample of Medicare beneficiaries. Subjects completed a detailed questionnaire assessing demographic, socioeconomic and other factors. These data are linked to Medicare claims, which document health services utilization and treated comorbidities. We distinguished two components of outpatient health care utilization: visits to physicians (MD visits) and non-physician providers (non-MD visits, including nurses, physical therapists and laboratory studies). We built multiple regression models accounting for sampling weights to determine whether knee OA independently affected utilization, controlling for comorbidities (<2 vs. ≥2 conditions), obesity (BMI ≥30), functional limitation (difficulty walking), education (≤ vs. > high school), race and working status (full/part-time or not working).



Results: The MCBS cohort included 12,486 Medicare beneficiaries. Of these, 1,410 (11%) met our definition of OA (OA+) and were matched to 2,820 OA free (OA-) individuals. Mean age in both cohorts was 77 years; 70% were female. OA+ and OA- differed significantly

in obesity (OA+: 29%, OA-: 19%), % with ≥ 2 comorbidities (OA+: 65%, OA-: 45%), and functional limitation (OA+: 38%, OA-: 27%). The OA+ cohort had significantly more MD visits (15.6) and non-MD visits (11.4) than the OA- cohort (9.8 and 7.5, respectively). In multivariable regression models controlling for age, sex, comorbidities, obesity, functional status, race, education and working status, knee OA independently predicted increased MD and non-MD visits. In particular, the OA+ cohort had on average 4.1 more MD visits (95% CI: 3.5, 4.8) and 2.6 more non-MD visits (95% CI: 2.1, 3.1) than the OA- cohort. The figure shows the incremental number of visits due to knee OA stratified by education and by number of comorbidities.

Conclusion: This first national, population-based study of health care utilization in OA documents considerable outpatient usage attributable to knee OA, independent of the effects of comorbidity, education and other patient characteristics. These findings should be considered in policy decisions affecting outpatient resource utilization in the elderly.

Disclosure: E. A. Wright, None; **J. N. Katz**, None; **M. G. Cisternas**, None; **C. L. Kessler**, None; **A. G. Wagenseller**, None; **E. Losina**, None.

1177

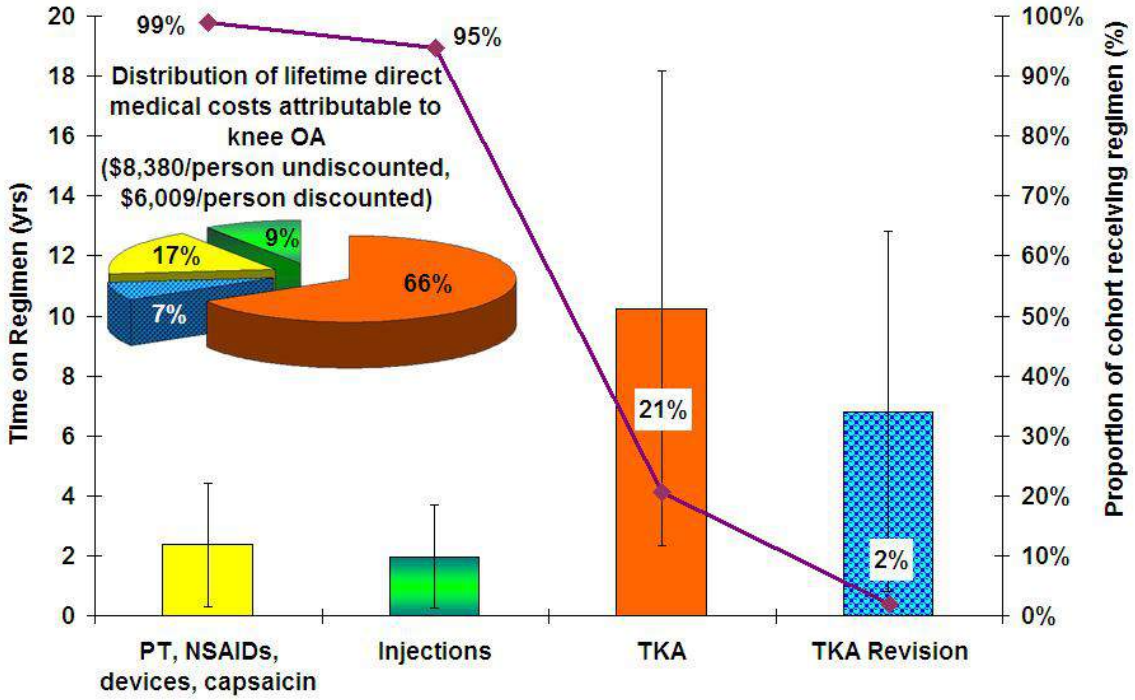
Cost-Effectiveness of ACR Guideline-Based Care and Lifetime Direct Medical Costs Attributable to Knee OA Management in the US. E. Losina[1], N.N. Niu[2], H.L. Holt[3], W.M. Reichmann[3], D.J. Hunter[4], L.G. Suter[5], D.H. Solomon[2], E.H. Yelin[6], J.M. Jordan[7], R.P. Walensky[8], A.D. Paltiel[5] and J.N. Katz[2], [1]Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]New England Baptist Hospital, Boston, MA, [5]Yale University, New Haven, CT, [6]UCSF, San Francisco, CA, [7]University of North Carolina, Chapel Hill, NC, [8]Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA

Purpose: Knee OA is debilitating and affects >4.5 million US adults. ACR treatment guidelines include pain management, physical therapy (PT), NSAIDS, intra-articular steroid injections and total knee arthroplasty (TKA) for those who reach end-stage disease. There have been no studies estimating cost-effectiveness (C-E) of ACR treatment guidelines or costs attributable to knee OA.

Method: We used a validated computer simulation model of knee OA natural history and management to follow a cohort of newly diagnosed knee OA patients (mean age 60, 54% female, 65% K-L 2, 30% K-L 3, 5% K-L 4) to death. Treatment efficacy and toxicity were derived from published literature; OA progression was derived from Johnston County Osteoarthritis Project and calibrated to published literature. Prevalence of comorbidities and quality of life estimates were derived from NHANES and mortality, from US life tables. Treatment costs were derived from Medicare reimbursement and Red Book (range: $609/yr for PT, NSAIDS, devices and capsaicin to $20,456 for TKA). The cost of background pain control was $551/yr. Costs related to other co-morbidities ranged from $557/yr for 0-1 to $3,603/yr for >3 co-morbidities. We considered four scenarios: 1) no treatment; 2) pain control only; 3) ‘ideal': 100% of patients on ACR-recommended treatment; 4) ‘real': acceptance ranging from 100% for NSAIDS, PT, capsaicin to 30% for TKA and 12% for TKA revision. The C-E of ACR recommended treatment was estimated as the ratio of incremental cost to incremental effectiveness (expressed in quality-adjusted life years, QALYs). Costs (in 2008 $US) are reported as total direct medical costs and costs attributable to knee OA. Both costs and QALYs were discounted at 3%/yr.

Results: Discounted life expectancy of persons with knee OA was 15.6 years (22.2 years, undiscounted) or 11.9 QALYs. Background (unrelated to knee OA) medical costs were $11,862. Pain control increased costs by $7,434 without altering QALYs. ‘Ideal' ACR guideline-based treatment yielded costs of $25,052 and improved QALYs by 0.47, yielding an incremental to ‘no treatment' cost-effectiveness ratio of $28,060/QALY. Figure 1 illustrates average time spent, distribution of cost attributed to and proportion of original cohort on each regimen according to ‘real' scenario.

Figure 1: Distribution of life time direct medical costs, time on regimens and proportion receiving each regimen



Conclusion: ACR guideline-based knee OA care is very cost-effective. Lifetime costs attributable to knee OA represent a relatively small part (24%) of total direct medical costs. Using a conservative estimate of 4.5M affected by knee OA in US, $27 billion will be spent on knee OA related care.

Disclosure: E. Losina, None; **N. N. Niu**, None; **H. L. Holt**, None; **W. M. Reichmann**, None; **D. J. Hunter**, None; **L. G. Suter**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 ; **E. H. Yelin**, None; **J. M. Jordan**, None; **R. P. Walensky**, None; **A. D. Paltiel**, None; **J. N. Katz**, None.

ACR Concurrent Abstract Sessions

Imaging - Clinical Applications

Monday, October 19, 2009, 2:30 PM - 4:00 PM

1178

Developing a Cartilage Scoring System for RA Using 3T MRI Scanning. Andrew Clarke[1], Alexandra McHaffie[1], Quentin Reeves[1], Nicola Dalbeth[2], Arista Chand[3], Elizabeth Robinson[3], Megan Williams[1] and Fiona M. McQueen[4], [1]Auckland District Health Board, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Auckland, New Zealand, [4]University of Auckland, Auckland

Purpose: To develop and test an MRI score for quantifying cartilage loss and/or damage at the wrist in RA using a high field 3T system

Method: MRI scans were obtained on a Philips Achieva 3T MRI scanner with a dedicated 8 element phased-array wrist coil in 22 early RA patients (duration less than 2 years), 16 established RA patients (duration 5 - 35 years) and 22 healthy controls. The following turbo spin echo sequences were used: T1 weighted and T2 weighted with fat saturation in the axial and coronal planes and proton density coronals including an ultra high resolution sequence. T1 weighted fat saturation axial and coronal sequences were obtained post intravenous

gadolinium. Eight sites were chosen within the wrist where cartilage could be profiled well including 1) distal radio-ulnar joint, 2) radiolunate joint, 3) radioscaphoid joint, 4) triquetrum-hamate joint, 5) capitate-lunate joint, 6) scaphotrapezoid joint, 7) 2nd metacarpal base-trapezoid joint and 8) 3rd metacarpal base-capitate joint (Figure 1 shows sites 2 - 6 on a coronal view of the wrist). Cartilage was scored using a system based on the Sharp van der Heijde score for XRay joint space narrowing: 0 (normal thickness), 1 (asymmetrical or minimal narrowing to maximum of 25%), 2 (definite narrowing with loss of up to 50% of the normal space), 3 (definite narrowing with loss of 50-99% of the normal space or subluxation, 4 (absence of joint space, presumptive evidence of ankylosis or complete luxation). Scores were obtained independently by 3 musculoskeletal radiologists. Sum scores were assessed for reproducibility. 15 sites at the wrist were also scored for synovitis, bone oedema and erosion using the RAMRIS system as published (1).

Results: Intraclass correlation coefficients (ICCs) for inter-observer reliability for cartilage scoring between the 3 readers was excellent: ICC= 0.91, (95% CI: 0.86, 0.94). For other RAMRIS components ICCs were as follows: bone erosion 0.79, (95% CI: 0.61, 0.88), bone oedema 0.80, (95% CI: 0.50, 0.91) and synovitis 0.63, (95% CI: 0.46, 0.77). Cartilage scores (median, range) were higher in the established RA group (12.5, 0-30) than the early RA group (2.0, 0-7) ($p = < 0.0001$) but early RA cartilage scores did not differ from healthy controls (2.0, 0-10). Cartilage scores correlated with RAMRIS synovitis ($r = 0.52$), bone oedema ($r = 0.63$) and bone erosion scores ($r = 0.66$), $p < 0.0001$ for all.

Conclusion: A scoring system has been devised to allow quantitation of cartilage thinning in the RA wrist, using high field 3TMRI. This has been shown to have excellent inter-reader reliability and should allow the measurement of cartilage loss to be added to other parameters of RA joint damage. Results suggest that cartilage loss may not be an early feature of disease.

1) Østergaard M et al. J Rheum 2003;30:1385-6

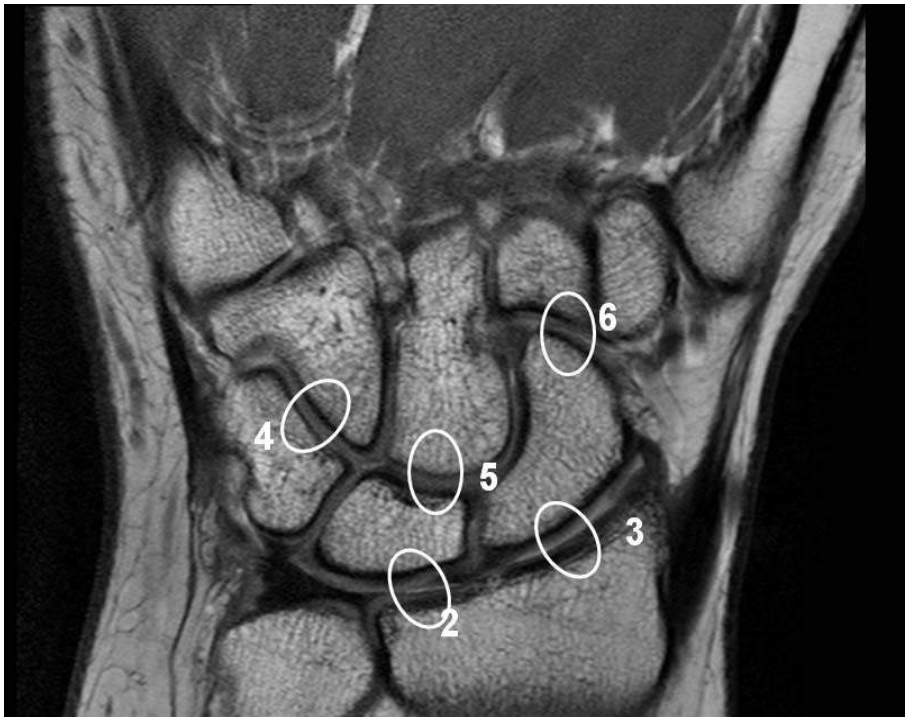


Figure 1. Coronal proton density image showing sites 2 – 6 as described in text.

Disclosure: A. Clarke, None; **A. McHaffie**, None; **Q. Reeves**, Specialist Radiology Group, 4 ; **N. Dalbeth**, None; **A. Chand**, None; **E. Robinson**, None; **M. Williams**, None; **F. M. McQueen**, None.

1179

Comparison of Diffusion-Weighted and Diffusion Tensor Magnetic Resonance Imaging of Abnormalities in the Muscles of Polymyositis Patients. Jane H. Park[1], Brittany C. Lee[1], Jing Qi[1] and Nancy J. Olsen[2], [1]Vanderbilt Medical School, Nashville, TN, [2]Univ TX Southwestern, Dallas, TX

Purpose: To characterize and compare diffusion abnormalities in areas of inflammation and fat infiltration in the thigh muscles of polymyositis (PM) patients using diffusion-weighted MRI (DWI) and diffusion tensor MRI (DTI).

Methods: Unaffected, inflamed, and fat-infiltrated muscles were identified in 2 PM patients based on T1- and T2-weighted images, STIR images, and T1 and T2 relaxation times. PM 1 showed focal inflammation in the vastus lateralis and adductor magnus. PM 2 with chronic disease had fat infiltration in the vastus lateralis, intermedius, medialis, and also the adductor. Both patients had 3 unaffected hamstring muscles (biceps femoris, semitendinosus, and semimembranosus) with normal imaging characteristics. For DWI, a diffusion-weighted echo planar imaging sequence with 23 different diffusion gradients (b-values) and 4 orientations was used. DTI images were obtained with a diffusion weighted spin-echo echo-planar pulse sequence in 6 directions at b = 600 s/mm^2. DWI data were analyzed for apparent diffusion coefficients (ADC), diffusion (D), and perfusion (D*) using exponential curve fits. For DTI, ADC and eigenvalue (λ_1, λ_2, λ_3) calculations and fiber tracking were performed using PHILIPS software (PRIDE).

Results: ADC values calculated from DWI and DTI images were similar and significantly correlated ($r = 0.925$, $P < 0.001$). Inflamed muscles in PM 1 had higher ADC values compared to unaffected hamstring muscles ($P < 0.05$) (Table 1). Fat-infiltrated muscles in PM 2 showed lower ADC values compared to unaffected muscles ($P < 0.02$). DWI data analyzed with a biexponential curve fit gave D values within the muscle compartment and capillary D* values relative to the X, Y, and Z axes of the magnet. For DTI, λ_2 and λ_3 were higher in inflamed muscles ($P < 0.05$), and λ_1 - λ_3 were lower in fat-infiltrated muscles compared to unaffected muscles ($P < 0.05$). ADC, λ_1, and λ_2 were negatively correlated with the percentage of fat in PM muscles ($P < 0.05$). Tractography showed affected muscles had more erroneous and curved fibers that were significantly shorter than those in unaffected muscles ($P < 0.05$).

Conclusion: DWI and DTI demonstrated similar ADC values with increased motion in inflamed muscles and decreased motion in fat-infiltrated muscles. DWI produced lower, more exact D values within the muscles, higher D* values in capillaries, and designated motion relative to the axes of the magnet. DTI detailed water movement parallel (λ_1) and perpendicular (λ_2, λ_3) to the long axis of the muscle fiber. DTI tractography also showed fiber tracts were shortened with inflammation and fat infiltration. DWI and DTI characterize fluid motion and fiber structure which are important for metabolite transport and fiber strength.

Table 1. DWI and DTI measurements. ADC, D, D* = (x 10^{-3} mm^2/s)

	DTI		**DWI**		
Patient	**Fiber length** (mm)	**ADC**	**ADC**	**Diffusion (D)**	**Perfusion (D*)**
Unaffected (1)	63.4	1.57	1.57	1.27	5.6
Inflamed (1)	26.9	1.75	1.69	1.46	9.9
Unaffected (2)	59.9	1.61	1.62	1.34	14.2
Fat Infiltrated (2)	14.4	1.37	1.45	0.96	7.9

Disclosure: J. H. Park, None; **B. C. Lee**, None; **J. Qi**, None; **N. J. Olsen**, None.

1180

Variable X-Ray Beam Angulation Improves Quality of Medial Tibial Plateau Alignment in Fixed-Flexion Knee Radiographs of Osteoarthritis (OA) Patients. Kalyan Alapati[1], Ilana Belitskaya-Levy[2], Mark Schweitzer[3], Nogah Shabshin[4], Jonathan Samuels[1], Steven B. Abramson[5] and Svetlana Krasnokutsky[1], [1]NYU Hospital for Joint Diseases, New York, NY, [2]NYU School of Medicine, New York, NY, [3]The University of Ottawa, Ottawa, [4]Chaim Sheba Medical Center, Tel Hashomer, Israel, [5]NYU School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Purpose: To assess whether variability in caudal X-ray beam angulation (CBA) improves alignment of the medial tibial plateau (MTP) versus a fixed 10° CBA, using non-fluoroscopic fixed-flexion knee radiographs.

Methods: 133 subjects with knee OA underwent fixed-flexion AP X-ray examinations as part of a longitudinal study. We performed a cross sectional substudy in which 90 subjects were imaged with a 10° CBA (Method 1) and 43 subjects were imaged using different CBAs (choosing from 5°, 10°, 15°) determined by a trained radiology technician, depending on MTP alignment assessed in real time (Method 2). After reading a blinded training set of radiographs, an experienced radiologist, who was blinded to patients and method used, read the x-rays for MTP alignment quality using a 1-5 scale (1,2=good, 3=acceptable, 4= poor, 5= unacceptable), and for Kellgren-Lawrence (KL) grade.

Results: Method 1 subjects (10° angulation): MTP alignment quality was scored as good or acceptable 62% and 69% of the time for the right and left knees, respectively. Method 2 subjects (variable angulation): Variable angulation resulted in good or acceptable MTP alignment quality on at least one x-ray 86% and 88% of the time for right and left knees, respectively. When CBA was changed, MTP alignment quality changed 84% of the time for the right knee and 77% of the time for the left knee in subjects who had at least 2 radiographs (n=43). The KL grade changed 28% and 46% of the time in the right and left knees, respectively, when MTP alignment quality changed in the same knee. The KL grade changed 38% and 36% of the time in the right and left knees, respectively, when there was no change in MTP alignment quality but there was a change in CBA. A change in CBA resulted in MTP alignment quality change in bilateral knees 66% of the time, of which this change was in the same direction (improved vs worsened) 86% of the time. Using a CBA of 10° resulted in improved (over other angulations) MTP alignment quality 53% and 50% of the time for the right and left knees, respectively. Using a CBA of 10° resulted in worsened MTP alignment 33% and 22% of the time for right and left knees, respectively.

Conclusion: While fixed 10° CBA in fixed-flexion radiographs results in acceptable or good MTP alignment quality the majority of the time, variable CBA improves this frequency in knee OA subjects. Changes in CBA often change the MTP alignment quality, usually in the same direction in both knees, and sometimes change the KL grade. More studies are needed to determine the optimal CBA for non-fluoroscopic fixed-flexion protocols and all radiographic knee OA studies should report the specific techniques used, including CBA.

Disclosure: K. Alapati, None; **I. Belitskaya-Levy**, None; **M. Schweitzer**, None; **N. Shabshin**, None; **J. Samuels**, None; **S. B. Abramson**, None; **S. Krasnokutsky**, None.

1181

Bone Marrow Edema Is An Independent Predictor of Progression of MRI Erosions After 3 Years in Patients with Early Rheumatoid Arthritis. Siri Lillegraven[1], Espen A. Haavardsholm[1], Pernille Bøyesen[1], Mikkel Østergaard[2], Till Uhlig[1] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Hvidovre and Gentofte, Denmark

Purpose: The presence of magnetic resonance imaging (MRI) bone marrow edema (BME) in early rheumatoid arthritis (RA) has been shown to be a predictor of erosive disease after one and two years (1;2). We examined predictors of 3-year progression in OMERACT RA MRI (RAMRIS) erosion score.

Methods: 50 RA patients were recruited from a cohort of consecutively enrolled patients with disease duration of less than one year. The patients were examined clinically and with MRI of the dominant wrist (GE Signa 1.5 Tesla MRI scanner, General Electric (GE) Signa, Milwaukee, WI, USA) at 0, 3, 6, 12 and 36 months, and serum was collected at all time points. Patients were treated according to standard clinical practice. MRI erosive progression of at least three RAMRIS units after three years was used as dependent variable in logistic regression analyses. Possible predictors of erosive disease (anti-ccp status, RF-status, ESR, CRP, DAS28, smoking, RAMRIS bone marrow edema, RAMRIS synovitis, tender and swollen joint count, DXR change from 0 to 3 months, MMP3 and YKL40 levels) were tested in univariate models, and variables with $p<0.2$ were included in further multivariate analyses, adjusting for age and gender.

Results: The median baseline age (25th percentil, 75th percentile) was 57.0 (46, 65) years, disease duration was 95 (72, 153) days, 76% were female, 50% were RF positive and 56% were anti-CCP positive. 13 patients (26%) were classified as MRI progressors. In the

univariate analyses, anti-CCP, RF, RAMRIS synovitis, RAMRIS BME and DAS28 were associated with 3-year change in RAMRIS erosions at the p<0.2 level. In the multivariate analysis, using backward elimination, BME was the only independent predictor of progressive erosive disease with an odds ratio of 1.19 (CI 1.03, 1.38, *p*=0.02) per unit BME. RAMRIS BME in patients with or without 3-year progression of erosions is shown in a cumulative probability plot (Figure).

Conclusion: Baseline amount of RAMRIS BME was the only independent predictor of MRI erosive progression after 3 years. These findings further support that presence of BME is an important predictor of long-term progression of bone erosions in RA.

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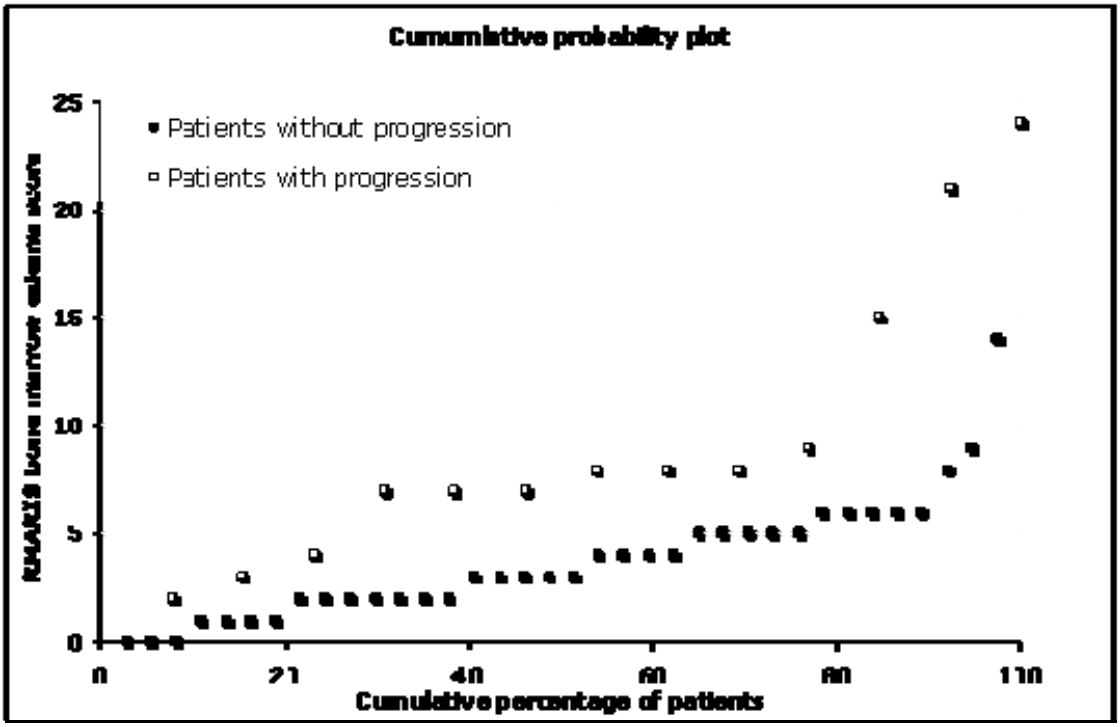


Disclosure: S. Lillegraven, None; **E. A. Haavardsholm**, None; **P. Bøyesen**, None; **M. Østergaard**, None; **T. Uhlig**, None; **T. K. Kvien**, None.

1182

Comparative Study of MRI and Power Doppler Ultrasonography (US) of the Heel in Spondyloarthritis (SpA) Patients with and without Heel Pain and in Controls: The ETERS Study. Marie-Charlotte Lavie[1], Laure Gossec[2], Frédéric Lavie[3], Henri Guerini[1], F. Rannou[4], Christelle Nguyen[4], Xavier Ayral[1], Antoine Feydy[5] and M. Dougados[6], [1]Cochin Hospital Paris France, Paris, France, [2]French Society of Rheumatology Patient Education, Paris, France, [3]Cochin Hospital, Rene Descartes University, Paris, Paris, France, [4]Paris Descartes University, Cochin Hospital, AP-HP; INSERM, Federative Institute on Handicap Research (IFR 25), Paris, France, [5]Paris Descartes University, Cochin Hospital, AP-HP, [6]Hôpital Cochin, Rene Descartes University, Paris, Paris, France

Purpose: Enthesitis of the heel is frequent in spondyloarthritis (SpA). However symptomatic heel pain occurs only in a minority of SpA patients. Magnetic resonance imaging (MRI) and Power Doppler ultrasonography (PDUS) may visualize posterior and inferior inflammatory heel lesions but their utility is debated. To assess the diagnostic capacities of MRI and of PDUS of the heel : a) to distinguish patients with SpA versus controls; and b) to distinguish SpA patients with versus without heel pain.

Method: Cross-sectional, monocenter study. In all, 72 patients (144 heels) were included: definite heels SpA patients according to Amor's criteria (n=96) were divided into 3 groups: (1) heels with no history of pain (n=57), (2) heels with history of pain (n=18), (3) heels with current pain related to enthesitis according to clinical examination and expert opinion (n=21). Patients with degenerative low back pain (48 heels) group (4)) were included as a control group. Bilateral heel MRI (coronal STIR, sagittal STIR and sagittal T1 images) and PDUS were performed by two different senior musculoskeletal radiologists blinded to other data, the same day as clinical evaluation. Imaging analysis was focused on inflammatory signs.

MRI was considered as positive if any of the following signs were observed: Intra or peri Achilles tendon or aponeurosis hypersignal, Achilles tendon thickness > 5.29 mm, retrocalcaneal bursitis, plantar fascia thickness > 4.4 mm, or calcaneus bone edema. PDUS was considered as positive if any of the following signs were observed: Achilles tendon or aponeurosis echostructure abnormality, Achilles tendon thickness > 5.29 mm, plantar fascia thickness > 4.4 mm, retrocalcaneal bursitis, or presence of abnormal Power-Doppler signal.

Results: For the whole population, mean age was 50+/- 18 yrs, and 53% were male. Among SpA patients, 82% were B27+ and 64% had sacro-iliitis (mean symptom duration, 13+/-12 yrs). Inferior bone edema was the only specific abnormality of SpA (18% of SpA heels vs 4 % of controls heels, p=0.020), but with a poor sensitivity. PDUS showed no specific abnormality of SpA, even when using the power Doppler. However, among patients with SpA, painful heels presented more inflammatory abnormalities than painless heels (81% versus 56% in MRI, p=0.045, and 58% versus 17% in PDUS, p=0.008, respectively).

Conclusion: Heel MRI and PDUS show frequent abnormalities (inflammatory lesions) in SpA and more so in painful heels. However, they are also frequently abnormal in controls. Our results suggest that heel MRI and PDUS cannot be used for the diagnosis of SpA. However, PDUS and MRI may be useful for the depiction and assessment of enthesis inflammatory lesions in SpA with heel pain.

Disclosure: M. C. Lavie, None; **L. Gossec**, None; **F. Lavie**, None; **H. Guerini**, None; **F. Rannou**, None; **C. Nguyen**, None; **X. Ayral**, None; **A. Feydy**, None; **M. Dougados**, None.

1183

Tenosynovitis On Ultrasonography Predicts Erosive Progression On MRI in Early RA Patients: AFollow-up Study. Siri Lillegraven[1], Espen A. Haavardsholm[1], Pernille Bøyesen[1], Hilde B. Hammer[1], Mikkel Østergaard[2], Till Uhlig[1] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Hvidovre and Gentofte, Denmark

Purpose: It has been shown that the presence of bone marrow edema (BME) on magnetic resonance imaging (MRI) in early rheumatoid arthritis (RA) is a predictor of erosive disease. Less is known about the predictive value of early ultrasonography (US) findings. The main objective of this report was to study US as predictor of progressive erosive disease in early RA.

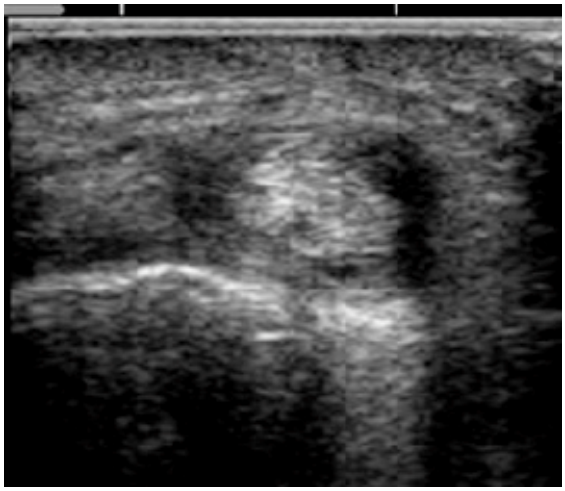
Methods: 61 RA patients from a cohort of consecutively enrolled RA patients with disease duration < 1 year were examined with US of the dominant wrist, MRI of the dominant wrist (performed on a GE Signa 1.5 Tesla MRI scanner) and clinical examination at 0, 3, 6, 12 and 36 months. All US examinations were performed by the same experienced ultrasonographer (HBH) with an 8-16 MHz linear array transducer (Diasus, Dynamic Imaging, Scotland). The degrees of B-mode synovitis and tenosynovitis were scored as 0=none, 1=minor, 2=moderate and 3= high. All patients were treated according to standard clinical practice. Erosive progression of one or more units on the OMERACT RA MRI (RAMRIS) erosion score after one year was used as dependent variable in logistic regression analyses. Possible predictors of erosive disease were tested in univariate models, and variables with a p-value < 0.2 were used in further model building. Age and sex were included in all models.

Results: The median (25th percentile, 75th percentile) baseline age was 57.0 (45, 65) years, disease duration was 107.5 (76, 190) days, 75% were female and 56 % were anti-CCP positive. In univariate analyses, extensor carpi ulnaris (ECU) tenosynovitis detected with US, total US inflammation score, CRP, RAMRIS synovitis, RAMRIS BME and swollen joint count were associated with 1-year change in RAMRIS erosions at the p<0.2 level. In the logistic regression model, using backward elimination, BME and US-tenosynovitis at the ECU tendon were independent predictors of progressive erosive disease after one year (table). The picture shows a cross-sectional view of B-mode ECU tenosynovitis.

	B	***p*-value**	**OR**	**CI for OR**
US Tenosynovitis at extensor carpi ulnaris	1.44	0.03	4.21	1.18 - 15.0

RAMRIS bone marrow edema	0.32	0.05	1.38	1.00 – 1.90

Conclusion: US tenosynovitis was an independent predictor of erosive progression measured by MRI during the subsequent year. This suggests that US may contribute to prediction of erosive progression in RA.



Disclosure: S. Lillegraven, None; **E. A. Haavardsholm**, None; **P. Bøyesen**, None; **H. B. Hammer**, None; **M. Østergaard**, None; **T. Uhlig**, None; **T. K. Kvien**, None.

ACR Concurrent Abstract Sessions

Orthopedics, Low Back Pain and Rehabilitation

Monday, October 19, 2009, 2:30 PM - 4:00 PM

1184

Natural History of Restricting Back Pain in Community-Living Older Persons. Una E. Makris[1], Liana Fraenkel[2], Leo M. Cooney[1], Linda Leo-Summers[3] and Thomas M. Gill[1], [1]Yale School of Medicine, New Haven, CT, [2]Department of Veterans Affairs, West Haven, CT, [3]Program on Aging, New Haven, CT

Background: Back pain is a common complaint among older persons, with prevalence rates as high as 47% in some groups. Prior research has shown that back pain in older persons is associated with subsequent disability in activities of daily living and mobility. It is also associated with depression, poor self-reported health, and increased utilization of health care resources. Despite the considerable morbidity and costs attributable to back pain, data describing the natural history of this disorder in older persons are sparse.

Purpose: To elucidate the natural history of restricting back pain in community-living older persons over an extended period of time.

Methods: We evaluated the 754 participants (mean age 78.4 years, 64.6% women) of the Yale Precipitating Events Project, a longitudinal study of community-living persons, aged 70+ years, who were all non-disabled in activities of daily living at enrollment. The participants completed monthly assessments of restricting back pain, defined as staying in bed for at least half a day and/or cutting down on one's usual activities due to back pain, for up to 10 years of follow-up. One or more consecutive monthly reports of restricting back pain defined an episode. Descriptive statistics, including the rate, number of episodes per participant, frequency, duration of episode, and time between restricting back pain episodes were calculated.

Results: The overall rate of restricting back pain, based on a median follow-up of 107 months, was 5.1 per 100 person-months. 550 participants (72.9%) had at least one episode of restricting back pain and 413 (54.8%) had multiple episodes. Among the 550 participants with restricting back pain, the median number of episodes was 3 (range: 1-29), and the average (SD) duration of each episode was 1.4 (0.9) months (range: 1-11). Restricting back pain lasting at least 2 months (i.e. persistent) was observed in 238 (31.6%) participants. Of the 2,508 episodes of restricting back pain, 78.5%, 14.0%, 4.4% and 3.0% had a duration of 1, 2, 3, and 4+ months, respectively. Overall, the time between episodes of restricting back pain decreased as the number of episodes increased ($P < .001$); for example, the median number of months (interquartile range) was 9 (4-24) between the 1st and 2nd episodes, 7.5 (3-20) between the 2nd and 3rd episodes, and 5.5 (3-12) between the 3rd and 4th episodes.

Conclusion: Among community-living older persons, restricting back pain is a common disorder that often recurs, although episodes are usually short-lived. Additional research is needed to further characterize the natural history, risk factors and precipitants of restricting back pain, with the ultimate goal of preventing the onset and/or recurrence of this common disorder.

Disclosure: U. E. Makris, None; **L. Fraenkel**, None; **L. M. Cooney**, None; **L. Leo-Summers**, None; **T. M. Gill**, None.

1185

Effectiveness of the Physical Therapy Agents On Lumbar Spondylosis Treatment. Mehmet Zeki Kiralp[1], Engin Cakar[2], Umit Dincer[2] and Oguz Durmus[2], [1]Associate Professor, Istanbul, Turkey, [2]MD, Istanbul, Turkey

Background: Lumbar spondylosis is a common reason of low back pain and disability in elderly people. Therapeutic approaches are range from physical therapies and noninvasive medications to some spinal interventions and surgery. Transcutaneous electrical nerve stimulation (TENS), ultrasound, hot pack and exercises are common physical therapy modalities.

Purpose: The objective of this study was to evaluate the effectiveness of physical therapy agents in lumbar spondylosis in regard to pain, disability, health quality, balance and fall risk.

Method: This was a prospective randomized controlled study. 57 patients who had lumbar spondylosis and radiological stages were 2-3 according to Kellgren Lawrence grading scale were recruited. The patients were randomized to two groups. One group was physical therapy group which the therapy contains therapeutic exercises, ultrasound, TENS, hot pack. The other group was only therapeutic exercise group. The therapy contained 15 sessions (1 session per day, 5 weekdays).

Result: At the end of the study, all of the outcomes of physical therapy group were improved significantly except the medial/lateral index of postural stability test. On the other hand, the only exercises group, only the VAS and Oswestry scores improved. Interrgroup comparisons of the final scores were also showed that physical therapy groups' all of the scores except the mental health score of the SF 12 and medial/lateral stability score (Table 1).

Conclusion:

The combination of the physical therapy agents (ultrasound, TENS, hot pack) with therapeutic exercises in the lumbar spondylosis therapy is an effective approach in regard to pain, disability, health quality, and balance and fall risk.

Table 1. The comparison of the outcomes.

		Physical therapy group (n: 30)	Only exercise group (n: 27)	
		(mean±SD)	(mean±SD)	p value*
Oswestry	Baseline	44,3±16,2	48,7±12,5	
	Final	34,5±15,4	41,8±9,6	**0.04**
	*p value***	0,001	0,002	
VAS	Baseline	60,0±12,8	64,9±17,2	
	Final	31,5±13,2	41,1±14,3	**0,01**

	*p value***	0,001	0,001	
Postural Stability Test				
Overall	Baseline	1,9±1,1	2,0±0,6	
	Final	1,2±0,6	1,6±0,6	**0.01**
	*p value***	0,001	0,02	
Anterior/Posterior stability	Baseline	1,4±0,7	1,5±0,4	
	Final	1,0±0,4	1,4±0,8	**0.04**
	*p value***	0,001	0,5	
Medial/Lateral stability	Baseline	1,1±0,6	1,1±0,5	
	Final	0,9±0,6	1,1±0,8	0.3
	*p value***	0,2	0,9	
Fall Risk Test				
Overall stability index	Baseline	1,6±0,9	1,5±0,6	
	Final	1,3±0,5	1,7±0,8	**0.03**
	*p value***	0,01	0,3	
Short Form 12				
Physical health	Baseline	11,9±2,4	12,0±2,4	
	Final	13,6±1.9	12,2±2,6	**0,03**
	*p value***	0,001	0,7	
Mental health	Baseline	15,3±4,5	15,7±2,4	
	Final	16,9±4,4	15,8±1,5	0,2
	*p value***	0,03	0,7	

* : Intergroup comparisons of the outcomes by using independent samples t-test.

** : Intragroup comparisons of the outcomes at the end of the therapy according to baseline by using paired samples t-test.

Disclosure: M. Z. Kiralp, None; **E. Cakar**, None; **U. Dincer**, None; **O. Durmus**, None.

1186

Modified Phalen's Test as An Aid in Diagnosing Carpal Tunnel Syndrome. Donald M. Loveman[1], Sayeeda Bilkis[2], Shabnam Asgher Ali[3], Abdul Kadir[4] and James A. Eldridge[5], [1]TTUHSC, Odessa, TX, [2]Reeves County Hospital, Pecos, TX, [3]Louisiana State Univ Hlth Sci Ctr, Shreveport, LA, [4]Odessa, TX, [5]University of Texas of the Permian Basin, Odessa, TX

Purpose: Carpal tunnel syndrome (CTS), the most common peripheral entrapment neuropathy, is typically evaluated in the outpatient setting by sensory and motor examination supplemented by two provocative tests, Phalen's Test and Tinnel's Test. A Modified Phalen's Test (MPT) in which sensory testing is performed in the Phalen's position has been thought to be useful, but the MPT, as previously studied, has not been widely used because of its complexity. We developed a simplified technique for performing the MPT. This study is designed to evaluate the usefulness of the MPT as a screening diagnostic tool for CTS in the outpatient setting. The electrodiagnostic study continues to be the gold standard for the diagnosis of CTS.

Method: The MPT combines the traditional Phalen's test with simultaneous objective sensory examination of the hand. The traditional Phalen's test is considered positive if paresthesiae are reproduced during the maneuver. The MPT is positive if a median nerve sensory deficit is demonstrated during the Phalen's maneuver. A positive electrodiagnostic study was used as the gold standard for diagnosing CTS. Chi-square analyses were used to test for equivalency between the MPT and the traditional Phalen's Test, the MPT and electrodiagnostic study, and the traditional Phalen's test and electrodiagnostic study. ROC curve estimations were developed to determine the specificity and the sensitivity of the MPT associated with the electrodiagnostic study results.

Results: Sixty-six hands were included in this study. The results showed a significant Chi-square analysis for the MPT compared with the gold standard with a Chi-square of 41.449 ($p<.001$) and the resultant Phi Coefficient of 0.792 ($p<.001$). When comparing the traditional Phalen's test to the gold standard, the Chi-square analysis resulted in a Chi-square of 15.349 ($p<.001$) with a Phi Coefficient of 0.482 ($p<.001$). The Chi-square results show that the MPT is equivalent to the electrodiagnostic study, and the MPT has an accuracy of 79.2% compared to the accuracy of the traditional Phalen's test of 48.2%. ROC curve estimates for the MPT reported a sensitivity level of approximately 84.4% compared to 50% for the traditional Phalen's test. The standard error of the estimate for sensitivity was lower for the MPT (3.3%) compared to the traditional Phalen's test (5.8%). Therefore the MPT is more sensitive.

Conclusion: The MPT is a highly useful screening diagnostic tool for CTS. The MPT is more accurate than the traditional Phalen's test at predicting a positive result from electrodiagnostic studies. The MPT is more sensitive than the traditional Phalen's test at predicting a positive result from electrodiagnostic studies.

Disclosure: D. M. Loveman, None; **S. Bilkis**, None; **S. A. Ali**, None; **A. Kadir**, None; **J. A. Eldridge**, None.

1187

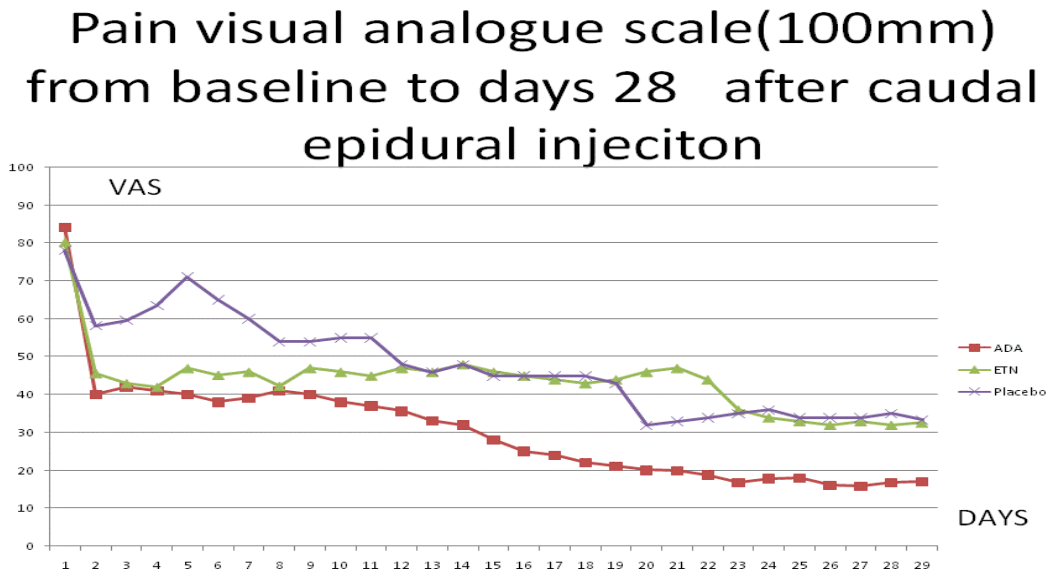
The Efficacy and Safety of Caudal Epidural Injection with the TNF Antagonist, Adalimumab and Eternacept, in Patients with Disc-Herniation-Induced Sciatica- Results of a Randomized, Controlled , 1-Month Follow-up Study. Kensuke Kume[1], Kanzo Amano[2], Amano Kuniki[3], Susumu Yamada[1] and Hideyuki Nagata[1], [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hiroshima, Japan, [3]Chief of Rheumatology, Hiroshima, Japan

Purpose: We determine the efficacy and safety of caudal epidural TNF blockade with adalimumab(ADA) and etanercept (ETN) injection, in patients with disk-herniated sciatica.

Methods: Inclusion criteria were unilateral acute severe sciatic pain with an MRI-confirmed disc herniation concordant with the symptoms and signs of radicular pain. All patients had to be candidates for discectomy, as evaluated bythree independent orthopedic surgeons. Thirty-eight patients were allocated to a single caudal epidural injection guided by fluoroscopy of either 40mg ADA or25 mg ETN or placebo.

Assessments at baseline and various time points(every day after injection) included clinical examination with straight leg raising restriction(SLR), questionnaires related to subjective symptoms(leg and back pain by 100-mm visual analog scale,VAS), number of discectomies ,and adverse events possibly related to treatment. The primary endpoint was a reduction in leg pain from baseline to 1 week, which was analyzed using a repeated-measures analysis (parametoric and non-parametric method).

Results: At 1 day after injection, a significant reduction in pain was observed in three groups. And pain on the VAS for ADA and ETN was a significant decrease than placebo. Pain on the VAS for ADA,ETN and placebo at baseline were mean 82.5(SD 16.5),80.3(SD 19.6)and 78.0(SD18.5)mm respectively, VAS at 1day after injection were mean 40.0(SD11.2),45.6(25.1),and 59.8(SD14.5)mm($p<0.001$),



At 1 month, a significant reduction in pain was observed inthree groups . ADA was significant reduction than both ETN and placebo(Fig 1), and similar efficacy was observed between ETN and placebo at 1 month after injection. Pain on the VAS for ADA,ETN and placebo after injection were mean 18.5(SD 11.5),32.3(SD 19.6)and 32.6(SD22.5)mm respectively. Three patients in ADA, five patients in ETN and 4 patients in placebo required surgery respectively. No adverse effects related to treatment (shock, allergy, infusion reaction, infection and etc.) were encountered within 1 month in all groups.

Conclusion: The results of this randomized study support that caudal epidural injection of ADA or ETN for lumbar radicular pain in patients with disc herniation-induced sciatica is efficacy and safety, is potential to be quick recovery from the pain. Caudal epidural injection of ADA is potential to be a good intervention for lumbar radicular pain in patients with disc herniation-induced sciatica.

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Disclosure: K. Kume, None; **K. Amano**, None; **A. Kuniki**, None; **S. Yamada**, None; **H. Nagata**, None.

1188

Predictors of Successful Long-Term Therapy Outcome in Patients with Chronic Non-Specific Low Back Pain Attending a Multidisciplinary Rehabilitation Programme. Pedro Machado[1] and Jan Gawronski[2], [1]Coimbra University Hospital, Coimbra, Portugal, [2]Royal National Orthopaedic Hospital, Stanmore, United Kingdom

Purpose: Chronic non-specific low back pain (CNSLBP) is common and imposes a huge burden on healthcare systems. Our aim was to identify predictive factors of improved long-term outcome for patients with CNSLBP attending the “Active Back Programme” (ABP).

Methods: The ABP is a 3-week intensive multidisciplinary rehabilitation programme designed to help people with CNSLBP. In this longitudinal study, 521 patients attending the ABP were included; 1-year follow-up data was available for 329 patients (63%). Significant improvements were observed in all the investigated domains (Wilcoxon test and McNemar test, as appropriate). Clinically meaningful improvements (CMI) and active working status were used to dichotomize patients 1 year after the ABP (dependent variable). CMI was defined as a change of at least 30% in the pain score by visual analogue scale (VAS) or in the Oswestry low back pain disability score (ODI) (1), and as a change of at least 3 points in the SF-36 physical component (QLPCS) or the mental component summary score (QLMCS) (2,3). Baseline independent predictors of 1-year CMI were investigated using forward multivariate logistic regression. All baseline variables were categorized and entered in the model as independent variables: gender, age, number of previous courses, time with low back pain, litigation, job status, pain VAS, ODI, QLPCS and QLMCS.

Results: Baseline predictors for CMI after 1 year are presented in table 1.

Table 1: Baseline independent predictors of CMI after 1 year

1 year outcome	Baseline predictors	OR (95% CI)	p-value
CMI in PAIN VAS	Better mental health status	2.1 (1.20-3.63)	0.009
	Better function (lower disability)	2.0 (1.15-3.49)	0.014
	Female gender	1.9 (1.09-3.41)	0.024
CMI in ODI	Lower pain	2.2 (1.20-3.98)	0.010
	Female gender	2.0 (1.05-3.62)	0.034
	Better physical health status	1.8 (1.00-3.22)	0.049
CMI in QLPCS	Better mental health status	2.1 (1.25-3.52)	0.005
	Lower pain	1.9 (1.16-3.28)	0.012
	Female gender	1.9 (1.09-3.16)	0.022
CMI in QLMCS	Better physical health status	2.6 (1.55-4.47)	<0.001
	Female Gender	2.3 (1.31-3.93)	0.004
Job yes, and working	Job yes, and working	49.5 (12.7-193.4)	<0.001
	Job yes, but on sick leave	15.6 (3.7-66.8)	<0.001
	Shorter duration of back pain (3M – 2Y)	5.4 (1.34-21.64)	0.018
	Better physical health status	2.3 (1.21-4.50)	0.011

Pain VAS, ODI, QLPCS and QLMCS were dichotomized at the median before entering the logistic regression model.

Conclusion: A better outcome 1 year after the ABP was independently determined by a better baseline physical and mental health status, lower pain and disability scores, active working status, shorter duration of back pain and female sex. Our study suggests that patients should be referred early to the ABP, before disease status becomes severe and while patients are still active workers.

References: 1) Ostelo et al. Spine 2008;33:90-4. 2) Kosinski et al. Am J Manag Care 2002;8:231–40. 3) Kosinski et al. Arthritis Rheum 2000;7:1478–87

Disclosure: P. Machado, None; **J. Gawronski**, None.

1189

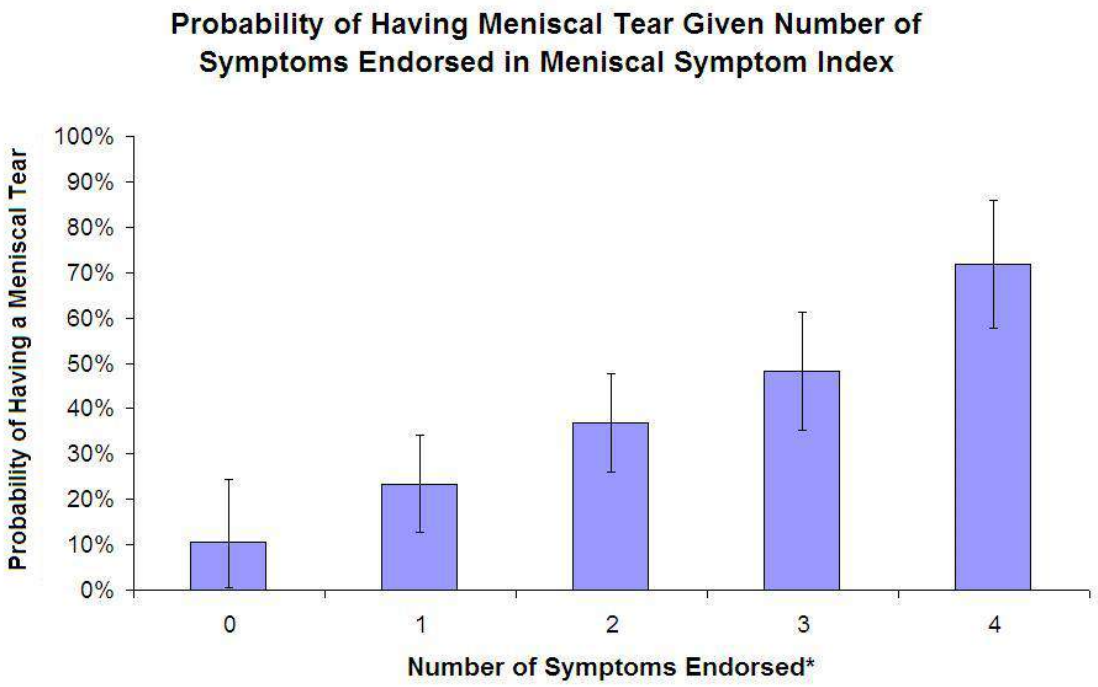
Development and Validation of a Meniscal Symptom Index for the Diagnosis of Meniscal Tear. N.N. Niu, E. Losina, J. Wright, S.D. Martin, D.H. Solomon and J.N. Katz, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Purpose: Eliciting clinical history is a crucial step in diagnosing meniscal tear (MT). There has been little research on the reliability or the diagnostic value of symptoms clinicians believe are commonly associated with MT. The aims of this study were 1) to test the reliability and discriminant validity of a newly-developed set of expanded descriptions for meniscal symptoms and 2) to develop a Meniscal Symptom Index and test its ability to discriminate patients with meniscal tear from patients with other knee disorders.

Methods: Based on input from clinicians and patients, we developed questions to elicit the presence of 11 symptoms commonly associated with MT (i.e. clicking, locking, catching, etc). These questions were administered in a survey to patients ≥ 18 years seeing orthopedic surgeons forknee pain at a single academic institution. The case definition of MT was determined by medical record documentation of the physician's diagnostic impression, made on the basis of findings from the physical exam, patient history and MRI. Diagnoses of other knee disorders such as osteoarthritis or patellofemoral syndrome were also based on medical record review. The test-retest reliability of the symptoms was assessed by mailing out the same survey to 30 patients 1 week after their visit. Item level discriminant validity for the expanded descriptions was assessed based on the association between presence of each symptom and diagnosis of MT. The Meniscal Symptom Index was calculated as a sum of items associated with MT with likelihood ratios (sensitivity / (1-specificity)) > 1.25, and which were independent predictors of diagnosis of MT in a multivariate logistic regression model that adjusted for other symptoms as well as age and sex.

Results: 250 individuals (mean age 51 ± 13 years, 66% female) completed the survey. Based on medical record review, 100 had MT and 150 did not (119 had either osteoarthritis or patellofemoral syndrome and 31 had ligamentous injuries). Test-retest reliability showed item-level Kappas in the range of 0.52 to 1 for the expanded descriptions. Those symptoms with likelihood ratios > 1.25 and which were independent predictors of MT in logistic regression included: localized pain, clicking, catching, and giving way. The Meniscal Symptom Index consisted of the sum of these 4 items with possible range from 0 (none of these symptoms present) to 4 (all 4 present). Among subjects with none of these symptoms, 11% (95% CI 0 – 24%) had MT, whereas among those with all 4 symptoms, 72% (95% CI 58 – 86%) had MT (Figure).

Conclusion: Preliminary assessment shows a newly-developed Meniscal Symptom Index of 4 symptoms to be reliable and valid in the diagnosis MT.



Disclosure: N. N. Niu, None; **E. Losina**, None; **J. Wright**, None; **S. D. Martin**, None; **D. H. Solomon**, None; **J. N. Katz**, None.

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Clinical Aspects: Early Arthritis

Monday, October 19, 2009, 2:30 PM - 4:00 PM

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Does Statin Use Protect against RA or Modify RA Disease Activity at Diagnosis? ME Holmqvist[1], IS Gallais[1], S. Wedrén[1], Lars Klareskog[2], L. Alfredsson[1] and Johan Askling[2], [1]Institute of Environmental Medicine, Stockholm, Sweden, [2]Karolinska University Hospital, Sweden

Background: Among patients with prevalent rheumatoid arthritis (RA), statins have been shown to reduce disease activity. Statin use has also been suggested to protect against RA development. Whether statins actually affect the risk of developing RA, or modulate disease activity at RA diagnosis, needs be confirmed.

Purpose: To assess the effect of statin use on the risk of developing RA and on disease activity measured via disease activity score 28 (DAS28) at RA diagnosis.

Method: To assess the risk of RA, we used 1,973 cases of incident RA and 2,230 randomly selected age-, sex-, and residential area matched population-based controls, all included in the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study between 1996 and 2007. All cases fulfilled the ACR criteria for RA. Information on use of medications during the last five years prior to RA was collected through questionnaires. Cases were further classified with regard to the presence or absence of antibodies citrullinated protein antigens (ACPA). To assess disease activity at RA diagnosis, we used 1468 of the EIRA cases who were also included in the Swedish Rheumatology Register, a clinical register used by the treating rheumatologist initially used to follow patients over time, where information on DAS28 at diagnosis was available and classified their RA activity as EULAR low (DAS28<5,1) or high (DAS28>5,1).

Analysis: To assess the risk of RA, we calculated odds ratios (OR) using logistic regression taking the matched study design into account, and adjusted for BMI and smoking. To assess the association between statin use and low DAS28 at baseline, we used unconditional logistic regression and adjusted for sex, age, residential area, smoking history and ischemic heart disease (IHD) history (table).

Results: Use of statins was neither associated with risk of RA (adj OR=1.0, 95% CI0.7-1.5), nor with decreased disease activity at RA diagnosis (adj OR= 1.0, 95% CI 0.5-2.0), Table.

	Total n RA ca/co	**N statin users among ca/co**	**Crude OR* (95% CI)**	**Adjusted OR[#] (95% CI)**
RA overall	1973/2230	59/62	1.1 (0.7-1.5)	1.0 (0.7-1.5)
ACPA positive RA	1144/2230	24/62	0.8 (0.5-1.2)	0.8 (0.5-1.2)
ACPA negative RA	697/2230	26/62	1.3 (0.8-2.0)	1.2 (0.8-2.0)
	Total n Low/high DAS28	**N statin users among low/high DAS28**	**Crude OR* (95% CI)**	**Adjusted OR[¤] (95% CI)**
RA overall	601/867	18/34	0.9(0.5-1.7)	1.0(0.5-1.8)
ACPA positive RA	370/502	7/13	0.8(0.3-2.0)	0.7(0.2-2.1)
ACPA negative RA	188/298	8/17	1.0(0.4-2.4)	1.1(0.4-2.9)

*adjusted for age, sex, residential area [#]crude+ BMI and smoking [¤]crude+ smoking, IHD

Conclusion: In our study of 1,973 cases of incident RA and 2,230 randomly selected controls, use of statins during the five years prior to RA diagnosis was neither associated with an altered risk of developing RA, nor with a decreased DAS28 at RA diagnosis.

Disclosure: M. Holmqvist, None; **I. Gallais**, None; **S. Wedrén**, None; **L. Klareskog**, None; **L. Alfredsson**, None; **J. Askling**, None.

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Prognostic Value of Patient History, Radiography and Serology On Poor Outcomes in Undifferentiated Inflammatory Arthritis Patients. Maria A. Petre[1], Carly K. Cheng[1], Gilles Boire[2], J. Pope[3], Boulos Haraoui[4], Carol A. Hitchon[5], Shahin Jamal[6], J. Carter Thorne[7], NEAR Researchers and Vivian P. Bykerk[1], [1]Mt Sinai Hospital, Toronto, ON, [2]Centre hospitalier universitaire de Sherbrooke, Sherbrooke, [3]St Joseph Health Care, London, ON, [4]Institut de Rhumatolgie de Montreal, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]St. Michael's Hospital, Toronto, [7]Southlake Regional Health Centre, Newmarket, ON

Purpose: To determine the clinical outcome of undifferentiated inflammatory arthritis (UIA) patients enrolled in 2 Canadian early arthritis cohorts and the prognostic value of patient history, physical exam, serology, and radiography for poor patient outcomes.

Methods: Data from patients (n=643) enrolled since Sept. 2003 were collected from the Toronto/Canadian Early Arthritis Cohorts (TEACH/CATCH). CATCH is a multi-centre observational prospective "real world" cohort of patients with early inflammatory arthritis (EIA). Inclusion criteria: age >16, symptom duration of 6-52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP/ PIP + ≥1 of: + RF, + anti-CCP, AM stiffness >45 minutes, response to NSAIDs, or painful MTP squeeze test. UIA was defined as not meeting 1987 ACR classification criteria for rheumatoid arthritis (RA) or criteria for other rheumatological diagnoses. The proportion of patients developing a classifiable diagnosis over time (survival analysis) and hazard ratios (HR) for the prognostic value of baseline age, gender, smoking status, initial use of DMARDs, RF status, 2nd-5th MTP involvement (including erosions), in the progression of UIA to RA were calculated. The feet were evaluated in this study due to their under-representation in the current ACR criteria for RA diagnosis.

Results: Baseline (BL) characteristics of UIA patients were: mean age 51±15 years, 75% female, median symptom duration 6.1 months, and mean DAS28 3.5±1.9. Of all the patients completing the study to 1 year (n=229), 23.1% were UIA at baseline (n=53). Of those who were UIA at baseline, 64.1% remained UIA at 12 months, while 35.8% developed RA. HRs are given in Table 1.

Conclusion: Early presence of MTP tenderness and erosions predicted which patients will develop RA, not accounting for anti-CCP status. Smoking was not predictive. Further analyses on the role of anti-CCP are planned.

Predictors for progression of UIA to rheumatoid arthritis (RA)

	Hazard Ratio (to RA by ACR Criteria)	Confidence Interval
Age (>65)	0.995	0.961-1.029
Female Gender	1.011	0.339-3.013
Smoking	1.526	0.403-5.777
DMARD	0.919	0.343-2.461
RF	0.147	0.019-1.157
2-5 MTP tenderness	1.111	1.001-1.233
2-5 MTP swelling	0.904	0.801-1.019
Foot erosions	4.428	1.231-15.930

Disclosure: M. A. Petre, Canadian Arthritis Network, 2 ; **C. K. Cheng**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **G. Boire**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **J. Pope**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **B. Haraoui**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **C. A. Hitchon**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **S. Jamal**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **J. C. Thorne**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **V. P. Bykerk**, Amgen, 2, Wyeth Pharmaceuticals, 2 .

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Predictors of HAQ Response After 3 Months of Treatment with Different Strategies in Recent Onset Active RA. L. Dirven[1], J.A.P.M. Ewals[2], T.W.J. Huizinga[1], P.J.S.M. Kerstens[3], A.J. Peeters[4], B.A.C. Dijkmans[5] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]Haga hospital, The Hague, Netherlands, [3]JBI, Amsterdam, Netherlands, [4]GDGG, Delft, Netherlands, [5]VUMC, Amsterdam, Netherlands

Background: Early clinical response is a strong predictor of later outcomes in rheumatoid arthritis (RA).

Purpose: To identify predictors of a HAQ score >= 1 after 3 months of treatment in patients with recent-onset RA. The results might help rheumatologists in weighing their first choice treatment.

Method: Data of 497 recent-onset RA patients from the BeSt study, randomized to initial monotherapy or initial combination therapy with prednisone or infliximab, were used. Treatment adjustments were made every 3 months aiming at a disease activity score (DAS) =< 2.4. Predictors for HAQ >= 1 after 3 months of treatment were identified with univariate and multivariate logistic regression analysis. The predicted risk of HAQ >= 1 after 3 months of treatment as well as the number needed to treat to prevent this, were determined per treatment group and for each subpopulation.

Results: At baseline, 76% of the patients had HAQ >= 1 (1.7 ± 0.5) and after 3 months this was 40% (1.5 ± 0.5). Baseline HAQ, visual analogue scale (VAS) pain, body mass index (BMI) and treatment group were significant independent predictors of HAQ >= 1 after 3 months of treatment; presence of rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies and baseline radiological damage were not. Compared to initial monotherapy, both combination therapy groups showed a reduced risk for HAQ >= 1, also in patients with an unfavorable risk profile. With cut-offs of <35% (low risk) and >60% (high risk), 47% of patients treated with initial methrotrexate monotherapy had a high risk for HAQ >= 1 after 3 months, 20% had a low risk and 33% had an intermediate risk. With initial combination therapy the risks were markedly reduced. The number needed to treat with initial monotherapy to prevent one patient from having a HAQ >= 1 after 3 months, ranged from 3-6 and 3-5 for patients with a high or intermediate risk to 6-9 for patients with a low predicted risk.

Conclusion: A high baseline HAQ, high VAS pain and high BMI are independent predictors of worse functional ability after 3 months of treatment, which is in itself a predictor of later outcome. The initial treatment choice determines early functional improvement. Since the number needed to treat is low in all risk profiles, it seems plausible that all patients start with combination therapy as their initial treatment.

Baseline predictor of HAQ		OR (95% CI)
HAQ	< 1.38	*ref*
(tertiles)	1.38- 2.00	2.39 (1.40-4.09)
	> 1.38	4.64 (2.43-8.86)
BMI	< 24	*ref*
(tertiles)	24-27	1.85 (1.07-3.18)
	>27	2.19 (1.22-3.93)
Treatment	mono	*ref*
	combo prednisone	0.27 (0.15-0.48)
	combo infliximab	0.37 (0.22-0.63)
VAS pain	< 40	*ref*
(tertiles)	40-60	2.72 (1.52-4.59)
	> 60	3.67 (1.85-7.27)

Disclosure: L. Dirven, None; **J. A. P. M. Ewals**, None; **T. W. J. Huizinga**, None; **P. J. S. M. Kerstens**, None; **A. J. Peeters**, None; **B. A. C. Dijkmans**, None; **C. F. Allaart**, None.

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Care Gap in Early Inflammatory Arthritis Patients with a High Fracture Risk Identified Using the FRAX® Tool. Vivian P. Bykerk[1], Carly K. Cheng[1], Gilles Boire[2], Janet E. Pope[3], Boulos Haraoui[4], Carol A. Hitchon[5], Shahin Jamal[6], J. Carter Thorne[7], NEAR Researchers and Heather McDonald-Blumer[8], [1]Mt Sinai Hospital, Toronto, ON, [2]CHUS - Sherbrooke University, Sherbrooke, [3]St Joseph Health Care, London, ON, [4]Institut de rhumatologie de Montréal, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]St. Michael's Hospital, Toronto, [7]Southlake Regional Health Centre, Newmarket, ON, [8]Mt Sinai Hospital, Toronto

Purpose: A fracture risk assessment tool (FRAX®; http://shef.ac.uk/FRAX) estimates a 10-year absolute risk of sustaining a hip or other major osteoporotic fracture. FRAX® identifies patients at low (<10%), moderate (10-20%) or high (>20%) risk of fracture using validated clinical risk factors ± bone mineral density (BMD) testing. This study determined the frequency of patients with early inflammatory and rheumatoid arthritis (EIA and ERA) at high risk of major osteoporotic fracture using FRAX® and evaluated the care gap in high risk patients.

Method: 239 patients were enrolled since July 2007 in the Canadian Early Arthritis Cohort (CATCH) study, a multi-centre observational prospective "real world" cohort of patients with EIA. Inclusion Criteria: age >16, symptom duration of 6-52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP or PIP + ≥1 of: positive RF, positive anti-CCP, morning stiffness >45mins, response to NSAIDs, or painful MTP squeeze test. FRAX® was calculated based on ethnicity assuming norms from the United States of America (USA) and United Kingdom (UK), without BMD. History of hip fracture in a parent hip was inconsistently reported in the CATCH standardized questionnaire and assumed to be absent if data were not available.

Results: Baseline characteristics: mean age 52±15 years, 80% female, 79% RA (ACR criteria), median symptom duration 6.1 months, mean DAS28 ESR 4.9±1.5, 16% treated with oral glucocorticoids. Based on USA norms, patients at high risk vs. low risk had a higher mean age ($p<0.011$), higher DAS28 ($p=0.036$), and received more glucocorticoids ($p=0.011$). DAS28 of patients at moderate risk was greater vs. low risk ($p=0.112$). The rate of Ca, Vit D and bisphosphonate use did not increase in low to moderate to high risk groups ($p=0.05$).

Table: FRAX® major osteoporotic fracture risk (n=239)

	Low Risk (<10%)		**Moderate Risk (10-20%)**		**High Risk (>20%)**	
	USA	**UK**	**USA**	**UK**	**USA**	**UK**
N (%)	155 (65%)	175 (73%)	52 (22%)	52 (22%)	32 (13%)	12 (5%)
Age (mean)	44±12	47±13	64±7	66±8	72±8	79±6
Oral glucocorticoids (base)	11.6%	25.7%	21.2%	26.9%	31.3%	75.0%
Received Ca or Vit D	13.6%	14.9%	19.2%	15.4%	15.6%	16.7%
Received a Bisphosphonate	4.5%	4.0%	3.9%	7.7%	9.4%	8.3%
DAS28 ESR (base mean)	4.9±1.5	4.8±1.5	5.3±1.5	5.0±1.5	5.5±1.0	5.3±1.2

Conclusion: FRAX® identified 5-13% of patients at high risk using a conservative analysis, as being older, having higher disease activity and more frequent glucocorticoid use at baseline compared to patients at low risk. Despite awareness that classic risk factors are associated with high risk, a very low proportion of patients are being treated with supplemental Ca, Vit D and bisphosphonates. These data highlight the need to identify and modify fracture risk in patients presenting with EIA/ERA.

Disclosure: V. P. Bykerk, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **C. K. Cheng**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **G. Boire**, Wyeth Pharmaceuticals, 2, Amgen, 2 ; **J. E. Pope**, Wyeth Pharmaceuticals, 2, Amgen, 2 ; **B. Haraoui**, Amgen, 2, Wyeth, 2 ; **C. A. Hitchon**, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **S. Jamal**, None; **J. C. Thorne**, Wyeth Pharmaceuticals, 2, Amgen, 2 ; **H. McDonald-Blumer**, Amgen-Wyeth, Novartis, The Bone Alliance, Scherring Plough, 5

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Cytokine Response Profiling in Rheumatoid Arthritis: A Correlative Study of Patients with Early or Late Disease Compared to Controls. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel, Mayo Clinic, Rochester, MN

Purpose: The long-term goal of our research is to identify immunologic signatures that can predict outcomes (i.e., response to therapy) in patients with rheumatoid arthritis (RA). The purpose of this analysis was to develop this concept by identifying *ex vivo* cytokine response profiles that discriminate patients with early or late RA from controls.

Methods: Patients with RA (1987 ACR criteria) and control subjects with no history of rheumatic disease were included. Data on demographic and clinical characteristics, including C-reactive protein (CRP) and the Health Assessment Questionnaire (HAQ), were collected. Fresh peripheral blood mononuclear cells (PBMC) from subjects were stimulated ex vivo under eight stimulation conditions, including: anti-CD3/anti-CD28 (CD3/CD28); cytomegalovirus and Epstein Barr virus (CMV/EBV) lysates; or human heat shock protein 60 (HSP60). The profiles of cytokine release in response to stimulation were determined using multiplex immunoassays with a 17-cytokine panel. For comparison, the cytokine profiles were also analyzed in serum samples. The fold-changes in the cytokine values between the RA and control groups were compared using mixed effects models, adjusting for age, sex, and cytokine plate effects.

Results: The study included 85 patients with RA and 15 controls. Of the patients, 25 had early active disease (mean duration: 0.2 yr; CRP: 40.3 mg/L; HAQ: 1.4), and 60 had established quiescent disease (mean duration: 13.6 yr; CRP: 4.1 mg/L; HAQ: 0.5). Analyses revealed recurring profiles of impaired Th1 and Th2 responsiveness to T cell activation and increased Th17 and myeloid responsiveness to stimulation with toll-like receptor ligands. A 9-cytokine signature was developed that clearly discriminated the patients with early and late RA from controls. Patients with early RA exhibited decreased responsiveness of Th1 (IL-12, MIP-1b, and TNF) and Th2 (IL-10) subsets to CD3/CD28, decreased IL-8 and increased IL-6 responsiveness to CMV/EBV, and increased responsiveness of Th17 (IL-17A) and myeloid subsets (GM-CSF, MCP-1) in response to HSP60 as compared to controls. Patients with late RA appeared to have recovered Th1 responsiveness, and partially recovered Th2, but had persistently increased Th17 and myeloid responsiveness to HSP60 as compared to controls. A similar 9-cytokine profile assessed in patient sera discriminated the early RA group, but not the late RA group, from controls.

Conclusion: Using *ex vivo* cytokine response profiling and multiparametric analyses, we have developed an immunologic signature that discriminates patients with early active as well as established quiescent RA from controls. These data provide a preliminary signature that has the potential to identify patients with persistent disease activity and also to stratify patients on the risk of adverse disease outcomes.

Disclosure: J. M. Davis, None; **K. L. Knutson**, None; **M. A. Strausbauch**, None; **C. S. Crowson**, None; **T. M. Therneau**, None; **E. L. Matteson**, None; **S. E. Gabriel**, None.

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The Season of First Symptoms Influences the Severity in Early Arthritis : Results From the ESPOIR Cohort. Gaël Mouterde[1], Nathalie Rincheval[2], Cedric Lukas[1], RM Flipo[3], Philippe Goupille[4], Jean-Pierre Daures[2] and Bernard Combe[1], [1]Lapeyronie hospital, Montpellier, France, [2]Epidemiology unit, Montpellier, France, [3]Rheumatology,Lille University, Lille, [4]Université François Rabelais de Tours, CNRS, UMR 6239; CHRU de Tours, Tours, France

Purpose: To determine predictors of radiographic progression in an inception cohort of early arthritis patients.

Method: Patients presenting with synovitis of at least 2 joints for 6 weeks to 6 months were included in the multicenter French ESPOIR cohort. Following data were collected at baseline : clinical and biological features of arthritis, IgM Rheumatoid factor (RF) and anti-CCP auto-antibodies (anti-CCP), HLA-DRB1* typing, socio economic factors, comorbidities. Radiographs of hands, wrists, and feet were scored at baseline, 6 and 12 months. A radiographic progression was defined by an increase of at least 1 point of the modified total Sharp score (mTSS) assessed at baseline and after 6 and 12 months.

The sensitivity and specificity of RF and anti-CCP at baseline in discriminating between erosive and non erosive disease at 6 months and one year were determined. Optimal cutoffs for these tests were derived from receiver operating characteristic (ROC) curves using a cost function. Logistic regression was performed to evaluate the association between the radiological progression and baseline variables.

Results: Of the 813 recruited patients, complete data were available for 736 patients : 48±12 years old, females 77%, mean disease duration 103+/-53 days, DAS28 5.11±1.31, HAQ score 0.97±0.68, CRP 21.9±32 mg/l, HLA-DRB1*01 or 04 57.5%. 341 (46.3%) of them were positive for RF and 290 (34.4%) were positive for anti-CCP.

Radiographic progression after six months was associated with the following initial factors : anti-CCP (OR=3.73 [2.04; 6.82], p<0.0001), median ESR (OR=2.52 [1.38; 4.61], p=0.0027), median mTSS (OR=2.18 [1.20; 3.94], p= 0.0105). Surprisingly, the season of first symptoms onset influenced the severity in early arthritis : mTSS after six months was worse if symptoms had occurred in winter (OR=2.82 [1.14;7], p=0.0255 *versus* summer), or in spring (OR=2.83 [1.10;7.37], p=0.0322 *versus* summer). Similarly, mTSS after six months was worse if symptoms had occurred in winter (OR= 2.61 [1.20; 5.71], p=0.0158) or in spring (OR=2.63 [1.13; 6.14], p=0.0025) *versus* autumn as reference season. Morning stiffness protect against radiographic progression in the cohort (OR=0.41 [0.20; 0.86], p= 0.0175).

A progression of the mTSS after one year was associated with anti-CCP (OR=5.38 [3.01; 9.65], p<0.0001) and age (≥50 years old, OR=2.57 [1,46; 4.54], p=0.0011). In univariate analysis, the progression of the mTSS after one year was worse if symptoms had occured in winter or in spring (OR=2.01 [1.22;3.32] and OR=1.68 [1.01;2.80] respectively *versus* summer.

Conclusion: Onset of arthritis symptoms during winter or spring was associated with a more severe radiographic outcome at 6 months in early arthritis patients. One explanation could be as a result of either a vitamin D deficiency or environmental factors, such as winter viruses, influencing protein citrullination.

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ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Epidemiology and Prognostic Considerations
Monday, October 19, 2009, 2:30 PM - 4:00 PM

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Scleroderma Pumonary Hypertension Quality Enhancement Research Initiative (QuERI): Use of Diagnostic Tests by Community Rheumatologists. James R. Seibold[1], Alina Dragomir[2], Mary Tan[2], Daniel E. Furst[3], Nicholas Hill[4], Vallerie McLaughlin[5], Richard M. Silver[6], Virginia D. Steen[7] and Anatoly Langer[8], [1]University of Michigan, Ann Arbor, MI, [2]Canadian Heart Research Center, Toronto, ON, [3]UCLA, Los Angeles, CA, [4]Tufts Medical Center, Boston, MA, [5]Cardiology, University of Michigan, Ann Arbor, MI, [6]Medical University of South Carolina, Charleston, SC, [7]Georgetown University Medical Center, Washington, DC, [8]Canadian Heart Research Centre, Toronto, ON

Purpose: Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the leading causes of death in systemic sclerosis (SSc, scleroderma). Evidence-based standards for diagnosis and classification are available but consensus suggests a “care gap” between published standards and community practice. We utilized a Delphi consensus to develop a diagnostic template judged accessible to the primary care rheumatologist and relevant to early recognition of both PAH and ILD. QuERI offers computer-based feedback to investigators. We report on the initial experience in 207 patients with scleroderma among 27 US rheumatologists including 22 community practice settings (168 patients) and 5 academic referral centers (39 patients).

Methods: Physicians were asked to enroll scleroderma patients (known or newly diagnosed) and provide data on a recommended panel of clinical features and diagnostic tests.

Results: (Median, 25th and 75th percentile): Patients enrolled were 57 years old (49, 66), 90% female. Raynaud phenomenon was present in 87.0%, duration 8 years (4,14). In spite of specific clinical focus on lung, CXR was performed in only 43.0% and was abnormal in 36.0%. V/Q scan was done in only 1% and HRCT in only 37.2%. PFT was performed in 82.6% and showed DLCO <55% predicted in 27.1%, and FVC/DLCO ratio >1.4 in 44.6%. Doppler echocardiogram was done in 85.0% of patients and revealed tricuspid jet of >3 m/sec in 11.1% and estimated RVSP >40 mm Hg in 20.0%. Right heart catheterization was performed in only 4.8% of patients. Practice setting influenced use of testing:

Recommended/Contingent Diagnostic	Community centre	University centre	P value

Tests	(22 centers N=168)	(5 centers N=39)	
PFT's	133 (79.2%)	38 (97.4%)	0.007
DLCO<55% of predicted	28/105 (26.7%)	10/35 (28.6%)	0.83
FVC/DLCO > 1.4	48/104 (46.2%)	14/35 (40.0%)	0.53
Echocardiogram	141 (83.9%)	35 (89.7%)	0.36
VQ lung scan	2 (1.2%)	0	1.0
ECG	17 (10.1%)	6 (15.4%)	0.40
Six minute walk	11 (6.6%)	11 (28.2%)	<.0001
High resolution CT scan	50 (29.8%)	27 (69.2%)	<.0001
Chest x-ray or CT scan	100 (59.5%)	31 (79.5%)	0.02
Right heart catheterization	5 (3.0%)	5 (12.8%)	0.02
Diagnostic criteria of PAH		0	
	4/5		

14 were treated with endothelin receptor antagonists and 8 were receiving chronic PDE-5 inhibitors although only 5 were treated for "PAH indication." ILD was confirmed by PFT and HRCT in 23 (96%) of 24 patients receiving agents of putative benefit including cyclophosphamide (6) and mycophenolate mofetil (18).

Conclusion: This preliminary assessment suggests that certain basic essential diagnostic tests, such as right heart catheterization for PAH, continue to be underutilized. The SSc QuERI offers stricter guidelines, adherence to which could optimize management of these high-risk patients.

Disclosure: J. R. Seibold, Fibrogen, 5, United Therapeutics, 2, Pfizer Inc, 5, Actelion Pharmaceuticals Ltd, 2, Bristol-Myers Squibb, 2, Actelion Pharmaceuticals US, 1, Actelion Pharmaceuticals Ltd, 5 ; **A. Dragomir**, None; **M. Tan**, None; **D. E. Furst**, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Genentech and Biogen IDEC Inc., 9, Gilead, 9, GlaxoSmithKline, 9, Nitec, 9, Novartis Pharmaceutical Corporation, 9, Roche Pharmaceuticals, 9, UCB, 9, Wyeth Pharmaceuticals, 9, Xoma Corporation , 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech and Biogen IDEC Inc., 9, gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9, Novartis Pharmaceutical Corporation, 9, Ucb, 9, Wyeth Pharmaceuticals, 9, Xoma, 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, Amgen, 9, Bristol-Myers Squibb, 9, Biogen Idec, 9, Centocor, Inc., 9, Genentech and Biogen IDEC Inc., 9, Gilead, 9, Merck Pharmaceuticals, 9, Nitec, 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, UCB, 9 ; **N. Hill**, Actelion Pharmaceuticals US, Gilead, Pfizer, Bayer, Epix, United Therapeutics, 2 ; **V. McLaughlin**, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5, Actelion Pharmaceuticals US, 8, Gilead, 5, Gilead, 8, united therapeutics, 2 ; **R. M. Silver**, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 8 ; **V. D. Steen**, Actelion Pharmaceuticals US, 2, Gilead, 2, United Therapeutics, 2, Bristol-Myers Squibb, 2, gilead, 8 ; **A. Langer**, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5 .

1197

Telangiectases in Scleroderma: A Potential Clinical Marker of Pulmonary Arterial Hypertension. Ami A. Shah, Fredrick M. Wigley and Laura K. Hummers, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Pulmonary arterial hypertension (PAH) is a significant cause of morbidity and mortality among patients with scleroderma. Clinical markers are needed to screen and identify scleroderma patients at risk for PAH since early therapy may result in a survival benefit. Telangiectases, lesions composed of vasodilated post-capillary venules, may be an easily accessible marker of scleroderma vascular disease.

Method: Consecutive subjects with scleroderma were enrolled and scored for the presence of matted, non-stellate telangiectases on the face, hands, arms, chest and abdomen, back, legs, and feet. For each body area, telangiectases were scored as 0 if no telangiectases were present, 1

if there were less than 10 telangiectases, and 2 if 10 or more telangiectases were counted (11 body areas for maximum score of 22). Subjects were grouped into tertiles of total telangiectasia score (0-3, 4-7, 8+). Differences in clinical variables between the 3 groups were assessed by analysis of variance and the Fisher's exact test where appropriate. The correlation between RVSP and telangiectasia score was assessed by Pearson's correlation coefficient. Linear regression analysis was performed to assess the association between RVSP and telangiectasia score, adjusted for age, race, smoking status, scleroderma subtype, disease duration, and autoantibody status. Logistic regression analyses were performed with the presence of PAH by right heart catheterization (RHC) as the dependent variable and telangiectasia score, age, subtype, disease duration, autoantibody status, and diffusing capacity as possible explanatory variables.

Results: One hundred forty seven patients with scleroderma were enrolled. Telangiectasia scores ranged from 0-20, and the mean telangiectasia score was 6.0 (SD 4.5). Fifty-four patients had a telangiectasia score of 0-3 (1st tertile), 50 had a score of 4-7 (2nd tertile), and 43 had a score of 8-20 (3rd tertile). Patients in the second and third tertiles of telangiectasia score were older ($p<0.0001$) and had a longer duration of scleroderma ($p<0.0001$). RVSP and telangiectasia score were positively correlated ($r=0.271$, $p=0.001$). The RVSP increased by 10.9 mmHg for a 10 point increase in telangiectasia score (95% CI 3.6 – 18.3mmHg, $p=0.004$), adjusted for age, race, disease duration, scleroderma subtype, smoking status, and autoantibody status. The relative odds of PAH by RHC was 12.4 for a 10 point increase in telangiectasia score after adjustment (95% CI 1.78 - 85.9, $p=0.01$).

Conclusion: Increased numbers of telangiectases are strongly associated with the presence of pulmonary vascular disease. Telangiectases may be a clinical marker of more widespread aberrant microvascular disease in scleroderma.

Disclosure: A. A. Shah, None; **F. M. Wigley**, None; **L. K. Hummers**, None.

1198

Heritability of Systemic Sclerosis: A Population Database Study. Tracy M. Frech and Allen D. Sawitzke, University of Utah Medical Ctr, Salt Lake City, UT

Purpose: Systemic sclerosis (SSc) is a heterogeneous chronic illness characterized by variability in clinical manifestations, internal organ involvement, and outcome, due to a complex interplay of inflammation, fibrosis, and vasculopathy. Despite its unpredictability, almost all patients with SSc have Raynauds phenomenon (RP), and one of the leading causes of mortality in this population is interstitial lung disease (ILD). Genetic predispositions to SSc have been described, but the genetic underpinnings that may predispose to specific disease presentations are unknown. Ideally, an approach to identify patients at highest risk for SSc would concurrently provide insight into its relationship to other autoimmune and fibrotic diseases which can also have RP and/or ILD. This study looks at the familiality and relative risks of SSc, in relation to RP, ILD, systemic lupus erythematous (SLE), Sjogrens (SS), dermatomyositis (DM), rheumatoid arthritis (RA), and unspecified connective tissue disease (UCTD).

Method: A unique genealogic resource, the Utah Population Database (UPDB) was used to examine heritability using records from more than 7.0 million individuals. For this study, diagnosis were defined by ICD-9 codes; SSc (710.1), RP (443), ILD (515), SLE (710.0), SS (710.2), DM (710.3), RA (714), and UCTD (710.9) collected in any of three sources a) death certificates, b) U of U enterprise data warehouse or c) state-wide hospital discharge data. The cases of SSc were mapped to pedigrees of the UPDB for analysis. Measures of risk to relatives of 1st, 2nd and 3rd degree to cases were calculated and for related diagnosis as above. Controls without any of the ICD-9 codes of interest were randomly selected from the UPDB to allow calculation of Familial Standardize Incidence Ratio (FSIR), relative risks (RR), and Population Attributable Risk (PAR). The FSIR computes an individual's familial risk for SSc, accounting for the number of biological relatives, their degree of relatedness to the proband, and their time at risk of detection.

Results: Over 1300 distinct patients statewide with a diagnosis of systemic sclerosis were used to compute PAR and find 30 families with the highest FSIR. First degree relatives have a RR of 3.07. The adjusted PAR, a measure of the familial contribution to risk for SSc, is about 8% (0.04-0.12). The RRs were significant at the 0.05 level for all kinship classes closer than second cousins. The P values given are the probability of a family having some observed number of cases under the null hypothesis of no familial disease aggregation. Excess clustering of fibrotic and autoimmune diagnoses in these families was found.

Conclusion: This data suggests that SSc pedigrees can be identified on a population basis and that these pedigrees include increased numbers of family members with RP, ILD, SLE, SS, DM, RA, and UCTD. It is likely that at least two factors contribute, one to fibrosis and another to a shared predisposition to autoimmunity.

Disclosure: T. M. Frech, None; **A. D. Sawitzke**, None.

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Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Two-Year Outcomes for Pre-Pulmonary Arterial Hypertension (PAH). Vivien M. Hsu[1], Hafiz Khan[2], Yijin Wu[3], Elena Schiopu[4], M. Mayes[5], Chris T. Derk[6], Lee S. Shapiro[7], ME. Csuka[8], Aryeh Fischer[9], Dinesh Khanna[10], Robyn T. Domsic[11], Jerry A. Molitor[12], Virginia D. Steen[13] and the PHAROS Investigators, [1]UMDNJ, New Brunswick, NJ, [2]Newark, NJ, [3]Rutgers University, New Brunswick, NJ, [4]Scleroderma program, University of Michigan, Ann Arbor, MI, [5]U.Texas Houston, Houston, TX, [6]Jefferson Medical College, Philadelphia, PA, [7]Albany, NY, [8]Med Coll of Wisconsin, Milwaukee, WI, [9]National Jewish Medical Center, Denver, CO, [10]University of California Los Angeles, Los Angeles, CA, [11]University of Pittsburgh, Pittsburgh, PA, [12]Univ of MN MMC108, Minneapolis, MN, [13]Georgetown University Medical Center, Washington, DC

Background: Pulmonary Arterial Hypertension (PAH) and pulmonary hypertension (PH) secondary to interstitial lung disease are the leading causes of systemic sclerosis (SSc) related deaths. Early detection and treatment should improve morbidity and mortality. PHAROS is a multi-center, prospective, observational study to determine risk factors and outcomes of patients who have definite or are at high risk for PAH/PH

Purpose: This analysis compares the clinical features and preliminary outcomes of the 206 pre-PAH subjects currently enrolled in PHAROS.

Methods: PHAROS defines pre-PAH by one of the following entry criteria: DLCO ≤ 55% predicted, FVC%/DLCO% ratio > 1.6, or echocardiographic (echo) PASP >40 mmHg. Data is collected bi-annually and includes patient generated, clinical and objective data. Right-heart catheterization (RHC) is performed in those suspected to have PH. Definite PH is defined as mean pulmonary artery pressure ≥25 mmHg at rest or ≥30 mmHg with exercise on right heart catheterization.

Results: *206 pre-PAH subjects have been enrolled: 26 (13%) males,* mean age 56.1, (standard deviation 11.5 SD), *m*ean disease duration (from onset of non-Raynaud symptoms) 13.7 years, 73% Caucasians, 18% blacks. Scleroderma antibodies known in 165 patients: 30% anti-centromere, 16% topo-isomerase, and 13% nucleolar ANA pattern. Mean PFT values: DLCO 49.8% predicted (19.5 SD), FVC/DLCO 1.79 (0.59 SD), and FVC 81.9% predicted (18.9 SD). The mean echo PASP was 39.8mm Hg (25.7 SD). 152 participants had additional follow up visits (mean 1.47years, range 0.5 to 3.5) and 110 had repeat studies. 18% patients did not fulfill echo entry criterion on follow up studies.

61 RHCs were performed in this population: 42 had normal RHC and 19 were abnormal. In those normal RHC, the mean echo systolic PAP was 42.6mmHg compared to the mean systolic PAP on RHC of 30.9mmHg ($p<0.001$) In the 19 patients who developed PH after first visit, 13 had PAH (Group I, mPAP>25 at rest or >30mmHg with exercise) and 6 had Group 2 PH (mPAP>25mmHg with a capillary wedge pressure ≥15 mmHg). Definite PAH developed in 3% of pre-PAH patients at 1 year and 16% by 2 years. Only a lower DLCO predicted the future development of PAH, 40% predicted vs 49.7% predicted ($p<0.03$).

Conclusion: 16% of subjects at increased risk for PAH have evolved to PAH at 2 years. A very low DLCO was the best predictor for PAH. Echo PASP were extremely variable over time and did not correlate well with RHC. This ongoing prospective study is a very important resource to elucidate outcomes and risk factors for development of PAH.

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1200

Point Prevalence of Pulmonary Hypertensions in Systemic Sclerosis: Results From Two Large Cohorts (of European Caucasian patients) and Meta-Analysis. J. Avouac[1], P. Airo[2], C. Meune[1], L. Beretta[3], P. Dieudé[1], P. Caramaschi[4], S. Cappelli[5], K. Tiev[6], E. Diot[7], A. Vacca[8], Jl Cracowski[9], J. Sibilia[10], A. Kahan[1], M. Matucci-Cerinic[5] and Y. Allanore[1], [1]Rheumatology, Paris, France, [2]Reumatologia, Brescia, Italy, [3]Rheumatology, Milan, Italy, [4]Rheumatology, Verona, Italy, [5]Rheumatology, Florence, Italy, [6]Internal Medicine, Paris, France, [7]Internal Medecine, Tours, France, [8]Rheumatology, Monserrato, Italy, [9]Pharmacology, Grenoble, France, [10]Rheumatology, Strasbourg, France

Purpose: To measure the point prevalence of pulmonary hypertensions (PHs) using the gold-standard method that is the right heart catheterization (RHC) in two large European cohorts of patients with systemic sclerosis (SSc) and to perform a meta-analysis of available data.

Method: A multicenter study was performed in France and Italy to recruit consecutive SSc patients systematically assessed for the existence of PH. Criteria for catheterisation were a systolic pulmonary arterial pressure (sPAP) >40mmHg on echocardiography or DLCO<50% or unexplained dyspnea. A proportion meta-analysis has also been performed including the present study and four published studies using similar definition of PH, identified after a systematic literature research (through electronic databases between 1966 and June 2009).

Results: We recruited 467 (86% females) and 698 (90%) from France and Italy respectively. The mean age was 57±13 and 62±14 years old in the French and Italian cohort respectively ($p<0.0001$) and the mean disease duration was 11±9 and 14±8 years respectively ($p<0.0001$) in the French and Italian cohort. The prevalence of PHs was 25/467 (5%) and 39/698 (6%) in French and Italian SSc patients respectively, providing a frequency of 5% in the combined populations. This group was constituted of 42 pulmonary arterial hypertension (PAH) and 22 PH related to interstitial lung disease (ILD). In multivariate analysis, decreased DLCO/VA (OR [CI95%]: 12.9 [4.7-33.3], $p<0.0001$), decrease forced vital capacity <75% (4.3 [2.2-8.2], $p<0.0001$) and age (1.1 [1.0-1.2], $p=0.0002$) were independent associated factors. The proportion meta-analysis of five studies that included 3818 SSc patients was based on random effects (DerSimonian-Laird) because of heterogeneity between the studies and gave a pooled proportion of 9% (CI95%: 6-12%). Among the PHs population, the mean age was 66±12 years, the mean disease duration: 13±9 years; 72% (CI95%: 66-77%) had the limited cutaneous subtype, 32% (CI95%: 26-38%) had pulmonary fibrosis, 63% (CI95%: 55-72%) had PAH and 36% (CI95%: 28-45%) had PH related to ILD.

Conclusion: Our study shows that 5% of this large series of European Caucasian patients affected by SSc have developed PHs, as defined by RHC. Among these patients, about 2/3 had PAH and 1/3 PH related to ILD. Our study supports that SSc patients with PHs were significantly older and confirm the association between PH and decreased DLCO/VA.The proportion meta-analysis of 5 studies found a pooled PH point prevalence of 9%. It confirms that PAH was predominant in comparison to PH related to ILD. Moreover, SSc-PHs appear to be a late complication within disease course, occurring in older patients and predominantly within the limited cutaneous subtype.

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1201

Myocarditis in Systemic Sclerosis Diagnosed through Endomyocardial Biopsy. Gaetano Zizzo[1], Maria De Santis[1], Silvia Bosello[1], Giusy Peluso[1], Stefano Alivernini[1], Michela Pinnelli[1], Mario Bocci[1], Giacomo De Luca[1], Luigi Natale[2], Maurizio Pieroni[3], Filippo Crea[3], Lorenzo Bonomo[2] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Rome, Italy, [2]Department of Radiology, Rome, Italy, [3]Institute of Cardiology, Rome, Italy

Purpose: Heart involvement in Systemic Sclerosis (SSc) is estimated to be present in almost all patients, although most often asymptomatic. To what extent ischemic injury, flogosis and fibrosis respectively contribute to myocardial damage is not clear. We describe 6 patients with biopsy-proven myocarditis.

Method: Among 189 scleroderma patients undergone ECG, the ones who showed ECG alterations (arrhythmias and conduction disturbances, with or without signs of ischemia) together with serum increase of cardiac enzymes were recruited, and studied by echocardiography, myocardial perfusion scintigraphy, late gadolinium-enhanced cardiac magnetic resonance imaging (MRI), coronarography and myocardial biopsy.

Results: 46 patients out of 189 (24.3%) showed ECG findings of conduction and/or rhythm disturbances: first degree atrioventricular block in 13%, right bundle branch block (RBBB) in 6.5%, left anterior fascicular block (LAFB) in 28.2%, sinus bradycardia in 17.3%, sinus

tachycardia in 2.1%, supraventricular ectopic beats in 17.3%, ventricular ectopic beats (VEB) in 19.5%. Among these, 7 (6 F, 1 M; 3.7% of all) also presented increased cardiac enzymes (CK-MB in all, troponin T in 5, total CK in 3). 2 showed VEB, 1 RBBB and VEB at times organized in bigeminal rhythm, 2 bradycardia, 1 tachycardia, 1 LAFB. 5/7 accused dyspnea. 4/7 showed positive late-gadolinium enhancement (LGE) on MRI (subepicardial pattern in 2, subepicardial and subendocardial in 1, midwall in 1); 1 among the others had pericarditis. Coronarography documented uninjured coronaries in all patients. In 6/7 endomyocardial biopsy proved myocarditis, according to Dallas Criteria, demonstrating myocyte necrosis and mononuclear cell infiltrate, associated to interstitial and perivascular fibrosis, subendocardial thickening with prominence of smooth muscle cells; none presented vasculitis; extended areas of substitutive fibrosis were observed in 2, the ones who also showed ECG changes for previous myocardial infarction, echocardiographic and MRI assessment of wall motion abnormalities and scintigraphic perfusion defects. Histology was normal in the patient with pericarditis. Among the 6 patients with biopsy-proven myocarditis, 4 had diffuse SSc, 3 were positive to antiSCL70, 3 to c-ANCA, 3 to antiphospholipids, 1 to p-ANCA.

Conclusion: Although cardiac MRI is considered the gold standard in the diagnosis of myocarditis, it was controversial (LGE midwall pattern) or falsely negative in half of patients with biopsy-proven myocarditis. c-ANCA positivity correlated with myocardial involvement, as it occurred in 57.1% of the patients with ECG and cardiac enzyme alterations, in 50% of those with myocarditis and in 3.1% of the whole cohort.

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ARHP Concurrent Abstract Sessions

Outcome Measures in Arthritis

Monday, October 19, 2009, 2:30 PM - 4:00 PM

1202

What Aspects Do Outcome Measures Used in Team Rehabilitation Really Measure? Sofia Hagel[1], Elisabet Lindqvist[2], Ingemar F. Petersson[3] and Ann B. Bremander[4], [1]Department of Rheumatology, Lund University Hopsital, Lund, Sweden, [2]Department of Rheumatology, Lund University Hospital, Lund, Sweden, [3]Section of Orthopedics and Section of Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden, [4]R & D Center, Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden

Purpose: To study the ability of well used and validated outcome measures for patients with chronic inflammatory arthritis to cover the ICF domains (International Classification of Functioning, Disability and Health), and the agreement and sensitivity to change among the included measures.

Method: HRQoL was measured by the Nottingham Health Profile (NHP), the EuroQol (EQ5D) and the Short Form-36 Health Survey (SF-36). Physical function was evaluated with the Health Assessment Questionnaire (HAQ), aerobic capacity (VO_{2max}), the Shoulder-arm-hand functioning test, grip strength, and the Signals of Functional Impairment test. The outcome measures were classified according to the ICF. Spearman correlations (r_s) were then performed between the measures belonging to the same ICF domain and in groups of HRQoL and physical function. Standardized response mean (SRM) was used to calculate responsiveness. Analyses were based on results from 216 patients participating in a multidisciplinary daycare rehabilitation program for 18 days, 149 (122 females) with peripheral arthritis median age 54 years (IQR 18), and 67 (31 females) with spondylarthritides (SpA) median age 44 years (IQR 21). Evaluations of agreement and sensitivity to change were performed at inclusion, after 18 days and after 12 months.

Results: The ICF domains body function, activity and participation were all covered by SF 36, EQ5D and NHP. All other instruments covered only one domain, while none covered ICF environmental. EQ5D showed correlations of $r_s<0.3$, with the other HRQoL instruments (baseline and change values). Correlations between NHP and SF36 subscales measuring similar aspects was the highest for SF36 MH and NHP emotion $r_s>0.7$, all other correlations varied between r_s 0.001and 0.7. Aerobic capacity had correlations of $r_s<0.2$, at all time points, with all other outcome measures on observed physical function, for all included patients. Aerobic capacity also had an SRM of 0.8 or higher at all time points for all patients while the SRM for HRQoL instruments was 0.4 or lower.

Conclusion: ICF environmental aspects were not covered by commonly used rehabilitation outcome instruments. For accurate comparison between studies HRQoL needs to be evaluated with the very same instrument, due to poor agreement between the different outcome measures. Aerobic capacity, when appropriate, should accompany other measures on the ICF domain body function, since it showed low correlations to all other outcome measures, indicating that it captures a different aspect, yet with a high SRM. The results of this study emphasis the need of consensus on a core set of outcome instruments to make comparison among rehabilitation programmes possible.

Disclosure: S. Hagel, None; **E. Lindqvist**, None; **I. F. Petersson**, None; **A. B. Bremander**, None.

1203

Development and Validation of the Osteoarthritis Burden Questionnaire (OA-Quest). Lucy Busija[1], Rachelle Buchbinder[2] and Richard H. Osborne[3], [1]The University of Melbourne, Melbourne, Australia, [2]Cabrini Medical Center, Malvern, Australia, [3]Deakin University, Melbourne, Australia

Purpose: This study describes the development and validation of the Osteoarthritis Burden Questionnaire (the OA-Quest), a new tool designed to measure the overall potentially modifiable burden of OA in a single measure. It is intended for use in a wide range of settings, particularly where the assessment of the full range of osteoarthritis-related consequences would be required. The questionnaire is non-joint specific and suitable for use in osteoarthritis of any joint.

Method: Item development for the OA-Quest was guided by concept mapping (CM) workshops with patients (N=26) and health professionals (N=27) conducted in Australia and in Sweden. Construction (N=394), evaluation (N=398) and validation (N=296) samples were drawn from community and clinical settings. The properties of the new questionnaire were investigated using exploratory and confirmatory factor analysis and Rasch analysis. The construct validity of the OA-Quest was assessed using correlations with existing measures of theoretically related concepts, including the WOMAC and the SF-36. The development and validation procedures meet recent FDA requirements for questionnaire development.

Results: 123 candidate items were generated from the results of CM, with 42 items selected for inclusion into the questionnaire. Each item underwent cognitive testing to ensure it was understood as intended. The OA-Quest was found to be comprised of seven independent dimensions of osteoarthritis burden, including Physical distress (7 items, Cronbach's α=0.93), Physical limitations (11 items, α=0.95), Psychosocial distress (7 items, α=0.93), Physical de-conditioning (4 items, α=0.87), Financial hardship (4 items, α=0.93), Sleep disturbances (5 items, α=0.96), and Lost productivity (4 items α=0.90). The concepts represented in the Financial hardship and Physical de-conditioning scales have not been previously measured in osteoarthritis. The construct validity of the OA-Quest scales was strongly supported by the expected pattern of correlations with existing questionnaires and these scales were able to distinguish the individuals who self-rated the severity of their osteoarthritis as mild or moderate from those who self-rated their osteoarthritis as severe or extremely severe. On all scales, the group with higher severity of osteoarthritis received significantly higher scores than the lower severity group, further supporting the construct validity of the OA-Quest.

Conclusion: The OA-Quest is a new measure of osteoarthritis burden, with strong evidence of face validity, reliability and construct validity. It provides very precise information (high reliability) efficiently (few items) across 7 areas important to patients, clinicians, and clinical trialists. The high precision of the scales will permit trial sample sizes to be minimized, thus reducing costs. The OA-Quest can be used flexibly, i.e., one or all scales can be used in a particular study. The OA-Quest delivers information that is pertinent to patients and clinicians on potentially modifiable domains linked to individual and society burden due to osteoarthritis.

Disclosure: L. Busija, None; **R. Buchbinder**, None; **R. H. Osborne**, None.

1204

Development and Initial Validation of the Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ). Joanna Nicklin[1], Fiona Cramp[1], Jr Kirwan[2], Marie Urban[3] and Sarah E. Hewlett[1], [1]University of West of England, Bristol, United Kingdom, [2]University, Bristol, United Kingdom, [3]Bristol Royal Infirmary, Bristol, United Kingdom

Purpose: As current fatigue scales do not adequately reflect the experiences of rheumatoid arthritis (RA), we developed a new scale based on patient interviews, focus groups and "think aloud" methods. From these previously reported studies we devised a 45 item draft questionnaire. Here we report the results of item reduction and initial validation of the final scale.

Method: These 45 items contained 12 fatigue concepts previously identified from patient interviews. RA patients with fatigue (≥5/10 on a VAS) completed the questionnaire and comparator fatigue scales with some validity in RA (FACIT(F), MAF, POMS, SF36) and scales measuring disability (HAQ), anxiety & depression (HAD), helplessness (AHI) and pain (VAS). A series of analyses (Cronbach's Alpha for internal consistency, factor analysis for dimensions, bootstrapping for stability of the factor analysis (50 repeat random sets of analyses)) and clinical judgements informed removal of less informative items and retention of more informative items. The resulting BRAF-MDQ was tested for criterion and construct validity (Spearman's correlation with other scales).

Results: 229 patients completed the study (54 males, mean VAS fatigue 7.2). Cronbach's alpha was very high (>0.9) and changed little with removal of the first 20 items. A further 5 items were removed to enhance the stability of repeated subset factor analysis. The resultant 20 item questionnaire retained excellent overall internal consistency (Cronbach's alpha 0.932). The BRAF-MDQ global score has criterion validity, showing good correlation with other fatigue measures: FACIT(F) r=-0.813, MAF r=0.815, POMS r=0.712, SF36 Vitality r=-0.643. Construct validity was shown by moderate associations with related constructs (HAQ r=0.501, Anxiety r=0.517, Depression r=0.627, AHI r=0.563, Pain VAS r= 0.334). Factor analysis consistently showed 4 dimensions: Cognition, containing forget things, concentration, think clearly, lack of mental energy, make mistakes (Cronbach's alpha 0.915); Emotion, containing upset, down / depressed, less control over life, embarrassment (Cronbach's alpha 0.889); Living, containing getting dressed, bath/shower, work/daily activities, social life, refuse invitations, avoid making plans, cancel plans (Cronbach's alpha 0.906); and Physical, containing level, duration and frequency of fatigue, lack of physical energy (Cronbach's alpha 0.713). Correlations between the BRAF-MDQ dimensions and MAF were also good: Cognition r=0.548, Physical r=0.834, Emotion r=0.658 and Living r=0.664.

Conclusion: The BRAF-MDQ is RA-specific was developed from language and concepts generated by patients, has criterion and construct validity, and four dimensions which can be measured separately. Each individual's fatigue experience may be unique. This questionnaire may assist the development of individually tailored fatigue management programmes, focusing on the dimensions of personal importance.

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1205

An Additional Core-Set Generated by People with Rheumatoid Arthritis: RA Patient Priorities for Pharmacological Interventions (RAPP-PI). Tessa Sanderson[1], Marianne Morris[2], Michael Calnan[3], Pamela Richards[4] and Sarah Hewlett[2], [1]University of West England, Bristol, United Kingdom, [2]University of West of England, Bristol, United Kingdom, [3]University of Kent, Canterbury, United Kingdom, [4]University of Bristol, Bristol, United Kingdom

Purpose: Existing core sets of outcomes in RA clinical trials and treatment decisions comprise function, patient global assessment and pain. This study aimed to determine RA patient priorities for treatment outcomes in drug interventions.

Method: A survey comprising 32 outcomes generated and prioritized by patients using interviews and nominal groups[1,2] was posted to RA patients, identified through 3 diverse databases at 3 different UK hospitals, and to people randomly selected from the National RA Society (NRAS) membership database. Patients were asked to rate the importance of each outcome (1-5) for a pharmacological intervention, and to rank their top 6 outcomes (1-6). Demographics, disease activity (DAS patient global VAS, pain Numerical Rating Scale, fatigue NRS and HAQ), self-efficacy (NRS for managing your RA, RASE scale) and well-being (NRS) were measured. Importance and priority scores were calculated, and chi squared tests computed.

Results: 254 surveys were returned, with a mean age of 62.41 yrs (SD 12.39), disease duration of 12.76 yrs (SD 10.64). 51.6% of patients were taking DMARDS, and 39.4% biologic therapies. Using the rankings of top 6 items, the RAPP-PI core set comprises 8 outcomes most highly prioritised by patients: pain, activities of daily living, visible joint damage, mobility, life enjoyment, independence, fatigue, and valued activities. In addition, 3 global outcomes were identified as important to measure from the patient perspective: quality of life, well-being and normality.

Priorities differed across patient and disease characteristics. For example, severe disability was significantly associated with the prioritisation of 'More mobility' (X^2= 24.80) and 'Able to do everyday things' (X^2=11.74), whereas mild disability was associated with the selection of 'Enjoy life' (X^2= 7.67), 'Able to work' (X^2= 17.28), and 'Valued activities' (X^2= 6.98, all $p<0.05$).

Conclusion: The RAPP-PI, a core-set of outcomes generated and prioritized by people with RA, indicates that current drug trials and clinical practice using existing core sets may be leading to treatment decisions based on data that excludes outcomes patients consider important. It is suggested consideration be given to using the additional outcomes of the RAPP-PI. An ongoing study will identify appropriate instruments to measure the RAPP-PI and determine the relative contribution of each outcome to global patient well-being.

[1]Sanderson T et al, Rheumatology 2008; 47 (2): 541
[2]Sanderson T et al, Arth Rheum 2008; 58; 9S: 1903

Disclosure: T. Sanderson, None; **M. Morris**, None; **M. Calnan**, None; **P. Richards**, None; **S. Hewlett**, None.

1206

Economic Modelling in Rheumatoid Arthritis in Real World Practice: The DAS Has Minimal Impact On Hrqol Data Categorized by the HAQ Score. Arto Ohinmaa[1], Liam Martin[2], Anthony S. Russell[3], Susan G. Barr[2] and Walter P. Maksymowych[4], [1]Institute of Health Economics, Edmonton, AB, [2]University of Calgary, Calgary, AB, [3]U Alberta, Edmonton, AB, [4]University of Alberta, Edmonton, AB

Purpose: Little information is available on cost-effectiveness of anti-TNF medications in real world clinical practice. A Provincial prospective observational cohort study of consecutive RA patients starting anti-TNF therapy (infliximab, etanercept or adalimumab) was started in 2004. In many jurisdictions, access to biologics and economic modeling is based on DAS scores. We aimed to assess the relationship between Health Related Quality of Life (HRQOL), the Health Assessment Questionnaire (HAQ), and the Disease Activity Score (DAS28) for use in economic modelling of HRQOL outcomes using data from real world practice.

Methods: Data in the registry is collected at baseline, 3 months, and every 6 months thereafter on patients receiving anti-TNF. Health-related quality of life is measured with the EQ-5D and single index scores were calculated using US value sets. For this analysis, clinical status was categorized into 0.5 units of the HAQ while the DAS28 was categorized according to 0 – 3.19, 3.2 – 5.1 and over 5.1 scores. We analyzed change in the mean EQ-5D index score in HAQ categories over time and determined if the DAS28 affects the distribution of the EQ-5D index in the HAQ categories. An intention-to-treat analysis was conducted up to 21 months of follow-up.

Results: 778 patients started on anti-TNF with mean age 54.4 (SD 14.6) years 69.8% of them being females. Twenty one month outcome data was available from 563 patients. At baseline the EQ-5D index score in the anti-TNF group was 0.483 and improved 0.281 units ($p<0.001$; t-test) during follow up. The results show that the EQ-5D index was consistently higher the better the HAQ index category the patient was in except for category 0 at baseline (Table 1). After baseline the EQ-5D index decreased by increasing DAS28 categories. Within HAQ categories the DAS28 categories did not consistently affect on the mean EQ-5D index scores.

Table 1. Mean EQ-5D index scores in biologics group at baseline and 21 month follow-up by HAQ categories.

HAQ categ.	0	0.01-0.5	0.51-1.0	1.01-1.5	1.51-2.0	2.01-2.5	2.51-3.0	Total
EQ-5D at	0.486	0.775	0.671	0.571	0.449	0.376	0.237	0.483
Baseline	n=7	n=22	n=48	n=91	n=154	n=93	n=33	n=448
EQ-5D at	0.908	0.840	0.758	0.713	0.606	0.540	0.398	0.763
21 months	n=71	n=96	n=95	n=67	n=49	n=14	n=8	n=400

Conclusion: Our data shows a significant shift of the EQ-5D values in different HAQ categories which indicates that it is inappropriate to use the same utility index (EQ-5D) values to measure Quality Adjusted Life Year outcomes at baseline and after starting anti-TNF therapy. The DAS28 has minimal additional impact on HRQOL data categorized by the HAQ score and is therefore much less relevant for economic modelling than the HAQ.

Disclosure: A. Ohinmaa, Schering Canada, Amgen/Wyeth, Abbott labs, 2 ; **L. Martin**, Schering Canada, Amgen/Wyeth, Abbott labs, 2 ; **A. S. Russell**, Schering Canada, Amgen/Wyeth, Abbott Labs, 2 ; **S. G. Barr**, Schering Canada, Amgen/Wyeth, Abbott labs, 2 ; **W. P. Maksymowych**, Schering Canada, Amgen/Wyeth, Abbott Labs, 2 .

1207

Rheumatoid Arthirtis Patients' Interpretation of the DAS Patient Global Used at Bristol Royal Infirmary. Tessa Sanderson[1], Marianne Morris[2], Michael Calnan[3], Pamela Richards[4] and Sarah Hewlett[2], [1]University of West England, Bristol, United Kingdom, [2]University of West of England, Bristol, United Kingdom, [3]University of Kent, Canterbury, United Kingdom, [4]University of Bristol, Bristol, United Kingdom

Purpose: The Disease Activity Score (DAS) provides evidence of clinical need for anti-TNF therapy in the UK, and is a composite score including patient opinion. However, the formulation of the patient VAS may vary between departments and may not capture the intended data. This abstract describes how RA patients interpreted the DAS patient VAS as routinely used at one busy outpatient clinic.

Method: Five focus groups (n=26) were held as part of a larger study for the development of a patient-generated core set of outcomes, purposively sampled for disease duration, disease severity, medication, age, gender and work status. The DAS patient VAS used in the clinic is “Considering all the ways your arthritis affects you, please mark the line to show how well you are doing”. Patients were asked their opinion of what the VAS was intended to measure, and subsequently, whether there was a better way of asking about global health/disease activity from the patient perspective. The discussions were tape recorded, transcribed verbatim and analysed for relevant items.

Results: Patients reported a range of interpretations of what the DAS patient VAS was measuring: general health, coping, emotions, function, and physical status. Speaking generally, one woman said “I think it's taking everything into consideration”. However, most patients gave uni-dimensional responses. Many participants interpreted the VAS as asking about coping or emotion: e.g. “How do you cope with it?” and “For me it's always an emotional thing”. Other patients interpreted the VAS as asking about function or physical status, e.g. “Day to day living”, “How much you can do”, and “If you've got a lot of pain or whatever”.

Many participants felt that a single global question would give an inaccurate answer because it was difficult to assess that global status from dimensions: “You could be alright physically, but not emotionally and you could be different with finances”. Overall, the preference was to have separate questions for different aspects of health: physical, emotional, adaptation, and impact of external stresses. Those on anti-TNF therapy were surprised that the patient opinion in the DAS was not more detailed if their clinical need was to be partially assessed in this way. In relation to the physical scale, one group suggested using the specific words “disease activity” with examples, such as pain, stiffness, swelling, fatigue and ability to carry out everyday activities.

Conclusion: There is evidence that patients interpret the DAS patient global used in this clinic in a range of ways, which may affect their response. The originators of the DAS have states that either the patient’s opinion of general health or disease activity can be used in calculating the DAS28. Efforts should be made to standardise the scale in all clinics and research studies.

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ACR Concurrent Abstract Sessions

Advanced Therapeutic Targeting In Experimental Arthritis
Monday, October 19, 2009, 4:30 PM - 6:00 PM

1208

Absence of Sphingosine Kinase 1 Alters Erosions in TNF-Alpha Induced Arthritis. DeAnna A. Baker, Lina M. Obeid and GS Gilkeson, Medical University of South Carolina, Charleston, SC

Purpose: Sphingolipids are constituents of the plasma membrane. Variations in their cellular levels lead to alterations of cellular functions. Sphingosine 1 phosphate (S1P) *in vitro* is required for TNFa induced production of COX-2 and PGE_2. Additionally, stimulation with TNFa

and S1P together leads to higher production of COX-2 and PGE_2 than either alone. Both sphingosine kinase (SphK) 1 and 2 are upregulated in the rheumatoid synovium compared to osteoarthritis synovium. $S1P_1R$ (EDG1), one of the receptors for S1P, is also upregulated in the joints of rheumatoid arthritis patients. Fibroblast-like synoviocytes (FLS), found in the synovial lining, proliferate in response to proinflammatory cytokines and produce COX-2 and PGE_2 in response to TNFa and S1P. We hypothesized that S1P, induced by TNFa, is a critical mediator of inflammation and joint damage in the rheumatoid joint. The following experiments were performed to test this hypothesis

Method: Transgenic hTNFa mice were crossed with SphK1-/- mice and genotyped by PCR. Arthritis in these mice develops independent of antigen, T cells or B cells. The mice were observed weekly for disease activity, while CT images and microarray analysis were used to evaluate disease activity in the joint and evaluate genetic profiles respectively. Mouse synoviocytes were isolated from the knee joints of WT and SphK1-/- mice, cultured, and stimulated with TNFa. OA and RA human synoviocytes were cultured, and stimulated with hTNFa.

Results: hTNF/Sphk1-/- mice (n=15) had significantly decreased clinical joint disease compared to hTNF/SphK1+/+ mice (n=18), with average arthritis scores of 1+/-0.5 vs. 5+/- 1.2 respectively at 5 months (based on joint swelling and deformity). An erosion Index, measured quantitatively from 3D CT images of the ankles was significantly decreased in hTNF/SphK1-/- mice at 4 and 5 months, with a 2 fold decrease in erosions in hTNF/SphK1-/- vs. hTNF/SphK1+/+ mice. Microarray analysis of ankle joint synovium, with RT-PCR confirmation, demonstrated significant modulation of a cluster of genes regulated by SOCS3 in hTNF/SphK1-/- mice compared to hTNF/SphK1+/+ mice. Synoviocytes from SphK1-/- mice, stimulated with TNFa, produced significantly less IL-6 and PGE_2 than synoviocytes from WT mice. Similarly, human RA synoviocytes stimulated with TNFa and treated with a specific SphK inhibitor produced significantly less IL-6 and PGE_2 than cells treated with TNFa alone.

Conclusion: Genetic deletion of SphK1 significantly decreased the severity of hTNFa induced arthritis, decreased erosions and led to upregulation of SOCS3 with impact on expression of SOCS3 related genes. Lack of SphK1 resulted in decreased PGE_2 and IL6 production by mouse and human synoviocytes in response to TNFa. These data indicate that S1P plays a key role in TNFa induced joint inflammation and erosions and is a potential target for therapeutic intervention in inflammatory arthritis.

Disclosure: D. A. Baker, None; **L. M. Obeid**, None; **G. Gilkeson**, None.

1209

Effective Anti-CD20 Therapy for Arthritis Is Associated with Increased Lymphatic Flow and B-Cell Depletion in Lymph Nodes. J. Li[1], S.T. Proulx[1], Q. Zhou[1], I. Kuzin[1], Robert Dunn[2], R. J. Looney[1], Christopher T. Ritchlin[1], Jennifer H. Anolik[1], I. Sanz[1], A. Bottaro[1], L. Xing[1] and E.M. Schwarz[1], [1]University of Rochester, Rochester, NY, [2]Biogen Idec, San Diego, CA

Purpose: B cell depletion therapy (BCDT) with anti-CD20 is effective for some RA patients; however, questions remain regarding mechanism of action and variability of response. Previously we utilized contrast enhanced (CE) MRI and near infrared (NIR) imaging of footpad injected indocyanine green (ICG) to evaluate arthritis in TNF-Tg mice. The results showed that “expanding” popliteal lymph nodes (PLN) with high lymphatic drainage capacity (LNcap) protect the afferent knee from inflammatory-erosive arthritis. Prior to the onset of synovitis, the PLN “collapses” and this volume change is associated with translocation of B cells into the sinus space, which decreases LNcap and triggers synovitis. Here we test the hypothesis that anti CD20 therapy restores lymphatic function by depletion of B cells from the sinuses of the PLN.

Method: TNF-Tg mice with ankle arthritis, collapsed PLN and baseline NIR-ICG foot pad clearance (Tclear) were treated with anti-CD20 (n=5; 10 knees) (10mg/kg/i.v. every two weeks) or placebo (n=4; 4 knees) for 6 weeks, with CE-MRI every 2-weeks, and terminal Tclear test. Some PLNs were harvested for flow cytometry, and others were analyzed by IHC for IgM, CD20, active caspase-3 and the lymphatic endothelium vessels marker LYVE-1.

Results: CE-MRI revealed two different responses to the anti-CD20. Responders (no synovitis @ 6-weeks; n=7 knees) had sustained LNcap, while non-responders (synovitis @ 6-weeks; n=3 knees) displayed a dramatic decrease in LNcap. Despite this variability, anti-CD20 significantly decreased synovial volume (p=0.02) at 6-weeks, and synovitis over time (p=0.0003), vs. the placebo group, which demonstrated a significant (p=0.0001) 0.81mm3/week increase in synovitis. Effective BCDT also increased lymphatic function (3.3-fold increase in Tcear). Flow cytometry confirmed effective (85-90%%) BCDT in PLN of both responders and non-responders, and staining for various surface markers failed to identify any significant differences in the remaining B cell populations. However, IHC revealed the presence of large numbers of IgM+/CD20-B cells/mm2 in the sinus spaces of placebo (22.1 +/- 5.1) and non-responder (20.9 +/- 1. 9) PLN, while the

sinuses of responder PLN were largely free of B cells (8.3 +/- 2.0; p<0.001). Staining for active caspase-3 demonstrate an 8.6-fold vs. 13.1-fold increase in the number of apoptotic cells in non-responder vs. responder PLN compared to placebo.

Conclusion: These results are consistent with our previous findings indicating that arthritic flares are mediated by centripetal B cell translocation in efferent LN, which obstructs draining lymph from the proximal joint. We also demonstrate a novel mechanism of action for BCDT in which effective clearance of B cells from the LN sinuses restores lymphatic drainage, while inadequate BCDT that fails to clear B cell from the LN sinuses has no effect on lymph drainage or arthritic progression.

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1210

Suppression of Rat Collagen-Induced Arthritis by Lentiviral Vector-Mediated Delivery of Toll-Like Receptor 7 Short Hairpin RNA Gene. Chrong-Reen Wang, Ai-Li Shiau, Shih-Yao Chen, Yi-Syuan Lin and Chao-Liang Wu, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan

Purpose: The effects of Toll-like receptor 7 (TLR7) gene knockdown were examined in a rat collagen-induced arthritis (CIA) model by intra-articular (i.a.) delivery of lentiviral vector-mediated TLR7 short hairpin (sh) RNA gene.

Method: After screenings, the pSuper/TLR7 shRNAs were further cloned into the lentiviral plasmid (Lt.shTLR7). After being immunized with type II collagen on days 0 and 7, SD rats received i.a. injection of Lt.shTLR7 into right ankles and scramble vectors (irrelevant oligonucleotides unable to suppress TLR7 expression) into left ankles on days 7 and 10. Ankle circumference and articular index were evaluated, and joint radiographic examination was done upon sacrifice of rats on day 16. Ankles joints were subjected to H&E stain and immunohistochemical analyses including small vessels and T cells. Western blot and immunohistochemical stain were performed for TLR7 expression on synovium tissues. ELISA was used for quantitation of proinflammatory cytokines (IL-1b, IL-6 and TNF-alpha) and VEGF in joint extracts and culture supernatants from TLR7-transfected synovial fibroblasts (SFs) stimulated with imiquimod or joint extracts containing endogenous TLR7 ligands. RT-PCR of IP-10, a chemokine attracting Th1 cells, was performed for imiquimod-stimulated SFs.

Results: Western blot revealed increased TLR7 expression from day 11. Immunohistochemical stain demonstrated notable TLR7 on synovium tissues and cultured SFs. Significant reductions in ankle circumference and articular index were detected in Lt.shTLR7-treated joints as compared with scramble vector-injected ankles. Radiological and histological scores on day 16 were significantly decreased in Lt.shTLR7-injected ankles. Microvessel densities and VEGF concentrations wthin synovium tissues were significantly lower in Lt.shTLR7-treated joints. VEGF production from imiquimod-stimulated SFs was significantly suppressed in the Lt.shTLR7 transfection group. IL-1beta and IL-6 concentrations were significantly reduced in Lt.shTLR7-injected ankles. IL-6 production from imiquimod-stimulated SFs was significantly decreased in the Lt.shTLR7 transfection group. Addition of ankle joint extracts could significantly up-regulate the production of IL-1beta and IL-6, and treatment with benzonase (a RNase) could significantly down-regulate their production. Furthermore, significantly lower T cell numbers were noted in Lt.shTLR7-treated joints, and the IP-10 induction in imiquimod-stimulated SFs was clearly demonstrated by RT-PCR.

Conclusion: These data demonstrated the effects of local injection of lentiviral vector-mediated delivery of shTLR7 RNA gene on inhibiting ankle arthritis of CIA rats. Our *in vivo* animal studies reveal the potentiality of TLR7 molecule as a future target for RA therapy.

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1211

Suppression of Collagen-Induced Arthritis by Natural Killer T Cell Activation with α-Carba-GalCer, a Novel Synthetic Glycolipid Ligand. Yohei Yoshiga, Daisuke Goto, Seiji Segawa, Makoto Sugihara, Taichi Hayashi, Yusuke Chino, Isao Matsumoto, Satoshi Ito and Takayuki Sumida, University of Tsukuba, Tsukuba, Japan

Purpose: Alpha-carba- galactosylceramide (GalCer), a novel synthetic analog of α-GalCer, stimulates natural killer T (NKT) cells to produce predominatly interferon (IFN)-γ. IFN-γ has been known to suppress T helper (Th) 17 cells differentiation. Thus, we think that α-carba-GalCer may be a potential agent for the treatment of Th17-mediated autoimmune diseases. This study was designed to evaluate the protective effects of α-carba-GalCer on collagen-induced arthritis (CIA) in mice.

Methods: 1) We injected glycolipid ligand into naïve DBA/1 mice, and cytokines in the serum were analyzed by enzyme-linked immunosorbent assay (ELISA). Naïve splenocyes were stimulated with glycolipid ligand and cytokine levels in cultures were determined by ELISA. 2) To clarify the effect of α-carba-GalCer on CIA, DBA/1 mice were immunized with bovine type II collagen (CII) with glycolipid, and we monitored the incidence and clinical symptom of disease. 3) To neutralize IFN-γ, anti-IFN-γ monoclonal antibody (mAb) was administered intraperitoneally (i.p.) at the same time of CII/glycolipid injection. 4) To examine CII-reactive T cell response, draining lymph node (DLN) cells from glycolipid treated mice were re-stimulated with CII in vivo. Anti-CII Ab titer in the serum from glycolipid treated mice were determined by ELISA. Frequency of memory/activated and Foxp3+ regulatory T cell were determined by flow cytometory. The function of antigen-presenting cells (APCs) was analyzed by the capacity of stimulation of CD4 T cells in vitro.

Results: 1) Alpha-carba-GalCer selectively induced IFN-γ compared with α-GalCer in CIA-susceptible DBA/1 mice in vivo/in vitro. 2) The mice treated with α-carba-GalCer exhibited lower incidence and clinical score of CIA. In addition, lower anti-CII antibody production was observed in α-carba-GalCer treated mice. 3) Interferon-γ neutralization at the time of CII immunization abolished the suppressive effect of α-carba-GalCer 4) We found the decreased number of Th1 and Th17 cells in DLN cells from α-carba-GalCer treated mice. However, the number of memory/activated and Foxp3+ regulatory T cells, and the function of APCs were not affected by α-carba-GalCer treatment.

Conclusion: These findings suggest that α-carba-GalCer activated NKT cells could protect CIA via the selective production of IFN-γ.

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1212

FLIP: The Master Regulator of Myeloid Differentiation and Survival-A Novel Therapeutic Target in Chronic Inflammation. Qi Quan Huang[1], Zan Huang[1], Robert Birkett[1], Lixin Kan[1], Sandeep Gurbuxani[2], John Crispino[1], Harris R. Perlman[1] and Richard M. Pope[1], [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]University of Chicago, Chicago, IL

Purpose: Macrophages are important mediators of chronic inflammation, and in rheumatoid arthritis synovial tissue macrophage apoptosis is inappropriately reduced. FLIP, an anti-apoptotic molecule induced by chronic inflammation, protects against death receptor mediated apoptosis. However, its essential *in-vivo* functions in the myeloid cell lineage have not been characterized. We have generated and characterized a mouse line with FLIP conditionally deficient in the myeloid lineage.

Method: Mice bearing floxed *flip* (*flip*^{f}) were employed to generate one allele of *flip* deleted (*flip*^{d}) and one floxed (*flip*$^{d/f}$). These animals were then crossed with LysM-cre mice to generate *flip*$^{f/d}$LysMcre$^{+/-}$ mice with FLIP knockout (KO) in myeloid cells. The mice were examined for complete blood count, serum cytokine concentrations, FLIP expression, linage-restricted colony-forming progenitors. Tissues were examined by flow cytometry, immunohistochemistry, and bacterial culture. Granulocytes were analyzed for apoptosis by Annexin V and Rhodamine 123. Serum transfer mouse model of arthritis was induced with anti-GPI serum.

Results: Myeloid specific KO mice exhibited severe postnatal growth retardation and premature death, but no indication of embryonic lethality. KO mice had significantly reduced body weight (50% that of control group), and 50% died before 7 months of age. There was a dramatic increase in neutrophils (>10 fold) in the peripheral blood, which was accompanied by multi-organ neutrophil infiltration. The neutrophils demonstrated a mature morphology and underwent normal apoptosis and oxidative burst response. The F4/80^{high} subset of macrophages was greatly reduced in the spleen and peritoneal cavity, both spontaneously and induced. KO mice exhibited splenomegaly with altered architecture, a marked reduction of B cells and extramedullary hematopoiesis. 30% of KO mice exhibited systemic infection with commensal intestinal flora such as entercocci and proteius species. Serum from KO mice exhibited significantly increased G-CSF (14.5 fold) and inflammatory cytokines TNF-alpha (10 fold) and IL-6 (25 fold). Nonetheless, when induced by anti-GPI serum, KO mice developed significant less severe arthritis.

Conclusion: The myeloid specific deletion of FLIP results in a massive systemic increase of neutrophils, a reduction of macrophages in the spleen and peritoneal cavity, and a reduction of serum transfer arthritis. These studies identify FLIP as a master regulator of myeloid cell differentiation and survival and identify macrophage expressed FLIP as a therapeutic target in chronic inflammation.

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1213

Specific Targeting of TNF Receptor I in Synoviocytes or Antigen-Presenting Cells in Secondary Lymphoid Organs Ameliorates Collagen-Induced Arthritis. Onno J. Arntz, Jeroen Geurts, Sharon Veenbergen, Miranda B. Bennink, Wim B. van den Berg and Fons A. van de Loo, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose: TNFα is a pleiotropic cytokine that plays a key role in RA and TNF blockade serves as the main biological therapy in RA patients. Signaling is mediated via two receptors (TNFRI/II) and the relative abundances of these determine the effects on different cell types. Recently it is shown that targeting of TNFRI in hematopoietic cells, i.e. leukocytes, aggravates disease in collagen-induced arthritis (CIA) [1]. Using RNA interference as a gene therapeutic strategy we investigated the role of TNFRI specifically in synoviocytes and antigen-presenting cells (APCs) in liver and spleen during experimental arthritis.

Methods: An adenoviral vector containing a short hairpin (sh) RNA was constructed and the functionality was evaluated *in vitro* and *in vivo* using qPCR and reporter assays. For targeting of synoviocytes or APCs viruses (scrambled- and TNFRI-shRNA) were injected intra-articularly or intravenously, respectively, shortly before CIA onset. Effects of TNFRI targeting were evaluated using macroscopic scoring of CIA progression, qPCR, histological and cytokine analyses and T-cell assays..

Results: *In vitro* TNFRI expression (mRNA) was three-fold downregulated resulting in a 70% reduction of TNF-induced activation of the pivotal pro-inflammatory transcription factor NFκB. Expression in synoviocytes and APCs was three- and eight-fold diminished, respectively. TNF-induced production of IL-6 was significantly reduced in splenic APCs. Targeting of TNFRI in synoviocytes resulted in a local protection against CIA, supported by a strongly reduced mRNA and protein levels of TNFα, IL-1β and IL-6. Knockdown of TNFRI in splenic and hepatic APCs led to an impressive amelioration of CIA. This led to a significant decrease of joint inflammation and cartilage erosion. Expression of IL-1β, IL-6 and the acute phase protein Saa1 were strongly reduced (75%) in liver. In the spleen, we observed a decreased expression of Th1/2/17-specific transcription factors T-bet, GATA-3 and RORγT. FACS analysis confirmed a reduced amount in the numbers of IFNγ (Th1), IL-4 (Th2) and IL-17 (Th17) producing cells in spleen.

Conclusion: In this study we showed that TNFR1 signaling mediates a clear pro-inflammatory response in synoviocytes and APCs in secondary lymphoid organs. This highlights that cell-specific targeting is of crucial importance for therapeutic strategies aimed at blockade of TNFRI-mediated signaling.

[1] Williams-Skipp et al.: Unmasking of a protective tumor-necrosis factor-receptor I-mediated signal in the collagen-induced arthritis model. Arthritis Rheum 2009;60:408-18

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ACR Concurrent Abstract Sessions

Clinical Aspects of the Antiphospholipid Syndrome

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1214

Antiphospholipid Antibodies Predict Future Arterial Events. Carolyn Neville[1], Joyce Rauch[1], Jeannine Kassis[2], Susan Solymoss[1], Lawrence Joseph[3], P. Belisle[3] and P. R. Fortin[4], [1]McGill University, Montreal, QC, [2]Université de Montréal, Montreal, QC, [3]MUHC, Montreal, QC, [4]U. Toronto, Toronto, ON

Purpose: To determine the role of antiphospholipid antibodies (aPL) in predicting new arterial (VE-A) and venous (VE-V) vascular events in an ongoing prospective cohort of individuals.

Method: Demographic and clinical data were obtained at baseline and semiannually. All events were confirmed by consensus with medical record review by a panel of physicians. Blood samples were collected at baseline and annually for four years, and stored frozen at -70°C. Assays performed included: IgG/IgM anticardiolipin antibodies (aCL), lupus anticoagulant (LA), and IgG/IgM anti-b2-glycoprotein I antibodies (aβ2GPI). Kaplan-Meier and proportional hazard survival analyses were used to compare the time to new VE-A or VE-V in aPL-positive (defined as aCL IgG/IgM >40, LA, and/or aβ2GPI positive) versus aPL-negative individuals. Multivariate regression analyses were performed using new VE-A or VE-V as outcome variable and aPL positivity as predictor variable. Covariates for outcome VE-A were age, gender, family history of CVD (FMH), smoking, systemic lupus erythematosus (SLE), hypertension (HTN), diabetes mellitus (DM), smoking, previous VE-A, activated protein C resistance (APCR), and hyperhomocysteinemia. Covariates for outcome VE-V were age, gender, SLE, previous VE-V, anticoagulation therapy (ACT), APCR, antithrombin III, factor V Leiden mutation and MTHFR mutations.

Results: 414 persons enrolled in 1997 with mean (SD) age 46.4 (14.1) years, 83.1% female; 53.3% had FMH, 20.5% had SLE, 27.8% were smokers, 15.9% had HTN, 5.6% had DM, and 16.4% had had previous vascular events (VE). Fifty-nine (14%) individuals were aPL-positive at baseline, and 38 more became aPL-positive during follow-up for a total of 97 (23.4%). During 11 years of follow-up (median 9.5 [IQR=4.0, 10.6] years), 52 (12.6%) individuals sustained 78 new events (36 had VE-A; 17 had VE-V; 2 had both). The proportion of VE-free survivors at 10 years was 88% (95%CI=84%, 92%) for aPL-negative and 67% (95%CI=54%, 81%) for aPL-positive individuals. The proportion of VE-A-free survivors at 10 years was 91% (CI = 88%, 95%) for aPL-negative and 76% (CI = 65%, 89%) for aPL-positive individuals. For VE-V-free survivors, the proportions were 97% (CI = 95%, 99%) for aPL-negative and 83% (CI = 73%, 95%) for aPL-positive individuals. Multivariate regression analyses revealed that VE-A were predicted by aPL positivity [HR= 2.52 (CI=1.17, 5.47)], age [HR=1.05 (CI=1.02, 1.07)], DM [HR=3.93 (CI=1.66, 9.32)], smoking [HR=2.31 (CI=1.15, 4.64)], and previous VE-A [HR=4.77 (CI=2.32, 9.82)]. While the effect of aPL positivity on VE-V cannot be accurately estimated from our data [HR=1.86 (CI=0.67, 5.20)], VE-V were predicted by previous VE-V [HR=4.00 (CI=1.35, 11.87)], ACT [HR=4.60 (CI=1.50, 14.08)], and APCR deficiency [HR=5.21 (CI=1.95, 13.90)].

Conclusion: aPL positivity independently predicts VE-A, whereas the effect of aPL on VE-V is less clear.

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1215

Association of Traditional and Novel Antiphospholipid Antibody Assays with Thrombosis in SLE. Ehtisham Akhter[1], Walter L. Binder[2], Zakera Shums[2], Laurence Magder[3] and Michelle Petri[4], [1]Johns Hopkins University, Baltimore, MD, [2]Inova Diagnostics Inc, San Diego, CA, [3]University of MD, Baltimore, MD, [4]Johns Hopkins Univ, Baltimore, MD

Purpose: The current APS classification criteria recognize the lupus anticoagulant, anticardiolipin (aCL) and anti-beta2 glycoprotein I (anti-beta2). We determined the association of anti-phosphatidylserine-prothrombin (PSPT) and D4/5 IgA (directed against the domain 4/5 fragment of beta2-GPI), as well as anti-beta2 and aCL, with thrombosis in SLE.

Method: Stored sera from 314 SLE patients in a prospective database were studied. 206 had a history of thrombosis (87% female, 43% African-American, 50% Caucasian) and 108 did not (45% female, 31% African-American, 53% Caucasian). Assays were performed at INOVA Diagnostics, Inc. **Results:** Comparison of those with and without history of any type of thrombosis with respect to the percent positive for each antibody.

	Thrombosis (n = 206)	No thrombosis (n = 108)	P-value	P-value when age, sex, and race are controlled
Assay	Number (% positive)	Number (% positive)		
anti-beta2 IgA	45 (22 %)	16 (15%)	0.18	0.23
anti-beta2 IgG	24 (12%)	3 (3%)	0.010	0.021

anti-beta2 IgM	18 (8%)	4 (4%)	0.11	0.12
aCL IgA	9 (4 %)	1 (1%)	0.171	0.21
aCL IgG	30 (15%)	5 (5%)	0.008	0.016
aCL IgM	27 (13%)	7 (6%)	0.086	0.11
anti-PSPT IgG	47 (23%)	10 (9%)	0.003	0.001
anti-PSPT IgM	43 (21%)	8 (7%)	0.002	0.011
D4/5 IgA	36 (18%)	16 (15%)	0.63	0.71

Comparison of those with and without a history of venous thrombosis with respect to the percent positive for each antibody.

	Venous Thrombosis (n = 123)	No venous thrombosis (n = 191)	P-value	P-value when age, sex, and race are controlled
Assay	Number (% positive)	Number (% positive)		
anti-beta2 IgA	29 (24 %)	32 (17%)	0.14	0.20
anti-beta2 IgG	19 (15%)	8 (4%)	0.001	0.005
anti-beta2 IgM	11 (10%)	10 (5%)	0.17	0.20
aCL IgA	5 (4 %)	5 (3%)	0.52	0.53
aCL IgG	22 (18%)	13 (7%)	0.003	0.006
aCL IgM	15 (12%)	19 (10%)	0.58	0.63
anti-PSPT IgG	34 (28%)	23 (12%)	0.001	0.001
anti-PSPT IgM	27 (22%)	24 (13%)	0.041	0.13
D4/5 IgA	20 (16%)	32 (17%)	1.00	0.94

No assay was significantly associated with history of arterial thrombosis.

Conclusion: For any thrombosis, the anti-PSPT assay performed the best after adjustment for age, sex, and race. For venous thrombosis, anti-beta2 GPI, aCL, and anti-PSPT IgG assays performed equivalently. For IgM assays, only the anti-PSPT was significantly associated with thrombosis. This study suggests that anti-PSPT may have value in APS in SLE, and that only IgG assays may be cost-effective.

Disclosure: E. Akhter, None; **W. L. Binder**, INOVA Diagnostics, , Inc , 4 ; **Z. Shums**, Inova Diagnostics, Inc., 3 ; **L. Magder**, None; **M. Petri**, None.

1216

Antiphospholipid Score (aPL-S) in the Antiphospholipid Syndrome: Diagnostic Significance and Predictive Value for the Development of Thrombotic Events in Autoimmune Diseases. Kotaro Otomo, Tatsuya Atsumi, Yuichiro Fujieda, Masaru Kato, Eriko Miyamoto, Kenji Oku, Olga Amengual, Hiroshi Kataoka, Tetsuya Horita, Shinsuke Yasuda and Takao Koike, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: 1) To define the Antiphospholipid Score (aPL-S) by testing multiple antiphospholipid antibodies, and 2) to evaluate its efficacy for the diagnosis of antiphospholipid syndrome (APS) and predictive value for the development of thrombotic events in autoimmune diseases

Method: 1) From our database of autoimmune disease clinic, the results of antiphospholipid antibodies in 233 patients were used to define aPL-S. Five clotting assays (the mixing studies: activated partial thromboplastin time (APTT), kaolin clotting time, the dilute Russel's viper venom test (dRVVT), and the confirmatory tests: APTT and dRVVT) and 6 ELISAs (IgG/M anticardiolipin antibodies, IgG/M anti-beta2-glycoprotein I antibodies and IgG/M phosphatidylserine dependent antiprothrombin antibodies) were analyzed. The aPL-S was calculated according to the number of positive tests and their titers (range 0-83), and compared with the history of thrombosis/pregnancy morbidity. 2) For further analysis, we retrospectively explored the predictive value of aPL-S for thrombotic events. This part of the study comprised 221 patients with autoimmune diseases (12 primary APS, 16 APS with systemic lupus erythematosus and 193 other autoimmune diseases). The aPL-S in 2002 was evaluated in all subjects. Among all the patients, 174 (78%) were followed-up with a mean duration of 66 ±16 months. To calculate the predictive value, the aPL-S was compared with the development of thrombotic events during the follow-up period.

Results: 1) The aPL-S was higher in patients with thrombosis/pregnancy morbidity (n=46) than in those without (22.3±26.3 vs. 4.13±10.8, p=0.00001). For the diagnosis of APS, the receiver operating characteristics (ROC) curve of aPL-S showed hyperbolic, and the area under the ROC curve (ROC AUC) are 0.752 and 0.686 for the aPL-S and for the Sydney revised Sapporo criteria, respectively. The prevalence of thrombosis/pregnancy morbidity was correlated with the levels of aPL-S (Figure). 2) Seventeen patients newly developed thromboses; 10 arterial and 10 venous thromboses. Although 18 out of 19 patients with aPL-S >30 received antithrombotic therapy (4 anticoagulant therapies, 14 antiplatelet therapies and 2 both therapies), six of them developed 8 thrombotic events during the follow-up. Patients with aPL-S >30 had a higher risk of thrombosis than those without (Odds-Ratio: 6.04[95%CI: 1.92-18.99, p=0.004]).

Conclusion: The aPL-S is a useful quantitative index for diagnosing APS, and may be a predictive marker of thrombosis in autoimmune diseases.

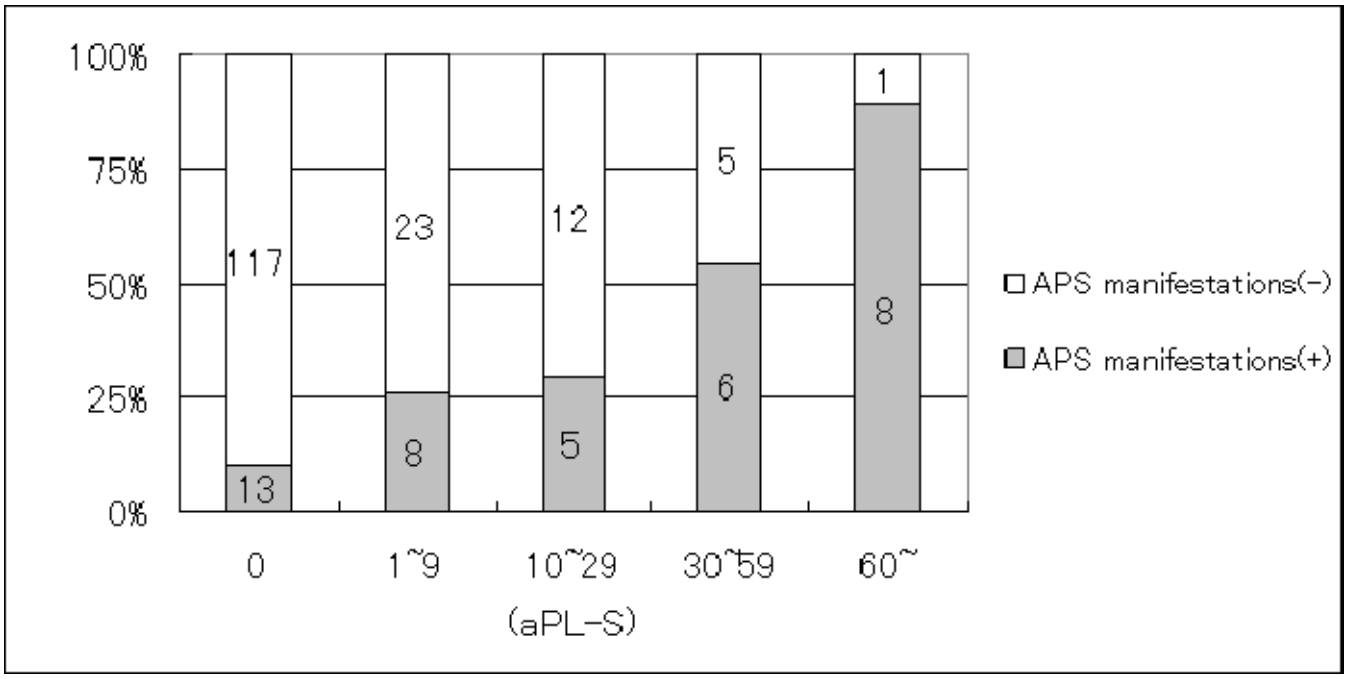

Figure: The bar charts indicate the percentages of the prevalence of APS manifestations in each groups of aPL-S. The values inside the bar indicate the number of the patients.

Disclosure: K. Otomo, None; **T. Atsumi**, None; **Y. Fujieda**, None; **M. Kato**, None; **E. Miyamoto**, None; **K. Oku**, None; **O. Amengual**, None; **H. Kataoka**, None; **T. Horita**, None; **S. Yasuda**, None; **T. Koike**, None.

1217

End-Stage Organ Damage and Mortality in Patients with Antiphospholipid Syndrome (APS): Prognostic Models for Serious Clinical Outcomes. Eleftheria P. Grika[1], Elias Zintzaras[2], Haralampos M. Moutsopoulos[3] and Panayiotis G. Vlachoyiannopoulos[3], [1]School of Medicine,National University of Athens, Greece, [2]School of Medicine, University of Thessaly,Larissa, Greece, Greece, [3]School of Medicine, National University of Athens, Athens, Greece

Purpose: APS is characterized by the presence of anti-phospholipid antibodies and recurrent venous (VT) and/or arterial thrombosis (AT) and/or pregnancy morbidity (PM). Prognostic factors for serious clinical outcomes; description of end-stage organ damage, mortality and reasons for death in consecutive patients with APS.

Method: Descriptive analysis of 135 patients (100 female, 35 male), 89 with primary and 46 with APS secondary to systemic lupus erythematosus (SLE) (average follow-up = 7.5 years, mean age ± SD=33.6± 11.8 years). Patterns of evolution according to initial event and the prevalence of organ damage were studied. Categorical data were compared between groups by Chi-square test and continues data with one-way analysis of variance with post-hoc test and Bonferroni's correction. Associations between initial and second event were tested using a log-lineal model and expressed as odds ratios (ORs) with their respective 95% confidence interval. Differences between initial events in proportion of undesired events over time were compared using a Kaplan-Meier survival analysis with an extension of Gehan's generalized Wilcoxon test.

Results: The patients were clustered according to their initial event relevant to APS; AT (n=15), VT (n=53), Stroke (S) (n=31) or PM (n=36). The diagnosis of SLE was rather common in those with S (52%) and PM (36%) vs those with VT (28%) and AT (13%) (p=0.051).Major organ involvement accounts mainly for patients with S (29%) vs those with PM (5%), VT (6%) and AT (13%) (p=0.008).The time for presentation of a second unwanted event did not differ if the first event was VT, AT or S or any other event. Patients with AT/S, as an initial event have a 5-fold chance to experience AT in the future [OR=5.091(1.120, 23.142) (p=0.035)] while patients with VT have a 6-fold chance to experience VT [OR=5.571(1.325, 23.435) (p=0.019)]. The prevalence of traditional risk factors for arterial occlusion in AT patients did not differ from that of the remaining patients. Twenty out of 46 patients with AT/S (43%) and 26 out of 53 patients with VT (49%) experienced a second thrombotic event; 17% and 19% of whom respectively occurred under intense anticoagulation. Anticoagulation after initial events lengthened thrombosis free survival (p< 0.008) as compared to no therapy. A total of 34 patients (25%) experienced end stage organ disease or died as follows: heart failure (n=2), renal failure (n=5), severe pulmonary arterial hypertension (n=3), movement or gait disability (n=22), cognitive dysfunction and dementia (n=8), amputation (n=3) and death [(n=5), catastrophic APS (n=3), pulmonary emboli (n=1) and acute pulmonary oedema (n=1)].

Conclusion: The pattern of initial involvement predicts the outcome of patients with APS . The syndrome is a cause of high morbidity and mortality among young individuals, despite current therapy.

Disclosure: E. P. Grika, None; **E. Zintzaras**, None; **H. M. Moutsopoulos**, None; **P. G. Vlachoyiannopoulos**, None.

1218

Simvastatin and Hydroxychloroquine Can Prevent the Procoagulant/Thrombogenic Properties of Antiphospholipid Antibodies in Monocytes. Anastasia Lambrianides[1], Katie Bell[2], Silvia S. Pierangeli[3], David S. Latchman[4], David A. Isenberg[1], Anisur Rahman[1] and Ian P. Giles[1], [1]University College London, London, England, [2]University College London, London, United Kingdom, [3]University of Texas Medical Branch, Galveston, TX, [4]DSc, FRCP, London, United Kingdom

Purpose: A major mechanism of hypercoagulability in the antiphospholipid syndrome (APS) is antiphospholipid antibody (aPL)-mediated up-regulation of tissue factor (TF) on monocytes. Recent attention has been focused on other therapeutic tools for the APS to ameliorate the risk of the hemorrhagic compications associated with the use of anticoagulant drugs currently used for treatment. Statins are potent inhibitors of cholesterol synthesis and have been shown to modify the function of endothelial cells and platelets by decreasing the expression of adhesion molecules, inhibiting TF expression and down-regulating inflammatory cytokines after treatment with aPL. Similarly, hydroxychloroquine (HCQ) has been shown to reduce the extent of thrombosis in an animal model of injury-induced thrombosis in APS and reversed aPL-induced platelet activation. The aim of this study was to determine whether simvastatin and HCQ have an effect on the APS-IgG-mediated up-regulation of p38MAPK and NFκB signalling pathways and TF activity in monocytes.

Method: We purified IgG from 7 APS patients with vascular thrombosis (VT) and 7 healthy controls. A human monocyte cell line was treated with 100μg/ml IgG for 6 hours. In some experiments, cells were pretreated with simvastatin or pravastatin (5μM) with or without mevalonate (100μM) or with HCQ (1μg/ml). The cell extracts were examined by immunoblot using total and phospho-specific antibodies to p38MAPK and NFκB p65. TF was extracted from the cell lysates and monocyte TF activity was determined using a chromogenic assay that measures factor Xa after activation by the TF-factor VII complex.

Results: IgG from patients with VT increased the up-regulation of p38MAPK, NFκB and TF activity in monocytes. Simvastatin and HCQ decrease the APS-IgG-mediated phosphorylation of phospho-p38MAPK and phospho-NFκB. Simvastatin inhibited the effects of APS-IgG on TF activity by 60% and 50% respectively, to levels comparable with healthy control IgG. Mevalonate only partly abrogated the inhibitory effects of simvastatin and the APS-IgG-mediated TF activity was restored to 75%. HCQ completely inhibited the up-regulation of TF activity produced by APS-IgG from patients with VT.

Conclusion: Our findings demonstrate, for the first time, that statins and HCQ inhibit the APS-IgG-mediated up-regulation of p38MAPK and NFκB and TF activity in monocytes and support the possibility that these drugs may offer an alternative nonanticoagulant therapeutic approach for treating APS.

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1219

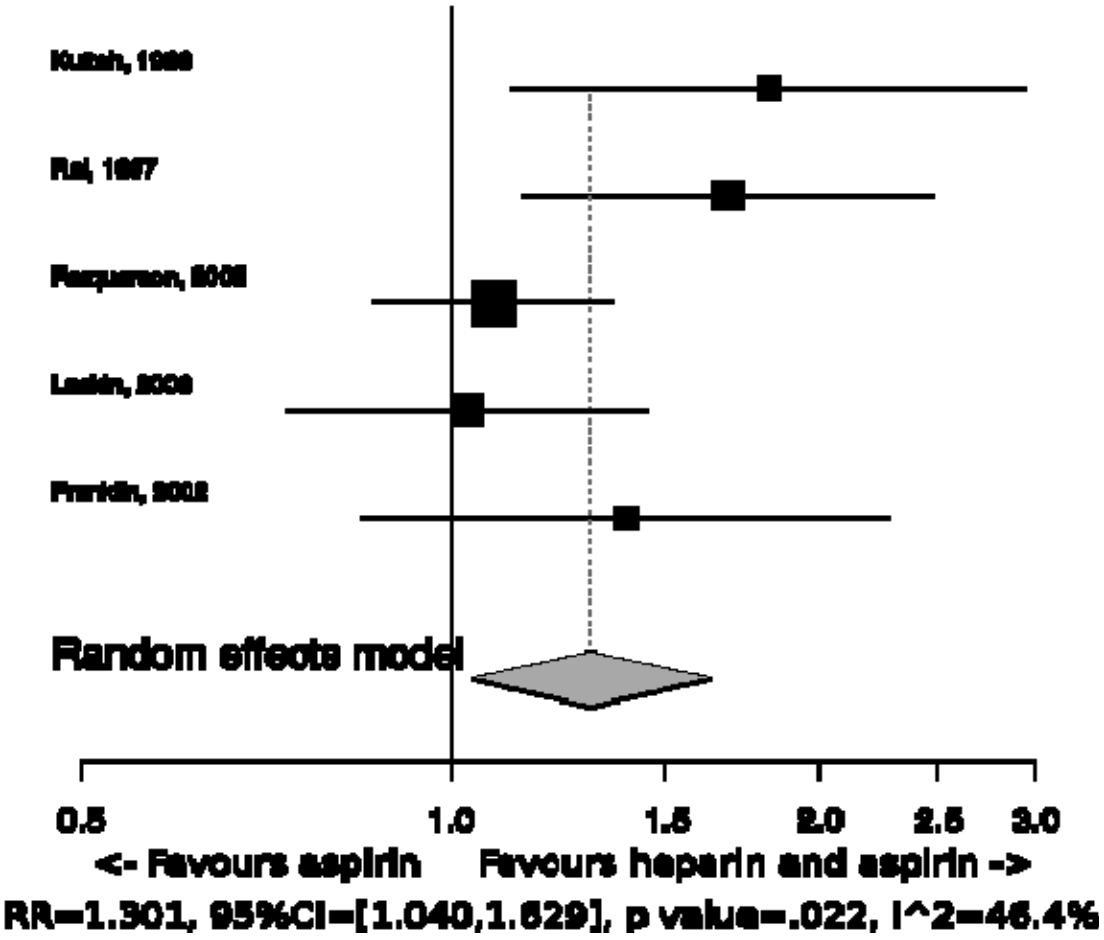
Combination of Heparin and Aspirin Is Superior to Aspirin Alone in Enhancing Live Births in Patients with Recurrent Pregnancy Loss and Positive Antiphospholipid Antibodies: a Meta-Analysis of Randomized Controlled Trials and Meta-Regression. Anselm Mak[1], Alicia AC Cheak[1] and Roger CM Ho[2], [1]National University of Singapore, Singapore, Singapore, [2]National University of Singapore, Singapore

Purpose: The combination of heparin and aspirin was regarded as the "standard therapy" for patients with recurrent pregnancy loss and positive antiphospholipid antibodies but it largely stems from expert opinion. We performed a meta-analysis of randomized controlled trials (RCTs) to assess whether such a combination works better than aspirin alone in enhancing live births and reducing obstetrical complications in these patients.

Method: RCTs investigating the safety and efficacy of heparin and aspirin versus aspirin alone were searched in electronic databases using the keywords "antiphospholipid", "pregnancy", "heparin", "aspirin", "antiplatelet", "lupus" and "anticoagulants". The primary outcome was proportion of live births. The secondary outcomes were obstetrical complications and birth weight. Outcomes were pooled for relative risks (RR) [and 95% confidence interval (CI)] for live births and obstetrical complications while standardized mean difference (SMD) was pooled for birth weight, using the random effects model. Meta-regression was performed to identify factors associated with the primary outcome.

Results: Five trials involving 334 patients were analyzed in this meta-analysis. Of these patients, 171 received heparin and aspirin while 163 took aspirin only. The overall live-birth rates were 74.27% and 55.83% in patients who received heparin/aspirin combination and aspirin alone respectively. Using the random effects model, patients who received heparin and aspirin had significantly higher live-birth rate (RR 1.301; 95% CI 1.040-1.629) than those on aspirin alone (see Figure for Forest Plot). The number needed to treat by adding heparin to aspirin to achieve one live birth was 5.6. There were no significant differences in birth weight (SMD 0.084; 95% CI -0.239-0.408) and the risks of preeclampsia (RR 0.471; 95% CI 0.096-2.314) and preterm labour (RR 1.027; 95% CI 0.399-2.645) between both groups. Meta-regression using age at randomization, previous history of live births and early and late miscarriages as covariates failed to predict the RR of live birth.

Conclusion: Combination of heparin and aspirin is superior to aspirin alone in achieving more live births in patients with positive antiphospholipid antibodies and recurrent pregnancy loss.



Disclosure: A. Mak, None; **A. A. Cheak**, None; **R. C. Ho**, None.

ACR Concurrent Abstract Sessions

Education

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1220

Training, Practice and Assessment of Arthrocentesis Procedure Skills without Risk to a Patient. Richard Brasington[1], Jane Miller[2], Vic Spitzer, V. M. Holers[3], Ann Sherzinger, Adam Lawson and Maren L. Mahowald[4], [1]Washington Univ Schl of Med, St Louis, MO, [2]University of Minnesota, [3]U Colo Denver, Aurora, CO, [4]Univ of MN, Minneapolis, MN

Purpose: The 'See One, Do One, Teach One' method for learning arthrocentesis is no longer acceptable because of risk to patients. However, trainees are not able to practice these procedures with sufficient repetition and supervision on patients to become proficient (Roberts et al 2002), and there is no objective, standardized method to document that the trainee is competent to perform these procedures independently. We developed a Virtual Reality-Based Joint Injection Simular (VR-JIS) (Touch of Life Technologies, Inc.) with haptically enabled virtual palpation and needle insertion for repeated simulated arthrocenteses.

Methods: As part of a systematic process of simulator validation and development of an Arthrocentesis Competency Level Assessor, we designed a "mini-Arthro CEX to use with the VR-JIS. A field test was carried out with 15 trainees in a regional ROSCE for 5 US rheumatology training programs. Using a haptically enabled virtual syringe and palpation device, the trainee attempted to locate the landmarks for anterior entry into the glenohumeral joint, to advance the needle into the virtual joint, and withdraw virtual fluid. Pre-specified performance metrics were assessed by the computer and by observational assessment. Each metric was scored on a 9 point Likert scale by a senior rheumatologist with extensive experience with arthrocentesis and using the simulator.

Results: Two clinical evaluators piloted a 13-item dichotomous checklist to establish a performance baseline as part of a validation study of the VR-JIS. An educational consultant collected field notes describing the conditions of each of the 15 residents' encounters with the simulator. Each of the residents was oriented briefly to the simulator. Nine of 15 fellows needed direction during each procedure. Most expressed discomfort and/or confusion over the virtual anatomical landmarks as represented on the simulator. Expert evaluators concluded that trainees would need more time practicing on the simulator prior to competency assessment and more time for immediate feedback and opportunity to repeat the procedure if they fail. Future field tests will include a revised assessment tool for clinical evaluators, modification of the tactile reality and more robust evaluation of the simulator by trainees.

Conclusion: The VR-JIS is a unique technology for arthrocentesis training and and practice as well as a method for objective competency testing without concern for patient disomfort. The simulator provides an objective consistent testing paradigm for multiple trainees and the Arthro-CEX contains a set of standard procedure metrics for preceptor assessment. Problems encountered included: 1)electronic complexity of the VR-JIS, 2)time required for the trainee to become oriented to using the VR-JIS, and 3) expense and fragility of the haptic devices. Thi work was supported by an NIH/SBIR Grant

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1221

An Evaluation of Knee Arthrocentesis Videos On YouTube for Content, Technical, and Instructional Quality. Paul Sufka[1] and Anne G. Minenko[2], [1]University of Minnesota, Minneapolis, MN, [2]University of Minnesota, MN

Purpose: The Internet is a growing resource of instructional medical procedural videos. Unrestricted by time or place, viewers can access knee arthrocentesis videos as unregistered users on non peer-reviewed public websites e.g. YouTube. To our knowledge, there is no instructional arthrocentesis video evaluation instrument. The purpose of this project is to review arthrocentesis videos currently on the Internet and evaluate them for content, technical, and instructional quality.

Method: YouTube, the public video sharing website, was searched on June 15, 2009, using the terms "knee arthrocentesis" or "knee aspiration". Data for determination of video length, viewership rate, and author credential were collected.

Videos were independently evaluated by one medical resident and one Rheumatology faculty:

a) **for content** using a 16 item checklist based on the New England Journal of Medicine[1] (NEJM) website knee arthrocentesis video (indications, contraindications, equipment needed, obtaining consent, limb positioning, identification of anatomy, skin cleansing, draping, anesthetics, needle direction/insertion, removal of fluid, instruction on "milking" the knee effusion, needle removal/safety, post-procedure care, fluid handling, complications)

b) **for instructional quality** by assigning the highest level achieved on Bloom's taxonomy/cognitive domain (from lower to higher levels of behavior: knowledge, comprehension, application, analysis, evaluation, creation)

c) **for technical visual and audio quality**.

Results:

The **NEJM video** was longest at 6:23, and was assigned the highest learning behavior category level of "analysis".

Seven **YouTube videos** (Table) were evaluated after excluding 2: one copied from NEJM, a second without audio. Compared to the video on NEJM, the 7 videos on YouTube vary in length (0:31–4:51), viewership (1–33.6 views/day), author credential (commercial, physician,

university residency), number of content items addressed (3–11), and highest level of cognitive learning behavior achieved. One commercial video, 1:32 in duration addressing 5/16 content items, reached the same level (analysis) of cognitive learning behavior as the 6:23, 16 item NEJM video.

Video technical quality was fair-good. Consistency of evaluation between the 2 resident/faculty raters was excellent.

Video	Length	Views/day	Author Credential	Content Items	Highest Learning Behavior Level
1	0:38	6.5	Commercial	4	Comprehension
2	0:31	1.0	Commercial	3	Application
3	4:51	4.1	University Residency	11	Application
4	0:35	2.9	Physician	4	-
5	1:32	6.7	Commercial	5	Analysis
6	0:25	9.7	Physician	3	-
7	0:34	33.6	Physician	3	-
8					Excluded (copied from NEJM)
9					Excluded (no audio)
NEJM	6:23		University Residency	16	Analysis

Conclusion: This sample of knee arthrocentesis videos published on the NEJM and YouTube websites are at best of moderate instructional quality. For the Internet's potential as a learning resource beyond convenience to be realized, authors of procedural videos should challenge themselves to produce higher quality instructional materials.

Disclosure: P. Sufka, None; **A. G. Minenko**, 1) ACR- REF Clinician Educator Scholar Award, Innovative Teaching Grant, , 2, 2) University of Minnesota Office of Information Technology Digital Media Center Faculty Fellowship., 9 .

1222

Immediate Station Feedback During the Annual New York Rheumatology Objective Structured Clinical Examination (NY-ROSCE) Increases Intra-Exam Scores. Jessica Berman[1], Theodore Fields[1], Anne R. Bass[1], Deana M. Lazaro[2], Svetlana Krasnokutsky[3], Elena S. Weinstein[4], Edward Dwyer[5], Huong Do[1], Stephen Paget[1] and Michael H. Pillinger[3], [1]Hospital for Special Surgery, New York, NY, [2]SUNY Downstate Medical Center, Brooklyn, NY, [3]NYU Hospital for Joint Diseases, New York, NY, [4]Albert Einstein College of Medicine, White Plains, NY, [5]Columbia U. College of P & S, New York, NY

Purpose: We have reported that the ROSCE is an effective tool for assessing competencies such as professionalism among rheumatology fellows. Our prior ROSCEs have excluded immediate feedback to participants due to concerns that station scores might be skewed by intra-exam effects on fellow performance. However, fellows have voiced a desire for immediate feedback, stating that it would improve the

ROSCE's educational value. This year we instituted immediate feedback, and assessed its impact on fellows' performance/ratings as they progressed through the ROSCE stations.

Methods: The 2009 NY ROSCE included four patient-centered stations focusing on rheumatic disease. Rheumatology trainees (n=22) and faculty MD-evaluators (n=24) participated from 6 NY rheumatology training programs. To accommodate feedback time, the 2009 NY ROSCE included fewer stations than prior ROSCEs (reduction of 2-3 stations). Professional actors were trained to role-play patients. At each station, fellows were evaluated by patient- and MD-evaluators (9-point Likert scales for patient care, interpersonal skills and professionalism). After each station fellows received immediate feedback from both evaluators, who were instructed to emphasize constructive criticism. Fellows also rated their own overall performance (immediately after each station but prior to receiving feedback). Following the exam, the average scores obtained as fellows moved from their initial to final stations were determined, and compared to station scores from the 2008 NY ROSCE, in which no immediate feedback was given.

Results: During the 2009 ROSCE, physician global assessments of fellows (n=22) increased progressively from first (mean 6.727) to last (mean 7.149) stations (p=0.05). Patient assessments of fellows demonstrated a similar increase (from 6.015 to 6.419), though this trend did not achieve statistical significance (p=0.14). In contrast, the 2008 ROSCE showed no progressive score improvements across stations. Fellows' self-assessments for individual stations (2009) showed progressive improvement for only 7/22 fellows. In a post-exam questionnaire, fellows reported satisfaction with the immediate feedback process.

Conclusion: A potential strength of the ROSCE is the opportunity for immediate feedback. However, our data indicate that giving immediate feedback improves trainee performance as the ROSCE progresses. Educators considering incorporating feedback into the ROSCE should be aware of both the positive benefits of feedback as a teaching tool, and the possibility that feedback may alter the performance of the ROSCE as an assessment instrument.

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Rheumatology Fellows Report Higher Satisfaction with VA-Based Training in Comparison to Other Internal Medicine Subspecialty Fellows. Grant W. Cannon[1] and T. Michael Kashner[2], [1]VAMC and University of Utah, Salt Lake City, UT, [2]VA Office of Academic Affiliations and University of Texas Southwestern, Dallas

Purpose: The Learners' Perception Survey (LPS) has been administered to trainees at Veterans Affairs (VA) medical centers since 2001. This validated survey assesses overall trainee satisfaction (OTS) on a 100 point scale with the higher score representing higher satisfaction. Using five point Likert scales, trainees also rated their experience in six domains listed in table 1. Each domain contained between 12 and 15 items (total 81). Domains and items were assessed as 1 = very satisfied, 2 = somewhat satisfied, 3 = neither, 4 = somewhat dissatisfied, 5 = very dissatisfied. Lower scores represent higher levels of satisfaction.

Methods: This analysis compared the LPS results for rheumatology (Rheum) fellows to other internal medicine subspecialty (Other) fellows during VA-based training for OTS, domain scores, and items scores. These results were adjusted for year of survey, year of training, and VA facility. Ratings are shown as mean ± standard error.

Results: The OTS for Rheum fellows (n= 109) was 84.1±1.3 in comparison to other fellows 81.3±1.3 (n=2,112) ($p<0.03$). For each of the domains, rheumatology fellows reported higher levels of satisfaction (Table 1).

	Rheum Fellows	Other Fellows	p-value
Clinical Faculty (CF)	1.50±0.08	1.62±0.09	0.166
Personal Experience (PEx)	1.53±0.08	1.70±0.08	0.037
Learning Environment (LE)	1.69±0.09	1.86±0.09	0.053
Working Environment (WE)	1.70±0.09	1.94±0.09	0.013
Clinical Environment (CE)	1.75±0.10	2.05±0.10	0.004

Physical Environment (PEn)	1.81±0.09	2.01±0.09	0.027

Rheum fellows reported higher satisfaction with 78 (96%) of the 81 elements within the 6 domains. The ten elements with highest satisfaction for Rheum fellows during VA training are listed in table 2.

	Rheum Fellows	Other Fellows	p-value
CF- Clinical Skills	1.31±0.07	1.52±0.07	0.005
CF-Patient-oriented	1.34±0.08	1.55±0.08	0.010
CF- Approachability/Openness	1.35±0.08	1.44±0.08	0.235
CF-Quality of faculty	1.35±0.09	1.57±0.09	0.012
PEx-Relationship with patients	1.37±0.07	1.44±0.07	0.310
CF-Teaching ability	1.39±0.07	1.61±0.07	0.011
CE-Hours at work	1.41±0.08	1.61±0.08	0.013
LE-Degree of autonomy	1.41±0.07	1.44±0.07	0.690
CF-Interest in teaching	1.43±0.09	1.61±0.09	0.044
PEx-Appreciation by patients	1.43±0.07	2.14±0.07	0.339

In an analysis of the impact of changes in domain scores and items scores on OST, all domains and items showed association with satisfaction score. The domains changes associated with the greatest OTS scores were personal experience, working environment and clinical environment.

Conclusion: Rheumatology fellows report higher training satisfaction with VA based training than other subspecialty fellows. Satisfaction with clinical faculty and personal experience was highest for the domains tested. Since working environment, personal experience, and clinical environment are most strongly associated with trainee satisfaction, these domains may have high potential for improving trainee satisfaction.

Disclosure: G. W. Cannon, None; **T. M. Kashner**, None.

1224

An Instrument to Provide Documentation (iPROD) of Practice-Based Learning and Improvement (PBLI): A Pilot Trial Conducted by the Carolinas Fellows Collaborative. Kenneth S. O'Rourke[1], Marcy B. Bolster[2], Lisa G. Criscione-Schreiber[3] and Beth L. Jonas[4], [1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]MUSC, Charleston, SC, [3]Duke University Med Ctr, Durham, NC, [4]Univ of North Carolina, Chapel Hill, NC

Purpose: Since 1999 the ACGME Outcome Project has required programs to assess trainee skills in PBLI – the ability of the fellow to improve patient care practices and appraise and assimilate scientific evidence into practice. Assessment of these activities has typically required mining information from multiple tools (e.g. patient logs, performance ratings, records review) as few individual tools evaluate all the essential components of PBLI: independent learning, self-evaluation of performance, and incorporation of feedback into improvement of clinical activity.

Method: Our collaborative group created a one-page, online form (iPROD) for fellow self-completion of PBLI activity. The form is divided into three sections: (1) summarization of the issue being addressed and site where it developed (e.g., clinic patient encounter), (2) results and resources used to resolve the issue, and (3) a description of how the results were applied. The form was piloted at a single institution over 7 weeks. Participants were to complete at least one form per week. A seminar was held once weekly during which all participants each presented the contents of one completed form over 3-5 minutes followed by a short 1-2 minute discussion with annotation. Hard copies of

the forms were (1) indexed and placed in a binder as a resource for future use, and (2) incorporated into the fellow's portfolio. Issues raised in the iPRODs will serve as a source for locally-generated 'inservice' questions.

Results: Three fellows and two faculty submitted a total of 23 forms. Issues involved questions of clinical manifestations or disease pathophysiology (n=9), pharmacology (5), diagnostic testing (4), therapy (4) and differential diagnosis (2). Two forms incorporated a systems-based practice concern. The majority (17/23) of issues originated from clinic encounters, and information learned in all cases was applied directly to patient care. Completion of the iPROD was straightforward and relatively rapid. Group discussion provided for feedback and reinforcement of major teaching points.

Conclusion: This pilot trial demonstrated the feasibility of a simple online tool, supplemented by presentation and discussion, to document and evaluate all essential components of PBLI. A larger study among all sites in our collaborative is planned.

Disclosure: K. S. O'Rourke, None; **M. B. Bolster**, None; **L. G. Criscione-Schreiber**, None; **B. L. Jonas**, None.

1225

Medical Education Preferences Among North American Rheumatologists: A 2009 Survey. John J. Cush, Baylor Research Institute, Dallas, TX

Purpose: Practicing rheumatologists (Rheums) regularly deal with changing therapies, limited time/resources for medical education and an ever expanding information glut. These hurdles are compounded by revisions in medical education imposed by ACGME, academic institutions and the pharmaceutical industry. This study intends to assess the current preferences and objections of Rheums with regard to professional and medical education.

Method: 2123 adult and pediatric Rheums from the USA and Canada (160) were invited (via 2 emails) to an online survey in June 2009. The survey included 16 questions regarding respondent demographics, practice type, educational opportunities and preferences regarding venue, attendance, educational resource evaluation, learning formats and preferred topics.

Results: There were 435 respondents (21% response rate), 74.5% male, with a mean age of 55.5 yrs. Responses came from private practice (51%), academic (34%), government/military (4%), Pediatric Rheums (6%); with an overall mean of 23 years in practice (43% > 25 yrs). 63% were engaged in full time patient care, 28% part-time patient care, 32.4% supervise resident/fellow run clinics and 11% are engaged in a single disease specific-only clinic (eg, PSS patients). Most devote either 1-3 hrs (38%) or >3 hrs (40%) per week to education with most online education being sought by private practitioners (>20%). 56% of academicians lecture at least 1 hr/week. Attendance at live meetings (26%) was more popular than on-line education (15%). Whereas the highest rated education sources included Rheum journals (76%), ACR meetings (52%), medical literature searches (45%); the least valued sources included free CME monographs/CDROMs (53%) and Dinner programs (42%). Nonetheless, most attend dinner programs (CME and non-CME) with a 10% high rating and 56 moderate rating. Factors most influencing meeting attendance included topic (79%), time away from practice (72%), site/venue (68%), 66% (cost), speaker reputation (58%) and CME credit (55%). Factors less important (20-25%) included title, evening vs Saturday programming, medical school affiliation and dinner programs. Top ranked meetings included ACR annual mtg (1), Review courses (2), meet the professor groups (3), advisory meetings (4) and post-ACR/EULAR reviews (5). Lowly ranked meetings included webcasts, podcasts and speakers who visit the clinics. Top ranked proposed changes for the future included topic reviews, year in review, case-based conferences, programs with more Q&A time and shorter lectures. Lastly nearly 2/3 of respondents would pay $10-50 per hour of CME but 20% refuse to pay for CME.

Conclusion: Regardless of age, type/focus of practice or country, N. American Rheums are demanding with regard to educational needs. Dinner programs, pharma promotional materials and online webcasts remain unpopular. However interest in convenient, local or regional, affordable education remains strong especially when review courses, post-meeting reviews, basic science reviews or advances in drug therapy are the focus.

Disclosure: J. J. Cush, None.

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Genetic Interactions Reveal a Novel B-Cell Pathway in Systemic Lupus Erythematosus. Casimiro Castillejo-Lopez[1], Angelica M. Delgado-Vega[1], Jerome Wojcik[2], Sergey Kozyrev[1], Juan R. Lopez Egido[1], Elena Sánchez[3], David Pöllmann[1], Serena Fineschi[1], Nicolas Dominguez[4], Rufei Lu[4], Judith A. James[4], Joan T. Merrill[4], Jennifer A. Kelly[4], KM. Kaufman[4], Kathy L. Moser[4], GS Gilkeson[5], Bernardo Pons-Estel[6], Nadia Barizzone[7], Torsten Witte[8], Jose Luis Callejas[9], Jb Harley[4], Patrick M. Gaffney[4], Javier Martin[3], Joel M. Guthridge[4] and Marta E. Alarcon-Riquelme[1], [1]Uppsala University, Uppsala, Sweden, [2]Merck Serono International, Geneva, Switzerland, [3]Instituto de Biomedicina y Parasitología López-Neyra, Granada, Spain, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Medical University of South Carolina, Charleston, SC, [6]Sanatorio Parque, Rosario, Argentina, [7]University of Eastern Piedmont, Novara, Italy, [8]Hannover Medical School, Hannover, Germany, [9]Hospital Clinico San Cecilio, Granada, Spain

Purpose: Epistasis, or genetic interactions, might explain larger genetic effects than single-gene associations on the susceptibility to diseases, and help to define functional pathways with potential therapeutic targets. We aim to identify genes that modify the susceptibility to SLE through their interaction with the B-cell scaffold protein with ankyrin repeats gene (*BANK1*).

Method: We searched for genetic interactions in an Affymetrix 100k genome-wide scan performed in 256 cases and 515 controls from Sweden. A subsequent replication study included two independent multi-center cohorts of European-Americans (n=676 cases and 850 controls) and Europeans (n=1265 SLE cases and 1506 controls). We developed a genotype interaction test based on contingency tables for all possible genotype combinations between pairs of SNPs with $r^2 < .80$ and calculated a Pearson *S* score of interaction association and its X^2 *P* value. Each interacting combination was tested against the hypothesis of independence to derive an epistasis score (S_e) and a *P* value (P_e) was obtained through permutation.

Results: *BANK1* showed genetic interactions with 29 genes, including the B-cell tyrosine kinase (*BLK*) and the inositol 1,4,5-triphosphate receptor 2 (*ITPR2*). One fifth of SLE patients (21%) vs. 8 % of controls were homozygous for the risk alleles of polymorphisms in these three genes with a significant epistatic effect ($P_e < 0.0002$). The interactions *BANK1xITPR2* and *BANK1xBLK* were replicated in two independent European-American ($P = 2.1 \times 10^{-6}$) and European sets ($P = 4.11 \times 10^{-9}$). The data was verified using multifactor dimensionality reduction (MDR) and logistic regression analysis. Moreover, BLK co-immunoprecipitated and co-localized with BANK1 in co-transfected HEK-293T. Exogenous expression of BANK1 in human Daudi B cells curbed BLK from reaching the plasma membrane with the subsequent accumulation in cytoplasmic compartments. Expression of BANK1 and BLK but not ITPR2 was modulated by IFNα

Conclusion: *BANK1*, *BLK* and *ITPR2* are genetically and functionally interacting partners and through their protein-protein interactions might results in a novel B-cell signaling pathway regulated by type I interferon α. This pathway may affect B-cell responses to self-antigens in human lupus.

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Evidence of Genetic Overlap Between Ankylosing Spondylitis and Crohn's Disease. Patrick Danoy, Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia

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Health Science Center at Houston, USA. [6]Botnar Research Centre, University of Oxford, UK. [7]Royal National Hospital for Rheumatic Diseases NHS Foundation Trust and University of Bath, UK.

Purpose: Inflammatory bowel disease (IBD) occurs in ~10% of AS cases and 70% of AS cases have subclinical terminal ileitis. Spondyloarthritis is also common in patients with IBD. We sought to test whether genes involved in Crohn's disease (CD) are also associated with ankylosing spondylitis (AS), potentially explaining the co-occurrence of the two conditions.

Method: Using Taqman and Sequenom technologies, we genotyped 1262 US and UK AS cases of white European descent for 37 established CD loci. Because 3 loci were in strong candidates, genes were typed using tagSNPs across all exons. Control genotypes were obtained from a white European ancestry historical dataset (n=1295, from the 1958 British Birth Cohort, typed by the Wellcome Trust Case Control Consortium), and imputation was carried out using MACH whenever control marker data was unavailable. Statistical analysis was carried out using a Cochran-Armitage test for trend and all associated markers ($P<0.1$) were genotyped on US and UK cases (n=854) and controls (n=858) for replication on the OpenArray platform (AB). P-values for the combined analysis are presented.

Results: Out of 62, 26 markers ($P<0.1$) were taken for genotyping in the 2nd phase and 9 achieved association ($P<0.05$) in the replication phase with P values ranging from 0.01 to $7.7x10^{-29}$ in the combined analysis. Association was confirmed for *IL23R* (rs11465804, $P=1.0x10^{-4}$) and MHC (rs3763313, $P=7.7x10^{-29}$). Outside the MHC, strongest association was detected at chromosome 1q32.1 (rs11584383, $P=8.2x10^{-8}$), in an intergenic region. Association was also confirmed for 3 markers in *STAT3* (rs6503695, $P=5.7x10^{-3}$; rs4103200, $P=1.1x10^{-2}$; rs744166, $P=1.5x10^{-3}$). Finally, association was identified in both datasets for markers in *MST1* (rs3924462, $P=2.7x10^{-3}$), *CDKAL1* (rs6908425, $P=1.4x10^{-3}$), and *LRRK2/MUC19* (rs11175593, $P=3.6x10^{-3}$). These associations did not significantly change when AS cases with clinical IBD were excluded.

Conclusion: Evidence has been demonstrated for strong association with an intergenic region on chromosome 1q32.1, and with *STAT3*. *STAT3* is a key gene involved in Th17 lymphocyte differentiation, and further enhances the case for a major role of this T-lymphocyte subset in AS pathogenesis. Finally these findings suggest a common aetiopathogenesis for AS and CD and further highlight the involvement of common risk variants across multiple diseases.

Disclosure: P. Danoy, None.

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Complete T- and B-Cell Receptor Repertoire Analysis in Rheumatoid Arthritis Using Massive Parallel Sequencing. P.L. Klarenbeek[1], M.E. Doorenspleet[1], B.D.C. van Schaik[1], M.M. Herenius[1], M.E. Jakobs[1], Tineke Cantaert[2], D.L.P. Baeten[1], A.H.C. van Kampen[1], F. Baas[1], Paul P. Tak[3] and N. de Vries[1], [1]Academic Medical Center/Univ. of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: T-cells and B-cells are likely to play important roles in the pathogenesis of rheumatoid arthritis (RA). Previous attempts to investigate the roles of T- and B-cell clones in RA by screening the T-/B-cell receptor (TCR/BCR) repertoires were hampered by the sheer size and complexity of the repertoires. Current techniques are unable to analyse the whole repertoire in sufficient detail, are vulnerable to artefacts, and do not provide quantitative data. Here, we used our newly developed protocol based on massive parallel sequencing which overcomes current limitations and produces the DNA-sequence of >100.000 receptors in a single experiment. Using this technique we performed the first quantitative, high- resolution analysis of the complete TCR and BCR repertoires in an RA patient. **Objectives:** Describe the complete BCR and TCR repertoires in synovial tissue (ST) and peripheral blood (PB) samples of an RA-patient and screen for dominant T- and B-cell clones.

Method: mRNA was isolated from paired PB and ST samples from an ACPA+ RA-patient with active disease despite treatment with methotrexate. A linear amplification with multiplex primers for all V(ariable)-families of the receptor beta-chain (TCR) or heavy-chain (BCR) was performed. The samples were analyzed on a Genome Sequencer FLX (Roche) resulting in 14000 reads/samples for TCR and 35000 for BCR analysis respectively, each containing the full CDR3 sequence. Bioinformatic algorithms were used to identify gene segments and correct for sequencing errors.

Results: *TCR-repertoire*: in ST most TCRs contained a Vbeta6(46%), 10(19%), and 27(13%) gene segment, while in PB V29(32%) and 7(26%) were most frequent. The TCR repertoire was dominated by low-frequency clones (>95%), both in the PB and ST. Several clones were clearly expanded (up to 217 and 121 copies/clone for PB and ST). However, the dominant clones in ST were different from those in

PB, as compared by V-segment and CDR3 sequence. *BCR-repertoire*: the ST sample showed preferential usage of the small V2,5,6,7 families (total 50%) when compared to published data in PB[1](20%). Several clearly expanded clones (up to 1892 copies) were found against a background of low-frequency clones.

Conclusion: This is the first high-resolution analysis of the TCR and BCR repertoire in RA, providing detailed insight into the presence of T- and B-cell clones. We found clear differences between the TCR-repertoire in ST compared to PB in an RA-patient. Several expanded clones were found only in ST, suggesting proliferation or local retention of T-cells. The BCR-repertoire also showed expanded clones within the ST. Further studies will elucidate the role of these clones in RA.

[1] van Dongen JJ et al. Leukemia 2003;17:2257-317.

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The Coding Variant within ITGAM Influences Lupus Nephritis. Xana Kim-Howard[1], Amit K. Maiti[1], Juan-Manuel Anaya[2], Gail R. Bruner[3], J. T. Merrill[4], Jeffrey C. Edberg[5], Michelle A. Petri[6], John D. Reveille[7], Elizabeth Brown[5], Graciela S. Alarcon[5], Rosalind Ramsey-Goldman[8], Timothy J. Vyse[9], GS Gilkeson[10], Robert P. Kimberly[5], Judith A. James[3], Joel M. Guthridge[1], John B. Harley[11] and Swapan K. Nath[1], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]CIB-Rosario University, Medellin, [3]Oklahoma Medical Rsrch, Oklahoma City, OK, [4]OMRF, Oklahoma City, OK, [5]University of Alabama at Birmingham, Birmingham, AL, [6]JHU, Baltimore, MD, [7]University of Texas Medical School at Houston, Houston, TX, [8]Northwestern University, Chicago, IL, [9]Imperial College, London, United Kingdom, [10]Medical University of South Carolina, Charleston, SC, [11]OMRF, OK, OK

Purpose: We recently demonstrated genetic association between a novel non-synonymous (R77H) variant (rs1143679) at exon-3 of *ITGAM* and systemic lupus erythematosus (SLE), a clinically heterogeneous disease. The relationship between this variant and clinical sub-phenotypes have not been studied. We hypothesized that rs1143679 could predict specific clinical outcomes (sub-phenotypes).

Method: We used 2366 SLE cases and 2931 unaffected controls of European descent to assess association between this coding variant and clinical sub-phenotypes. SLE patients were classified by the presence or absence of individual ACR criteria. Logistic regression and Pearson chi-square tests were used to assess statistical significance with rs1143679 in case-control and case-only analyses.

Results: First, for overall case-control analysis between SLE and rs1143679, we detected highly significant ($P = 2.22x10^{-21}$, OR = 1.73) genetic association. Second, we performed case-only analysis between individual ACR criteria positive cases and negative cases. This variant was significantly associated with lupus nephritis (P = 0.0003, OR = 1.39), discoid rash (P = 0.02, OR = 1.27) and immunologic criteria (P = 0.04, OR = 1.30). Third, to further assess the magnitude of associations between significant ACR criteria, we compared them with normal controls. The strongest statistical association was with lupus nephritis versus controls ($P = 4.69x10^{-22}$, OR = 2.15), and immunologic manifestations versus controls ($P = 3.49x10^{-22}$, OR = 1.86); both were more significant than all SLE cases together versus controls. Conversely, significant associations were also detected with ACR-negative versus controls for nephritis ($P = 4.05x10^{-7}$, OR = 1.50) and discoid rash negative ($P = 2.58x10^{-6}$, OR = 1.55). However, significantly different ORs were only detected between nephritis positive and nephritis negative cases when compare with all controls. The minor allele frequency increased from 10.6% (controls) to 17.0% (SLE cases) and 20.4% (lupus nephritis). All associations remained significant after 10,000 permutations.

Conclusion: Clinical sub-grouping yielded the strongest association with rs1143679 in SLE patients with lupus nephritis, both in case-only and case-control analyses. SLE nephritis patients were highly enriched with the risk allele. These results suggest a correlation between a coding variant of *ITGAM* (rs1143679) and lupus nephritis.

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Towards Genetic Correlates of Cardiac Manifestations of Neonatal Lupus: A Genome-Wide Association Study. Robert M. Clancy[1], Miranda C. Marion[2], Kenneth M. Kaufman[3], Adam Adler[3], John B. Harley[4], Carl D. Langefeld[2] and Jill P. Buyon[1], [1]NYU School of Medicine, New York, NY, [2]Wake Forest University Health Sciences, Winston-Salem, NC, [3]Oklahoma Medical Research Foundation, OK, OK, [4]Oklahoma Medical Research Foundation, OK

Purpose: Maternal anti-Ro antibodies are highly associated with heart block and/or cardiomyopathy (cardiac neonatal lupus (NL) in an offspring. Monozygotic twin studies and the 10 fold increased recurrence rate of cardiac NL in a subsequent pregnancy implicate a strong genetic influence on risk of disease. Here, we report the first genome-wide association study of cardiac NL.

Methods: Caucasian children (n=117) with cardiac NL were identified from an extensive collection of DNA in the U.S. Research Registry for Neonatal Lupus (RRNL). Two criteria were required: 1) cardiac NL defined as heart block (1st, 2nd ,3rd, degree) documented by electrocardiogram (if 1st degree), echocardiogram, history of pacemaker, or statement in the medical record; and/or presence of cardiac injury which included autopsy evidence of a mononuclear infiltrate in the endocardium, myocardium and pericardium and/or endocardial fibroelastosis on echocardiogram always associated with cardiac dysfunction 2) maternal antibodies to 52kD SSA/Ro, 60kD SSA/Ro, or 48kD SSB/La. In 96%, 2nd or 3rd degree block was present. Cardiac NL subjects were genotyped using the Illumina 370K SNP platform and merged with 3351 Illumina "out-of-study" controls from SLEGEN (Harley 2008). Standard quality control and admixture adjusted tests of association were computed.

Results: The HLA region (6p21) showed strong evidence of association. Two HLA SNPs in high linkage disequilibrium were rs3135353 (p_{dom} = 3.99E-08; OR = 2.87; 2.8 kb from HLA-DRB5) and rs3129963 (p_{dom} = 8.96E-07; OR = 2.57; 75 kb from HLA-DRA). Outside the HLA region, rs1810636 near 20p13 showed significant association to cardiac NL (p_{rec} = 1.53E-12, OR = 4.07). In proximity to this region are the DNA sequences of five noncoding RNAs that associate with the spliceosome. An additional suggestive association at 5q11.2 includes rs 2432143 (p_{dom}=5.87E-05, OR=2.28) within the integrin, alpha 1, a receptor involved in cell-cell adhesion, which may play a role in inflammation and fibrosis. Importantly, none of the fifteen prominent non-HLA polymorphisms reported in SLE association studies were associated with cardiac NL at less than 1E-5.

Conclusion: These analyses are the first genome-wide association study for cardiac NL and identify several strong statistical associations. These associations, including the HLA region, corroborate the genetic influences on cardiac NL and may provide a basis for exuberant fibrosis of the conduction system.

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Genomewide Scan in Acute Anterior Uveitis: Similarities and Differences with Genes Associated with Ankylosing Spondylitis.
Tammy M. Martin[1], David M. Evans[2], Patrick Danoy[3], Justine R. Smith[1], Michael M. Ward[4], Michael H. Weisman[5], The Australo-Anglo-American Spondylitis Consortium, John D. Reveille[6], Matthew A. Brown[3] and James T. Rosenbaum[1], [1]Oregon Health & Science Univ, Portland, OR, [2]University of Bristol, Bristol, United Kingdom, [3]Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia, [4]NIH/NIAMS, Bethesda, MD, [5]Cedars-Sinai Med Ctr, LA, CA, [6]University of Texas Medical School at Houston, Houston, TX

Purpose: Acute anterior uveitis (AAU) or iritis, complicates ~40% of cases of ankylosing spondylitis (AS), and can occur in the absence of AS. Both AS and AAU are associated with HLA-B27, and there is evidence to suggest that other genes are involved in each disease. This study aimed to identify genes involved in AAU and to compare those genes with the known genes involved in AS.

Method: 952 cases with uveitis (with or without AS) and 1380 AS cases without uveitis were available for study. These were identified from cases enrolled in the TASC AS genomewide association study (n=2082), or were recruited separately having presented with AAU (n=250). TASC cases were genotyped with lllumina 370CNV chips and non-TASC samples with Illumina 610 chips. Healthy controls used were from the Illumina iControl database, and had been cleaned for white European ancestry using ancestry informative markers. Datasets were compared using the Cochrane-Armitage test for trend as implemented in PLINK. Study activities were conducted under approved human subjects protocols.

Results: Comparing uveitis cases with AS cases without uveitis, association was observed at chromosome 1p35.1 with SNPs in the gene *CSMD2* (CUB and Sushi multiple domains 2; rs732889, P= 1.8x10-7). Association was also observed with SNPs in the chromosomal regions

4q32.3 (rs11100530, P=2.0x10-6) and 15q22.1 (rs1122208, P=5.7x10-7). No genes are encoded in these regions. No association was seen between *CSMD2*, or the chromosome 4 or 15 regions, with AS in comparisons of AS cases vs healthy controls, suggesting that the associations observed are with AAU rather than primarily with AS. The CSMD2 protein is expressed primarily in brain and related tissues, including the ciliary ganglia. It has unknown function and belongs to a family of transmembrane proteins with large extracellular domains containing alternating CUB and Sushi motifs. Based on the absence of differences between uveitis compared to AS without uveitis at known AS loci, these data also support uveitis associations with MHC, *IL23R*, *ERAP1*, chromosome 2p15, 21q22, *IL1R2* and *ANTXR2*.

Conclusion: This study suggests that there is great similarity between the genes involved in AS and in AAU, and that the major genes involved in AS that are known thus far are similarly associated with AAU. In addition, three loci were identified, including the gene *CSMD2*, which have a greater association in AAU cases than in AS alone, suggesting that these genes are independent risk factors for AAU. Funding: NIH, RPB, NHMRC.

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ACR Concurrent Abstract Sessions

Miscellaneous Rheumatic and Inflammatory Diseases

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1232

Is Infliximab Effective and Safe for the Treatment of Refractory Non Infectious Inflammatory Uveitis?-A Systematic Literature Review. Ana M. Ortiz[1], Estibaliz Loza[2], Miguel Abad[3], Felix Francisco[4], Jesús Maese[2], Santiago Muñoz-Fernández[5], Loreto Carmona[2] and Esperanza Pato[6], [1]Hospital Universitario de la Princesa, Madrid, Spain, [2]Fundación Española de Reumatología, Madrid, Spain, [3]Hospital Virgen del Puerto, Plasencia, Cáceres, Spain, [4]Hospital Doctor Negrin, Las Palmas de Gran Canaria, Spain, [5]Hospital Infanta Sofía, Madrid, Spain, [6]Hospital Clínico San Carlos, Madrid, Spain

Infliximab (INF) has successfully been used for the treatment of different inflammatory diseases. Non infectious inflammatory uveitis (NIIU) might develop a severe course with poor visual prognosis if an adequate control of the disease is not achieved. INF has been used for the treatment of these patients.

Purpose: To systematically review the published evidence regardingthe efficacy and safety of INF in NIIU refractory to conventional immunosuppressive drugs.

Method: Systematic review of studies retrieved by a sensitive search strategy in Medline (1961-October 2007), Embase (1961-October 2007), Cochrane Library (up to October 2007). Selection criteria: (population) studies analyzing patients with uncontrolled NIIU in spite of immunosuppressive drugs; (intervention) studies had to test INF; and (outcomes), studies reporting visual acuity, Tyndall, vitritis, retinal vasculitis, macular edema, pars planitis and adverse events. Randomized controlled trials, observational studies and case series were included. Three reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently and collected the data by using *ad hoc* standard forms. One of them also graded the quality of the selected studies using a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update. A hand search was completed by reviewing the references of the included studies.

Results: A total of 105 articles were studied in detail, of which 40 were included (7 open studies, 1 cohort study, 10 retrospective studies, 16 cases series and 1 literature review). A total of 409 patients with NIIU were analyzed (139 associated with Beçhet disease, 90 with idiopathic juvenile arthritis and 180 with other diagnoses). Although the great variability in the study design, study samples, drug dosing and treatment duration and outcomes, most patients on INF showed an important improvement in the visual outcomes. Few major adverse events were reported.

Conclusion: Treatment with INF is effective and safe for the treatment of patients with NIIU refractory to conventional immunosuppressive drugs (level of evidence 4, grade of recommendation C).

Disclosure: A. M. Ortiz, Schering-Plough, 2 ; **E. Loza**, None; **M. Abad**, Schering-Plough, 2 ; **F. Francisco**, Schering-Plough, 2 ; **J. Maese**, Schering-Plough, 2 ; **S. Muñoz-Fernández**, Schering-Plough, 2 ; **L. Carmona**, None; **E. Pato**, Schering-Plough, 2 .

1233

Cardiac Sarcoidosis: Clinical, Diagnostic, Therapeutic and Outcome Features From a Series of 126 Patients. Damien Sène, Catherine Chapelon-Abric, David Saadoun, Alexis Mathian, Nathalie Costedoat-Chalumeau, Julien Haroche, Du Li Thi Huong-Boutin, Jean -Charles Piette, Patrice P. Cacoub and Zahir Amoura, Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France

Purpose: To analyze clinical, diagnostic and therapeutic features and the outcome of 126 patients with a cardiac sarcoidosis (CS).

Methods: Patients with a definite CS, prospectively followed in a single centre, were included. SC was diagnosed using the following procedures: electrocardiogram, myocardial echography, MRI and scintigraphy. The diagnosis of CS was defined by the evidence of myocardial abnormalities to at least two different procedures. Patients with a CS were analyzed regarding their clinical, diagnostic, therapeutic and outcome features.

Results: Out of a cohort of 502 patients with a systemic sarcoidosis, 126 patients (25%) presented a CS: mean age 41 ± 12 years; male gender 59%; Caucasian 70%; Black 28% and Asiatic 2%. Extracardiac sarcoidosis involvement included: chest 79%, central nervous system (CNS) 44%, peripheral lymph nodes 31% and skin 25%. **Diagnosis**: Dyspnea was present in 19% of patients. ECG abnormalities were present in 64% of patients including conduction (54%) and rhythm (63%) disturbances. The echocardiography (n = 125) showed pathological signs for 88 patients (70%): hypokinesia (33%), low *left ventricular ejection fraction* (22%), interventricular septum thickness (10%). Myocardial scintigraphy (n = 112) was pathological for 81 patients (72%) with localized (61%) and diffuse (12%) defects. Cardiac MRI (n = 64) showed abnormal signals and gadolinium uptake in 37 patients (58%). Morphological and electrocardiographic troubles were both present in 80 patients (63.5%) and 46 patients (36.5%) had isolated morphological abnormalities. The highest diagnostic accuracy was reached between MRI and echocardiography (67%), followed by MRI and scintigraphy (63%) and echocardiography and scintigraphy (56%).**Treatment and Outcome**: A first line treatment with steroids was initiated for 111 patients (88%), among whom 48 patients (43%) received an additional immunosuppressive drug (ISD) including methotrexate (71%), cyclophosphamide (23%), mycophenolate mofetil (6%). After a mean follow-up of 74.8 ± 63 months, 122 patients were evaluable: 89 patients (73%) recovered, 28 patients (23%) were stable, and 5 patients (4%) worsened. After multivariate analysis, two factors were associated with the absence of CS recovery: CNS involvement (OR = 3.2; 95%CI: 1.3-7.5; P = 0.0025) and a left heart insufficiency (OR = 2.5; 95%CI = 1-6; P = 0.05). Thirteen patients (10%) died and only two deaths (1.6%) were imputable to CS.

Conclusion: Our results show that CS has a good prognosis under steroids alone or in association with an ISD. Up to 70% of patients may recover and the CS related death rate is less than 2%. The absence of a stable recovery is associated with the severity of systemic sarcoidosis, i.e. left heart insufficiency and CNS involvement.

Disclosure: D. Sène, None; **C. Chapelon-Abric**, None; **D. Saadoun**, None; **A. Mathian**, None; **N. Costedoat-Chalumeau**, None; **J. Haroche**, None; **D. Li Thi Huong-Boutin**, None; **J. -. C. Piette**, None; **P. P. Cacoub**, None; **Z. Amoura**, None.

1234

Wrist Pain in 7-12 Year Olds Playing with Game Consoles/Handhelds: Younger Children Have More Pain, Independent From Time Spent Playing. Deniz C. Ince[1], C.J. Swearingen[2] and Yusuf Yazici[3], [1]Rossman Elemantary School, St Louis, MO, [2]MUSC, Charleston, SC, [3]NYU Hospital for Joint Diseases, New York, NY

Purpose: Game consoles such as Xbox, PS3 and Wii, in addition to handheld unit PSP, iTouch and iPhone are used by many children. Data regarding wrist and finger pain that may be caused by excessive use of these devices do not exist, especially in young children. We examined the possible association device type, age of children and hours played may have with wrist and finger pain.

Method: 7-12 year olds attending Rossman Elemantary School in St Louis, MO, were administered a questionnaire asking about game consoles and hand-held devices used, hours played, and wrist or finger pain as reported on a 10cm VAS. Summary statistics of playing habits, devices played and pain levels were estimated. Multivariable generalized linear models associating consoles played, age and hours played to pain were constructed using standard backward selection techniques, determining the most significant independent predictors for pain.

Results: 171 children completed the survey (mean age 9.7 years, 93 were female (54.4%). 84 (49.1%) reported 0-1 hours of play a day, 58 (33.9%) 1-2 hours, 12 (7%) 2-3 hours and 11 (6.4%) over 3 hours. 20 (11.7%) children reported finger pain and 17 (9.9%) reported wrist pain limiting their playing time. The mean (SD) pain level was 0.83 (1.82). Among the consoles Wii was the most commonly used (n=77, 45%), followed by Xbox/PS3 (n=9, 5.3%). 28 (16.4%) children played with none and 57 (33.3%) played both. For handhelds, Gameboy/PSP were played by 103 (60.2%) and iTouch/iPhone by 10 (5.8%). 39 (22.8%) played both and 19 (11.1%) played with neither. In beta regression, increasing age was independently associated with decreased odds of reporting pain (OR=0.65 (95% CI 0.57 – 0.75)); increasing hours played was associated with increased odds of reporting pain (OR=1.52 (95% CI 1.16-2.00)). Playing the Wii only was also independently associated with increased odds of reporting pain (OR=2.39 (95% CI 1.81-3.73)). In logistic regression, age was the only significant predictor of wrist pain (OR=0.68 (95% CI 0.48-0.96).No significant predictor of finger pain was observed.

Conclusion: In children aged 7-12, 80% of which played with a console or handheld, younger age was associated with more wrist pain. Wii use was associated with more self-reported pain independent of age and hours played. Seven year olds reported the most pain as compared the other age groups. These findings may have implications for which age children should start playing with gaming consoles and handheld devices and possibly some limits in the hours they play.

Disclosure: D. C. Ince, None; **C. J. Swearingen**, None; **Y. Yazici**, BMS, Roche, UCB, Centocor, Celgene, 5 .

1235

Efficacy and Safety of Canakinumab (Ilaris) in A Large Cohort of Patients Across Different Severity Phenotypes of Cryopyrin Associated Periodic Syndrome (CAPS). J.B. Kuemmerle-Deschner[1], H.J. Lachmann[2], E. Hachulla[3], J. Hoyer[4], J. Smith[5], K. Leslie[6], I. Kone-Paut[7], J. Braun[8], A. Widmer[9], N. Patel[10], R. Preiss[10] and P.N. Hawkins[2], [1]Universitätsklinikum Tübingen, Klinik fuer Kinder-und Jugendmedizin, Germany, [2]Royal Free and University College Medical School, London, United Kingdom, [3]Hopital Claude Huriez, Lille Cedex, France, [4]Univ.-Klinikum Gießen und Marburg, Marburg, Germany, [5]University of Wisconsin Hospital and Clinics, Madison, WI, [6]UCSF, School of Medicine, San Francisco, CA, [7]Hopital Kremlin Bicetre, Le Kremlin Bicetre, France, [8]Rheumazentrum Ruhrgebiet, Herne, Germany, [9]Novartis, Basel, Switzerland, [10]Novartis, East Hanover, NJ

Purpose: CAPS (disease spectrum consisting of FCAS, MWS, NOMID) is a rare hereditary, autosomal dominant, systemic inflammatory disease associated with excessive production of IL-1β. The fully human monoclonal antibody canakinumab provides prolonged selective blockade of IL-1β.

Method: Patients enrolled in this open-label multi-center study were canakinumab naïve or rolled over from earlier Phase II/III studies. Patients received canakinumab 150 mg s.c. or 2 mg/kg s.c. (≤40 kg) every 8 weeks. The primary objective of this ongoing trial is to assess the long-term safety and tolerability of canakinumab in CAPS patients. Secondary objectives included assessment of response (for naïve patients), maintenance of response, percentage of patients requiring dose adjustment, and immunogenicity of canakinumab. A relapse was defined as: serum levels of CRP and/or serum amyloid A protein (SAA) >30 mg/L and physician's global assessment of disease activity >minimal or physician's global assessment of disease activity =minimal along with the assessment of skin disease >minimal.

Results: Out of 98 patients (19 FCAS; 69 MWS; 9 MWS/NOMID; 1 cold urticaria/protocol deviation; 19 pediatric) aged 5-69 years enrolled in the study, 44 patients were canakinumab-naïve, while 54 had previously received canakinumab in another study. The median duration of exposure to canakinumab was 113 days (range 9-232 days) and the mean number of injections per patient was 2.9 (range 1-9) at the time of this interim analysis. A complete response by Day 8 was seen in 41/44 (93.2%) canakinumab-naïve patients. 13 patients had missing relapse assessment data at the interim analysis cut off. Of the remaining 85 patients, 77 had no relapse (90.6%), 5 experienced a relapse (5.9%), and 3 naïve patients did not achieve a complete response. At least one dose adjustment was required in 16 patients (16.3%). AEs were predominantly mild to moderate in severity, the most frequent AE was nasopharyngitis. Two patients discontinued due to AEs (1 due to worsening of multiple sclerosis like lesions and another due to MWS flare). Serious AEs were reported in 5 patients and resolved while on treatment. The majority of patients (94.9%) had no injection site reactions, 5.1% reported reactions, which were all mild. No anti-canakinumab antibodies were observed.

Conclusion: For CAPS patients, canakinumab administered every 8 weeks, provided rapid improvement of symptoms and sustained remission in a large cohort of patients across all disease severity phenotypes.

Disclosure: J. B. Kuemmerle-Deschner, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 5 ; **H. J. Lachmann**, EU framework 7grant, 2, Novartis Pharmaceutical Corporation, 5 ; **E. Hachulla**, Novartis Pharmaceutical Corporation, 5 ; **J. Hoyer**, None; **J. Smith**, None; **K. Leslie**, None; **I. Kone-Paut**, Novartis Pharmaceutical Corporation, 5 ; **J. Braun**, Novartis Pharmaceutical Corporation, 2, Centocor, Inc., 6, Schering-Plough, 6, Wyeth Pharmaceuticals, 6, Amgen, 6, Abbott Laboratories, 6, BMS, 6, Roche Pharmaceuticals, 6, Chugai, 6, Pfizer Inc, 6, MSD, 6 ; **A. Widmer**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **N. Patel**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **R. Preiss**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **P. N. Hawkins**, Novartis Pharmaceutical Corporation, 5 .

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Familial Mediterranean Fever (FMF)-Associated B30.2 (PRYSPRY) Mutations Activate a NLRP3-Independent Inflammasome and Induce Autoinflammatory Disease in Mice. Jae Jin Chae[1], Young-Hun Cho[2], Jun Cheng[3], Maria Mosaico[4], P. Paul Liu[3], Lionel Feigenbaum[4], Stephen I. Katz[2] and Daniel L. Kastner[1], [1]Inflammatory Biology Section, Laboratory of Clinical Investigation, NIAMS, NIH, Bethesda, MD, [2]Dermatology Branch, NCI, NIH, Bethesda, MD, [3]Genetics and Molecular Biology Branch, NHGRI, NIH, Bethesda, MD, [4]Laboratory Animal Sciences Program, SAIC-Frederick, NCI, NIH, Frederick, MD

Purpose: Familial Mediterranean fever (FMF) is the prototype and the most common of a group of disorders, termed systemic autoinflammatory diseases, that are characterized by recurring spontaneous episodes of fever and localized inflammation. FMF is caused by mutations of a 781-amino acid protein denoted pyrin. Most patients carry missense mutations in the C-terminal B30.2 domain of pyrin. However the molecular pathogenesis of FMF remains poorly understood. In order to study the pathogenesis of FMF *in vivo*, we have generated various knock-in (KI) mouse models with FMF-associated B30.2 mutations.

Method: KI mice were generated by inserting the B30.2 domain of wild-type (WT) or FMF-associated M680I, M694V, and V726A mutant pyrin into mouse pyrin that ordinarily does not include a B30.2 domain. The KI mice were analyzed by histology, flow cytometry, multiplex cytokine assay, and Western blot. The KI mice were also used in bone marrow (BM) transplantation and crossed with Pyrin KO, Rag-1 KO, IL-1R KO, ASC KO, and NLRP3 KO mice.

Results: While the WT B30.2 KI mice were embryonic lethal, the KI mice for FMF mutations exhibited a phenotype similar to the human disease, but more severe, with growth retardation, spontaneous dermatitis and arthritis, and increased CD11b+ cells (especially granulocytes) in the blood. These inflammatory phenotypes could be observed only in homozygotes, but not in heterozygous KI, pyrin KO, and hemizygous KI mice expressing only mutant pyrin from a single allele. BM cells of KI mice transferred the KI phenotype into WT mice, and WT BM cells rescued the diseased KI mice. Rag-1 deficient KI mice showed phenotypes similar to Rag-1 sufficient KI mice. Pro-inflammatory cytokines, such as IL-1beta, are significantly increased in KI mouse sera. In the steady state, the inflammasome is constitutively activated in CD11b+ cells in KI mice, and subsequently CD11b+ cells secrete active IL-1beta when stimulated with LPS alone without ATP *in vitro*. Moreover, the autoinflammatory phenotype was abrogated when KI mice were crossed with IL-1R KO or ASC KO mice. On the other hand, NLRP3 deficient KI mice exhibited the autoinflammatory phenotype.

Conclusion: Taken together, these results suggest that the pathogenesis of FMF can be explained by gain of function of the mutant B30.2 domain with gene dosage effects, and BM derived cells are necessary and sufficient for the induction of FMF inflammation characterized by increased CD11b+ cells. Moreover, in addition to confirming earlier data implicating IL-1beta in pathogenesis of FMF, our results provide evidence for a heretofore unrecognized ASC-dependent, NLRP3-independent, pyrin inflammasome.

Disclosure: J. J. Chae, None; **Y. H. Cho**, None; **J. Cheng**, None; **M. Mosaico**, None; **P. P. Liu**, None; **L. Feigenbaum**, None; **S. I. Katz**, None; **D. L. Kastner**, None.

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Rilonacept: Long-Term Safety Profile in Patients with Cryopyrin-Associated Periodic Syndromes (CAPS). Hal M. Hoffman[1], Douglas R. Nadler[2], Warren P. Brooks[2] and Steven P. Weinstein[2], [1]University of California at San Diego, La Jolla, CA, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Purpose: IL1-β inhibition with weekly rilonacept (IL-1 Trap) provided marked, durable improvement in clinical and laboratory signs and symptoms associated with CAPS (Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)) while exhibiting a generally well-tolerated profile during a 24-wk double-blind, placebo-controlled pivotal study and a subsequent single arm, 24-

wk, open-label extension (OLE) study. The results described herein report on the safety profile in patients throughout the OLE and subsequent 64-week long term extension (LTE).

Methods: Patients enrolled into the consecutive OLE and LTE by either continuing from the pivotal study (44 patients) or entering directly (57 patients). All patients received SC rilonacept 160 mg/week (for a maximum of 112 wks). Safety assessments were performed at baseline and periodically throughout the study, including physical examinations, vital signs, documentation of adverse events (AEs), routine laboratory tests ,and assays to detect anti-rilonacept antibodies.

Results: Safety data were available for 104 pts with more than 125 patient exposure years (mean age 43.6 years; 66.3% female). The most common treatment-emergent AEs were injection-site reactions (erythema, swelling, pruritis, bruising), which occurred in 60.6% of patients; these were mild to moderate in severity and did not cause patient withdrawal. The most common treatment-emergent infections were: nasopharyngitis (10.6%), sinusitis (11.5%), upper RTIs (11.5%), UTIs (8.7%) and bronchitis (6.7%) which occurred in 32.7% of patients. None of the serious AEs (sciatica, cholelithiasis, hyponatremia, hypokalemia, pulmonary embolism, GI reflux, renal colic) were considered drug-related. During the OLE/LTE, one patient withdrew due to pregnancy and one due to chronic sinusitis. One death occurred due to pneumococcal meningitis and one to coronary atherosclerosis, respectively; the causes of death were assessed by the treating physician and considered not to be treatment-related. Through Week 56 (up to 80 weeks of rilonacept treatment) small to modest mean reductions in platelet (67K/mm3) counts occurred, but levels were stable throughout and did not fall below reference range. Mean neutrophil counts decreased (-1.9 K/mm3); no patients reported with neutropenia (<1.0 K neutrophils/mm3). Small and expected increases (16.9 mg/dL) in mean total cholesterol occurred. Change in weight and BMI was 2.9kg and 1.0 kg/m2, respectively, at Week 72. Other vital signs were without notable changes. Among the 96 patients who received at least 6 weeks of treatment through Week 72 of the OLE, 39 (40.6%) and 20 (20.8%), respectively, were anti-rilonacept Ab positive or positive at last assessment. Titers were generally low to moderate and had no apparent impact on rilonacept levels.

Conclusion: Rilonacept is generally well tolerated in both the long- and short-term when administered as a weekly SC injection of 160 mg.

Disclosure: H. M. Hoffman, Regeneron, 5 ; **D. R. Nadler**, Regeneron, 1, Regeneron, 3 ; **W. P. Brooks**, Regeneron, 3 ; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1 .

ACR Concurrent Abstract Sessions

Molecular Modulation of Gene Expression

Monday, October 19, 2009, 4:30 PM - 6:00 PM

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Suppressive Influences of IFN-α On IL-17 Expression and Th17 Differentiation. Shunsei Hirohata[1] and Hideki Shibuya[2], [1]Kitasato Univ School of Med, Kanagawa, Japan, [2]Tokyo Teishin Hospital, Tokyo, Japan

Purpose: T cells secreting IL-17 (Th17) have been implicated in the pathogenesis of a variety of inflammatory diseases, including inflammatory bowel disease, multiple sclerosis and Behçet's disease. Since IFN-α has been shown to have beneficial effects in the treatment of ulcerative colitis and uveitis in Behçet'sdisease, it is possible that IFN-α might regulate the development of Th17. The current studies were therefore undertaken to explore the direct effects of IFN-α on the development of Th17 with a system using immobilized anti-CD3, which permits activation of CD4+ T cell in the complete absence of accessory cells.

Method: Highly purified CD4+ T cells obtained from healthy volunteers were stimulated with immobilized anti-CD3 with or without IFN-α. The production of IL-17 and TGF-β was measured by ELISA, and that of IL-6 was determined using a bioassay with IL-6 dependent murine hybridoma MH60.BSF2 cells. The expression of mRNA for IL-17 and retinoic acid receptor-related orphan receptor C (RORC) was evaluated by using quantitative PCR.

Results: The production of IL-17 could not be dtected at 24 h of cultures, but markedly increased between 24 h and 72 h and appeared to reach the peak at 72h of cultures with immobilized anti-CD3. IFN-α suppressed the production of IL-17 of immobilized anti-CD3-stimulated CD4+ T cells at 72 h of cultures in a dose-response manner. Accordingly, IFN-α inhibited IL-17A mRNA expression in immobilized anti-CD3-stimulated CD4+ T cells from 7 healthy individuals as early as at 3 h of cultures. TGF-β and IL-6 have been shown to play a critical

role in the development of Th17. However, IFN-α did not affect the production of TGF-β or IL-6 at 24h or 72 h of cultures. Of importance, IFN-α inhibited the expression of mRNA for RORC (a key transcription factor for Th17 development) in anti-CD3-stimulated CD4+ T cells as early as at 3 h.

Conclusion: The data indicate that IFN-α suppresses IL-17 expression and Th17 differentiation through direct actions on CD4+ T cells, resulting in down-regulation of RORC mRNA expression without influencing the production of TGF-β or IL-6. It is therefore suggested that these effects might be involved in the mode of action of IFN-α in the treatment of various inflammatory diseases, in which Th17 plays an important role in the pathogenesis.

Disclosure: S. Hirohata, None; **H. Shibuya**, None.

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Essential Role for the ER Stress Induced Transcription Factor, CHOP10 in IL-23 Gene Expression. Jane Goodall[1], Changxin Wu[1], Lou Ellis[1], Louise O'Brien[1] and J. S. Hill Gaston[2], [1]University of Cambridge., Cambridge, United Kingdom, [2]Univ of Cambridge/Clin Med, Cambridge

Purpose: We have previously shown that ER stress and TLR signalling synergistically enhance IL-23 p19 expression in myeloid cells. Furthermore these combined stimuli substantially enhance the secretion of IL-23 but not IL-12 by dendritic cells. The aim of this study is to investigate the mechanism of this synergy.

Method: We examined the human *IL-23* promoter for potential binding sites for ER stress induced transcription factors and identified a putative site for CHOP10. U937 cells were stimulated with LPS or the ER stress inducing chemical thapsigargin (TP), alone or in combination for 1, 3 and 5 hours and nuclear lysates were isolated. Immunoprecipitation (ChIP) assays using anti CHOP10 and isotype control Mab were performed and IL-23 promoter DNA was detected by qPCR. To confirm the role of CHOP10 in IL-23 gene transcription, U937 cells expressing shRNA's specific for CHOP10 or non specific gene target were tested for their ability to express IL-23 following TLR and ER stress stimulation for 8 hours. Live or γ-irradiated *Chlamydia trachomatis* (CT) was used to infect U937 cells at a multiplicity of infection of 10:1 for 12 hours.

Results: CHOP10 binding on the *IL-23* promoter was detected following stimulation of U937 cells with LPS or TP alone, but this was significantly enhanced when ER stress and TLR stimuli were combined. Maximal CHOP10 binding was detected at 5 hours post stimulation with LPS and TP. IL-23 promoter DNA was not detectable following ChIP with a isotype control antibody. U937 expressing three independent shRNA targets for CHOP10 exhibited a significant reduction in IL-23p19 mRNA (up to 87% reduction of the response to LPS+TP) compared to U937 expressing a control shRNA. CHOP10 shRNA expression did not affect the expression of other LPS induced genes including IL-1, IL-8, CCL3 and SOD2.

To identify if ER stress induction of IL-23 mediated by CHOP10 expression plays a role in a more physiological setting, we examined the role of CHOP10 in the induction of IL-23p19 gene expression following CT irradiated–infection. The infection of U937 cells with live but not γ- CT induced the expression of ER stress response genes, including CHOP10. U937 infected with live CT exhibited increased IL-23p19 mRNA expression compared to U937 infected with nonviable bacteria. CHOP10 silencing substantially reduced the ability of live CT to induce IL-23p19mRNA, confirming the important role of CHOP10 in the response to infection.

Conclusion: We have shown that ER stress signals make a significant contribution to the control of IL-23 expression. Here we show that the ER stress induced transcription factor, CHOP10, is a critical factor that regulates IL-23p19 gene expression. These data suggest that the initiation of ER stress by infection or other physiological processes would contribute significantly to the pathology associated with diseases where IL-23 plays an important role in their pathogenesis.

Disclosure: J. Goodall, None; **C. Wu**, None; **L. Ellis**, None; **L. O'Brien**, None; **J. S. H. Gaston**, None.

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Receptors for TSLP and IL-7 Strongly Promote Proteoglycan-Induced Arthritis. Sarita A.Y. Hartgring[1], Cynthia R. Willis[2], Johannes W. J. Bijlsma[1], Femke Broere[3], Floris P.J.G. Lafeber[1] and Joel A.G. van Roon[1], [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Amgen Inc., Seattle, WA, [3]University Utrecht, Utrecht, Netherlands

Purpose: IL-7 is a potent T cell activating cytokine that can lead to T-cell-dependent activation of monocytes, B cells, and osteoclasts. IL-7 effects are mediated through the high affinity IL-7 receptor-alpha chain (IL-7Rα) in conjunction with the common-gamma chain. Another cytokine, thymic stromal lymphopoietin (TSLP), shares the IL-7Rα for signaling, but has a distinctive receptor subunit, the TSLP receptor. TSLP acts on dendritic cells, mast cells, and CD4 T cells and plays a key role in Th2-type inflammatory responses. We used the proteoglycan-induced arthritis (PGIA) model to determine whether there are distinct roles for IL-7Rα and TSLPR in the immunopathology of arthritis.

Method: PGIA was initiated by immunizing aged female wild type BALB/c (WT) or TSLPR knockout BALB/c (TSLPR-/-) mice with human PG. Mice were treated with PBS as a control, or with an anti-IL-7Rα antibody. Clinical arthritis was determined by visual examination of swelling and redness of the paws. Joint destruction on day 33 was assessed on basis of radiographs and histological examinations of the ankle joints. Cellularity of thymus and spleen and numbers of T-cell subsets, and B cells were assessed. Proinflammatory mediators were assessed by multi-analyte profiling in serum and paw protein lysates.

Results: Anti-IL-7Rα treatment in WT mice significantly reduced arthritis, compared with PBS WT (mean inhibition 55%, $p=0.007$). The TSLPR-/- mice also showed decreased arthritis severity compared with PBS WT (56%, $p=0.019$). Ablation of the TSLPR toghether with IL-7Rα blockade showed an even stronger reduction of arhritis (70%, $p=0.002$). Total numbers of thymocytes or splenocytes in TSLPR-/- mice were not different compared with the PBS WT mice. Splenic CD4 and CD8 T cells were modestly decreased by treatment with anti-IL-7Rα as compared with the non treated mice (PBS WT vs anti-IL-7Rα treated WT 22% decrease; PBS TSLPR-/- vs TSLPR-/- anti-IL-7Rα treated 26% decrease, both $p<0.01$ for CD4 T cells). The additive effect of blocking both IL-7 and TSLP signaling was clearly shown by radiological scoring of joint damage (PBS WT vs anti-IL-7Rα treated WT 59% decrease, PBS WT vs PBS TSLPR-/- vs 75%, and PBS WT vs anti-IL-7Rα treated TSLPR-/- 94%, all $p<0.01$). This was consistent with the histological joint damage, showing additive ($p<0.05$) reduction of cell infiltrates, bone and cartilage erosions. Furthermore, multi-analyte profiling of serum and paw lysates showed decreased (at least $p<0.05$) concentrations of cytokines, chemokines, acute phase reactants, and factors associated with tissue destruction.

Conclusion: Our data show that both IL-7Rα and TSLPR signaling promote arthritis and joint destruction. Blocking both pathways results in additive disease suppression indicating the distinct contributions of TSLPR and IL-7Rα in arthritis and the potential of targeting these receptors in arthritic conditions, including RA.

Disclosure: S. A. Y. Hartgring, None; **C. R. Willis**, Amgen Inc., 3, Amgen Inc., 1 ; **J. W. J. Bijlsma**, None; **F. Broere**, None; **F. P. J. G. Lafeber**, None; **J. A. G. van Roon**, None.

1241

Dendritic Cell-Specific Transmembrane Protein (DC-STAMP) Is An Immunoreceptor Tyrosine-Based Inhibitory Motif (ITIM)-Bearing Molecule Regulating Osteoclast Development Thru the SHP-1 Signaling Cascade. Yahui Grace Chiu, Yawen Ju, Kofi A. Mensah, Changyong Feng, Edward. M. Schwarz and Christopher T. Ritchlin, University of Rochester, Rochester, NY

Purpose: DC-STAMP is a 7-pass transmembrane protein required for cell-to-cell fusion during osteoclastogenesis. Our previous studies showed that DC-STAMP can serve as a biomarker for osteoclast precursors (OCP), and importantly, the expression patterns of DC-STAMP differ significantly between healthy individuals and PsA patients. Herein, we examined the molecular mechanism underlying the regulation of osteoclast (OC) formation by DC-STAMP. We evaluated the role of DC-STAMP as a signaling molecule in the receptor activator of NF-kB ligand (RANKL)-induced osteoclastogenesis pathway. Moreover, we investigated the effects of a novel monoclonal anti-DCSTAMP antibody 1A2 on OC formation.

Methods: We compared the sequence of DC-STAMP with the ITIM consensus sequence (I/V/L/S)-X-Y-X-X-(L/V) where X denotes any amino acid. Proteins isolated from fresh human monocytes, monocyte-derived OC or dendritic cells (DC) were immunoprecipitated and immuno-blotted with either anti-DCSTAMP, anti-SHP-1 or anti-phosphorylated tyrosine antibodies. To test the effect of a monoclonal anti-DC-STAMP antibody 1A2 on osteoclastogenesis, human monocytes were cultured in the presence or absence of 1A2 and were TRAP-stained for OC quantification on day 8. The permutation test was performed on the data for 1A2 inhibition for statistic analysis.

Results: We identified an important immuno-regulatory motif ITIM on the cytoplasmic tail of DC-STAMP. By immunoprecipitation and western blotting, we showed that DC-STAMP is phosphorylated thru its tyrosine residues and interacts with SHP-1, a SH2 domain-

containing tyrosine phosphatase 1 and an inhibitory element for osteoclastogenesis. Interestingly, we found DC-STAMP also associates with CD16, a molecule bearing the counteracting immunoreceptor tyrosine-based activation motif (ITAM). Monocyte-derived DC showed less phosphorylation on DC-STAMP than OC. Addition of 1A2 to the monocyte cultures significantly inhibited OC formation (489±284 vs. 61±107 OC without or with 1A2 per 10^6 monocytes, respectively, p=0.013), and staining revealed that the majority of monocytes were arrested at the TRAP-positive pre-OC stage.

Conclusion: In addition to its current role considered as a fusogen in mediating the cell-to-cell fusion during osteoclastogenesis, our finding of ITIM on the cytoplasmic tail of DC-STAMP defines its new role in OC development as a signaling molecule. Our data show that DC-STAMP regulates osteoclastogenesis possibly by interacting with SHP-1 thru its tyrosine residues on ITIM. Intriguingly, the levels of DC-STAMP phosphorylation differ in DC and OC. Most importantly, the observation that the anti-DC-STAMP antibody 1A2 can inhibit OC formation in vitro emphasizes the potential of 1A2 in therapeutic application for prevention of inflammatory and metabolic bone loss.

Disclosure: Y. G. Chiu, None; **Y. Ju**, None; **K. A. Mensah**, None; **C. Feng**, None; **E. M. Schwarz**, None; **C. T. Ritchlin**, None.

1242

MiR-155 and Mir-34a Regulate TNF-Alpha Production by Human Monocytes. Mariola Kurowska-Stolarska, Lucy E. Ballantine, Bartosz Stolarski, J. Alastair Gracie, Foo Y. Liew and Iain B. McInnes, University of Glasgow, Glasgow, United Kingdom

Purpose: Dysregulated pro-inflammatory activation of synovial monocyte and macrophage is of fundamental importance in pathogenesis of rheumatoid arthritis (RA). Recently microRNA (miRNA) have been identified as critical post-transcriptional regulators of many components of immune responses. The aim of our study was to investigate the role of candidate miRNAs, miR-155 and mir-34a in the activation of RA synovial fluid (SF) and blood monocyte / macrophages.

Method: CD14+ cells from SF or peripheral blood (PB) of RA patients (n=7) and CD14+ cells from PB of healthy controls (n=6) were isolated using CD14 MACS MicroBeads. PB CD14+ cells were stimulated with LPS (100 ng/ml), Pam3CSK4 (300 ng/ml), PolyI:C (50 μg/ml), CPG (3 μg/ml), control CPG (3 μg/ml) or protease activated receptor-2 (PAR2) agonist (SLIGKV-NH2; 50μM) for 24h. PB CD14+ cells were transfected with miR-155, miR-34a or scramble mimics (all 3.5 mg/3x10^6 cells) by electroporation (Amaxa). Expression of AXL (receptor tyrosine kinase) and TNF production were tested 36 h later. Total RNA was isolated by miRNeasy kit. TaqMan miRNA and mRNA assays were used for semiquantitative determination of the expression of miR-155, miR-34a and AXL, respectively. The expression of U6B small nuclear RNA and beta-actin were used as endogenous controls. To identify the cellular targets of candidate miRs, multiple target prediction programs and mRNA transcriptomic signatures of SF CD14+ cells were employed.

Results: Synovial fluid CD14+ cells expressed higher levels of miR-155 (64 fold, $p<0.05$) and miR-34a (4.5 fold, $p<0.05$) than PB matched CD14+ cells. Expression of miR-155 was up-regulated by TLR2, TLR3, TLR4 and TLR9 ligands ($p<0.05$) but not by PAR2 agonist in PB CD14+ cells. In contrast, miR-34a expression was either not affected (Pam3CSK4, SLIGKV-NH2) or down-regulated (LPS, PolyI:C, CPG; $p<0.05$) under the same conditions. Overexpression of miR-155 and miR-34a mimics in PB monocytes induced TNF production (10170 ± 385 pg/ml) and (991 ± 33), respectively. Using computational target ranking system combined with mRNA transcriptomic data we identified a negative regulator of TLR/IL-1R signalling, AXL, to be targeted by miR-34a. Overexpression of miR-34a and miR-155 mimics decreased the expression of AXL in PB monocytes by (48 ± 3%) and (38 ± 16%), respectively.

Conclusion: These data suggest that overexpression of miR-155 and miR-34a in CD14+ cells can result in downregulation of AXL expression which in turn can lead to the overproduction of TNF. We provide a novel mechanism for deregulated TNF production in RA synovial macrophages amenable to therapeutic intervention in due course.

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1243

IL-17 Acts through Act1 and TRAF6 to Mediate the Canonical NF-κB Signaling Pathway to Upregulate RGS16 Expression in Autoimmune B Cells of BXD2 Mice. Shutao Xie[1], Hui-Chen Hsu[1], John Wang[1], Qi Wu[1], Jun Li[1], Lesley E. Smythies[1] and John D. Mountz[2], [1]The University of Alabama at Birmingham, Birmingham, AL, [2]The University of Alabama at Birmingham and Birmingham VAMC, Birmingham, AL

Purpose: BXD2 mice spontaneously develop erosive arthritis and lupus that progresses as the mice age. We previously found that BXD2 mice express high levels of IL-17, which correlate with upregulated expression of *Rgs* genes and results in suppression of B cell migration in response to CXCL12 and CXCL13, leading to the development of spontaeous germinal centers. This study is to elucidate the signaling mechanisms underlying this regulation mediated by IL-17 in autoimmune B cells of BXD2 mice.

Method: Purified splenic B cells from BXD2, BXD2-*Il17r*$^{-/-}$ or B6 mice and pre-B cell line 70Z/3 were incubated with or without IL-17 for varying times. Intracellular location of phosphorylated p65 (P-p65) was determined by fluorescent microscopy. Antibodies against phosphorylated IκBα (P-IκBα), P-p65, p65, p50, phosphorylated p100 (P-p100), p52, RelB, and RGS16, GAPDH and SP1 were used for western blotting analysis. siRNAs for *Act1*(*Traf3ip2*) or *Traf6* were transfected into 70z/3 pre-B cells to knockdown them respectively. Expression of *Rgs* genes, *Act1* and *Traf6* were determined by quantitative real-time PCR.

Results: Treatment of isolated splenic B cells with IL-17 resulted in rapid phosphorylation of IκBα and p65 (>2.5-fold, $p<0.01$) and lead to P-p65 nuclear translocation. IL-17 did not affect the non-canonical NF-κB pathway, as indicated by no significant increase or nuclear translocation of P-p100, p52 or RelB in either splenic B cells or 70Z/3 cells. Compared to B6 or BXD2-*Il17r*$^{-/-}$ B cells, BXD2 B cells exhibited dramatically higher endogenous P-p65 (>5.0-fold, $p<0.01$), and this was suppressed after blockade of IL-17 signaling *in vivo* via administration of AdIL-17R-Fc. Pretreatment of BXD2 B cells or 70Z/3 pre-B cells with a permeable peptide inhibitor of p65-ser276 phosphorylation resulted in significant inhibition of IL-17 induced RGS16 (>4-fold, $p<0.01$) and abrogated the IL-17 mediated chemotactic arrest of B cells. Suppression of TRAF-6 and Act-1 using siRNAs of *Traf6* or *Act1* led to decreased induction of *Rgs* genes in 70z/3 pre-B cells by IL-17 (>1.5-fold, $p<0.05$).

Conclusion: IL-17 activates the canonical NF-κB signaling pathway to upregulate *Rgs* genes expression in B cells. The activation of NF-κB signaling by IL-17 is especially evident in autoimmune B cells of BXD2 mice. In addition, TRAF6 and Act1 may be important factors in the upstream signaling for the IL-17 mediated activation of NF-κB pathway in B cells. Our findings suggest that blockade of IL-17 receptor recruitment of TRAF-6 and Act-1 or IL-17 mediated NF-κB P-p65 activation and translocation may provide important mechanisms to block the IL-17-mediated production of pathogenic autoantibodies, lupus, and erosive arthritis.

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ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Clinical Aspects: Outcomes and Outcome Measures

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1244

Fatigue Is Not An Inflammatory Marker of RA. Martin J. Bergman[1], Shadi H. Shahouri[2], Timothy S. Shaver[2], James D. Anderson[3], David N. Weidensaul[2], Ruth E. Busch[2], Shirley Wang[2], Kaleb D. Michaud[4] and F. Wolfe[5], [1]Drexel University College of Medicine, Ridley Park, PA, [2]Arthritis & Rheum Clinics KS, Wichita, KS, [3]Arthritis & Rheum Clinics KS, Leawood, KS, [4]University of Nebraska Medical Center and NDB, Omaha, NE, [5]National Data Bank, Wichita, KS

Purpose: To investigate whether fatigue is an inflammatory (RA) variable, the contributions of RA variables to fatigue, and the levels of fatigue in RA and osteoarthritis (OA).

Method: We studied 2096 RA patients (1577 with DAS-28 scores) and 1440 OA patients in a clinical setting, and 14607 RA and 3173 OA patients in survey research. Individual components of the DAS28 and ACR core data set were obtained and analyzed for individual

correlations. We partitioned variables into inflammatory and non-inflammatory factors using a 2-factor analysis and examined variable contribution to VAS fatigue.

Results: There were significant correlations between the levels of pain in patients with RA as compared to patients with OA. The mean clinic fatigue scores were RA= 4.9 and

OA= 4.8 on a 0-10 scale; mean survey pain scores were RA =4.5 and OA=4.4. Mean pain differences for both the clinical group and the survey group were 0.1 units (scale 0-10). Adjusted for age and sex, RA and OA fatigue scores were not significantly different. Factor analysis identified DAS-28 and swollen (SJC) and tender joints (TJC) as a physician-inflammation factor, and patient global, pain, HAQ, and fatigue as patient components. Fatigue demonstrated weak correlations with ESR (r=0.071) and SJC (r=0.112), weak to fair correlations with TJC (r=0.294), physician global (r=0.384), and DAS-28 (r=0.399), but strong correlation with patient global (r=0.567). In hierarchical regression analysis, patient global explained 43.1% of DAS-28 fatigue variance; when SJC, TJC, and ESR were entered the explained variance increased to 43.7%. In reverse order, SJC, TJC, and ESR explained 9.2% of the variance, but explained variance increased to 43.7% when patient global was added.

Conclusion: Inflammatory components of the DAS-28 contribute minimally to fatigue. RA and OA fatigue levels do not differ. Fatigue is not an inflammatory variable and has no unique association with RA or its therapy. Although the impact of fatigue on patients with RA cannot be understated (mean Pain=4.9 in the clinical setting),t he need to measure fatigue in clinical trials, as an independent marker of disease activity, has to be questioned.

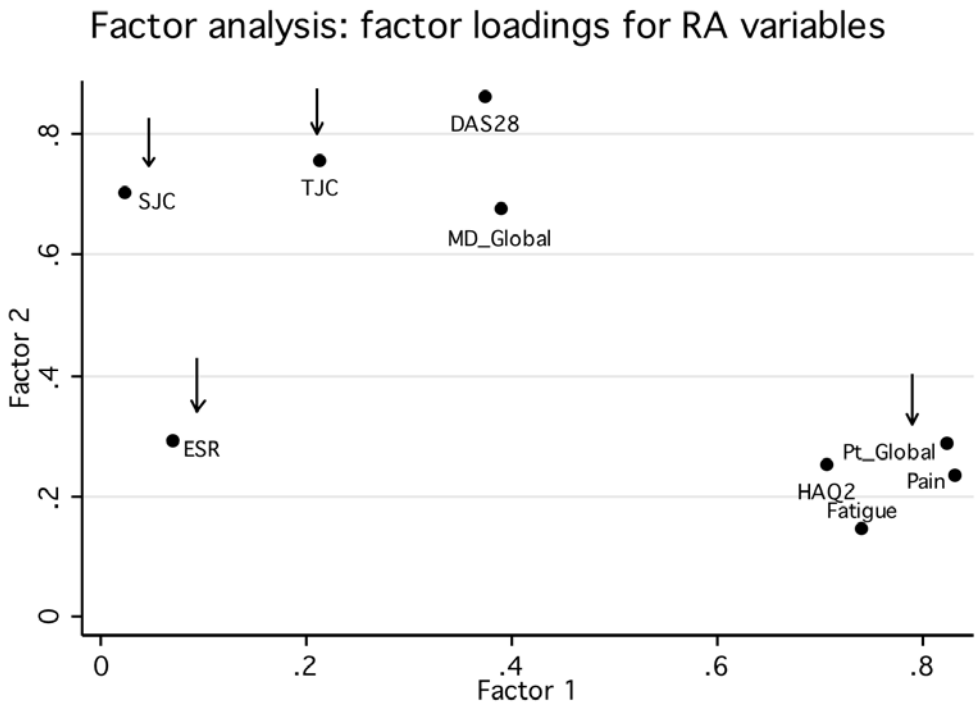

Figure 1. Factor loadings. Arrows indicate components of DAS-28. Fatigue clusters with patient variables, not with inflammatory (physician) variables. SJC = swollen joint count; TJC = tender joint count; ESR = erythrocyte sedimentation rate; DAS28 – Disease Activity Scale-28; MD_global – physician global activity; Pt_global = patient global severity; HAQ2 = Health Assessment Questionnaire II.

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1245

Patient's Global Assessment of Disease Activity and Patient's Assessment of General Health in Rheumatoid Arthritis: Are They Equivalent? Nasim A. Khan[1], Tuulikki Sokka[2] and QUEST-RA Investigators, [1]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [2]Central Hospital, Jyvaskyla, Finland

Purpose: Patient's global assessment of disease activity (PGA) and patient's assessment of general health/global health (GH) are part of several composite indices used to assess rheumatoid arthritis (RA) disease activity. Though originally each composite index used either PGA or GH, subsequently they have been used interchangeably for calculating indices that they were not a part of . We assessed whether PGA and GH are equivalent as individual variables, and if they can be used interchangeably in calculating common composite indices used for RA activity assessment.

Method: This analysis is based upon 7568 (6949 with complete data) patients in the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database who received usual care from rheumatologists in 83 sites in 30 countries. PGA and GH were assessed by patient self report questionnaire with 0-10 cm visual analog scales. Bland Altman 95% limits of agreement (BALOA) were calculated to assess equivalence of GH and PGA. The impact of using PGA and GH interchangeably was assessed by calculating disease activity score (DAS28), clinical disease activity index (CDAI) and routine assessment of patient index data 3 (RAPID3) and looking at the level of agreement in classifying RA activity in 4 states (remission, low, moderate & high) using Kappa statistics.

Results: The mean (SD) value for PGA and GH were 4.01 (2.70) and 4.04 (2.59) respectively. As individual measures, GH and PGA had good correlation (r = 0.64). The BALOA was - 4.41 to 4.54 and is too wide an interval for a 0-10 scale indicating that PGA and GH are not equivalent. Both DAS28 (absolute agreement: 98.5 to 99.5%, kappa = 0.98) and CDAI (absolute agreement: 81.2 to 96.2% kappa = 0.83) showed excellent agreement between RA activity categories calculated using PGA and GH. However, the level of agreement was lower for RAPID3 (absolute agreement: 68.7 to 91.4%, kappa = 0.75).

Conclusion: Though, individually PGA and PGH are not equivalent, they may be used interchangeably for calculating composite index like DAS28/CDAI for RA activity assessment.

Disclosure: N. A. Khan, None; **T. Sokka**, None.

1246

A Comparison Between the Simplified Erosion and Narrowing Score (SENS) and the Sharp-Van Der Heijde Score (SHS) in Assessing Radiological Damage in RA Patients During 5 Years of Follow-up. N.B. Klarenbeek[1], M. Güler-Yüksel[1], Désirée M.F.M. van der Heijde[2], P.J.S.M. Kerstens[3], C. Mallée[4], M.L. Westedt[5], T.W.J. Huizinga[1], B. A. C. Dijkmans[6] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]JBI, Amsterdam, Netherlands, [4]Kennemer Hospital, Haarlem, Netherlands, [5]Bronovo Hospital, The Hague, Netherlands, [6]VUMC, Amsterdam, Netherlands

Background: The Simplified Erosion and Narrowing Score (SENS) is an easy to learn and quick method to assess the number of joints with erosions and/or joint space narrowing on radiographs of hands and feet in patients with RA. Since SENS does not take severity of damage per joint into account, sensitivity to change may decrease over time.

Purpose: To compare the reliability and sensitivity to change of SENS and SHS during 5 years of follow-up in a large number of recent onset RA patients.

Methods: Annual radiographs of year 0 to 5 of 508 patients participating in the BeSt study were scored in one session per patient by two readers independently using SHS. X-rays were scored in random order, blinded for patient identity. The SENS scores were derived from the SHS scores. Interobserver reliability (intra-class correlation coefficients (ICCs)) was calculated for different time intervals. Sensitivity to change was compared using the ratio of Standardized Response Means (SRMs) of SHS and SENS and Effect Size (ES) ratios. Progression % > smallest detectable change (SDC, calculated each time interval) between the methods were compared. Sensitivity and specificity of SENS were defined, with SHS as gold standard. Non-parametric tests were used to assess the discriminative ability between treatment arms.

Results: Mean baseline scores for SHS and SENS were 7.1 and 3.8. The interobserver ICCs of SENS and SHS were comparable and constant over time (ICC of progression between annual SHS and baseline: 0.91, 0.91, 0.90, 0.91, 0.91 for SENS and 0.93, 0.93, 0.93, 0.91, 0.95 for SHS). Using change scores with time intervals of 1 year, the ICCs of SENS and SHS highly correlated as well, although the ICCs of both methods were lower after year 1, when there was less progression (ICCs for year 1-5 SHS vs SENS: 0.93 vs 0.91, 0.65 vs 0.57, 0.69 vs 0.59, 0.66 vs 0.51, 0.68 vs 0.62). SRM ratios ranged from 0.73 to 1.18 without a clear pattern over time. ES ratios showed similar results. Percentages with progression >SDC for both methods were comparable over time. Specificity and sensitivity of SENS varied between 92% and 99% for change scores between each follow-up year and baseline. For change scores with a 1 year time interval, specificity was high at all years (94-99%), but sensitivity was lower with more variance over time (86%, 84%, 62%, 70%, 81% in year 1-5 for reader 1, 93%, 90%, 57%, 66%, 89% for reader 2). The ability to discriminate between the treatment arms was comparable in both methods.

Conclusion: The properties of SENS are comparable to SHS. There is no decrease in sensitivity to change over 5 years time. Therefore SENS seems a valuable method for assessing radiological joint damage in daily practice.

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1247

The BeSt Matrix Model in Recent-Onset Rheumatoid Arthritis Patients: Individual Prediction of Rapid Radiographic Progression and Numbers-Needed-to-Treat with Initial Combination Therapy. K. Visser[1], Y. P. M. Goekoop-Ruiterman[1], J.K. De Vries-Bouwstra[1], H.K. Ronday[2], P.E.H. Seys[3], P. Kerstens[4], T.W.J. Huizinga[1], B. A. C. Dijkmans[5] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]HAGA hospital, The Hague, Netherlands, [3]Franciscus hospital, Roosendaal, Netherlands, [4]JBI, Amsterdam, Netherlands, [5]M.D., PhD, Amsterdam, Netherlands

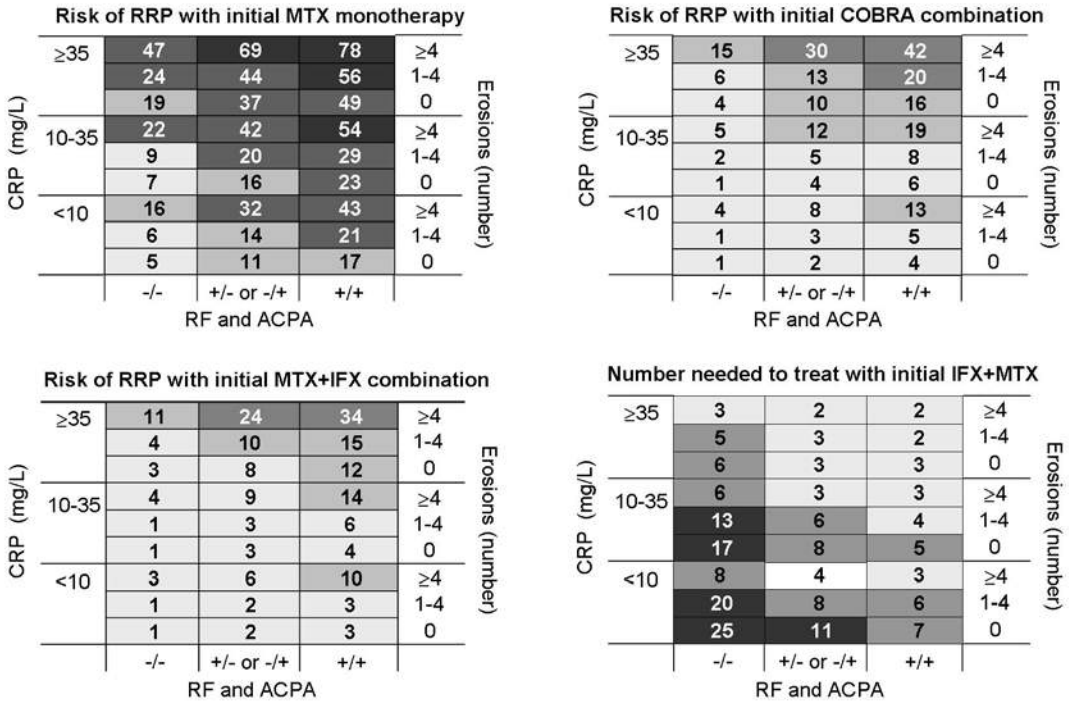
Background: Early treatment and the initial treatment choice determine the chance of a favorable outcome in patients with rheumatoid arthritis (RA). At the group level, initial combination treatment is superior to initial monotherapy. For individual patients, physicians may find it difficult to choose the initial treatment.

Purpose: To develop a matrix model for the prediction of rapid radiographic progression (RRP) in recent-onset RA patients with specific combinations of risk factors, if treated with different dynamic treatment strategies. To calculate numbers needed to treat with initial combination therapy versus initial monotherapy.

Method: Data from 465 recent-onset RA patients, randomized in the BeSt study to initial monotherapy with methotrexate (groups 1 and 2) or initial combination therapy including either prednisone (COBRA) or infliximab (group 3 and group 4) were used. Treatment was dynamically adjusted, aiming at a disease activity score (DAS) of =<2.4. Predictors for RRP, defined as a change in Sharp-van der Heijde (SvdH) score α 5 after one year, were identified with logistic regression analysis. From the fitted multivariate model, the predicted risk for RRP for patients with a specific combination of risk factors per treatment group was visualized in a matrix. A receiver operating characteristic (ROC) curve was fit and the positive (PPV) and negative predictive value (NPV) of the model were calculated. Compared with initial monotherapy, the number needed to treat (NNT) with initial combination therapy to prevent one patient from RRP was calculated and likewise presented in a matrix.

Results: The presence of rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA), C-reactive protein (CRP), the baseline SvdH erosion score and treatment group were significant independent predictors of RRP. With cut-offs at 20% (low risk), and 50% (high risk), the matrix shows a low risk for 23% of the patients treated with initial monotherapy (NPV 91%), a high risk for 25% of the patients (PPV 62%), leaving a midgroup of patients with intermediate risk (20-50%). In the combination therapy groups the risk of RRP was markedly reduced. The area under the ROC curve was 0.81 (0.77-0.86). The NNT with initial combination therapy including prednisone or infliximab to prevent one patient from RRP with monotherapy ranged from 2 for patients with unfavorable prognostic characteristics to 25 for patients with more favorable prognostic factors.

Conclusion: Based on dynamic treatment outcomes of the BeSt study, a matrix risk model was developed, which visualizes the risk of RRP for patients with recent-onset RA, with specific combinations of prognostic factors, if treated with initial mono or combination therapy, and which illustrates the risk for over- and undertreatment. Rheumatologists might use the matrix for weighing their initial treatment choice.



Disclosure: K. Visser, None; **Y. P. M. Goekoop-Ruiterman**, None; **J. K. De Vries-Bouwstra**, None; **H. K. Ronday**, None; **P. E. H. Seys**, None; **P. Kerstens**, None; **T. W. J. Huizinga**, Schering-Plough, 5 ; **B. A. C. Dijkmans**, None; **C. F. Allaart**, None.

1248

Changes in the Rates of Joint Surgery Among Patients with Rheumatoid Arthritis in California, 1983-2007. Grant H. Louie and Michael M. Ward, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD

Purpose: Treatment of rheumatoid arthritis (RA) has improved markedly over the past 25 years. We previously reported that rates of total knee arthroplasty, a long-term sequela of poorly-controlled RA, decreased among patients with RA in California in 1998-2001 after peaking in the 1990s. Because it is uncertain whether these rates have continued to decrease, we examined rates of total knee arthroplasty through 2007, and investigated whether rates of other joint surgery decreased between 1983 and 2007.

Methods: In this population-based, serial cross-sectional study of California residents aged 40 years and older with RA, we analyzed trends in annual rates of total knee arthroplasty, total hip arthroplasty, total ankle arthroplasty or arthrodesis, and total wrist arthroplasty or arthrodesis from 1983-2007. We computed age-, sex-, and race-adjusted rates of joint surgery and pooled data in 5-year intervals to provide more stable estimates of rates. We used Poisson regression models to compare changes in adjusted rates across time periods, and performed stratified analyses by age and sex.

Results: Rates of joint surgery peaked in the 1990s and since have decreased (Table). Among patients aged 40-59 years, rates of total knee arthroplasty in 2003-2007 were 19% lower than in 1983-1987 (adjusted rate ratio 0.81; 95% confidence interval (CI) 0.74 – 0.87, $P <$ 0.0001), while rates of total hip arthroplasty in 2003-2007 were 40% lower than in 1983-1987 (adjusted rate ratio 0.60; 95% CI 0.54 – 0.66, $P < 0.0001$). Rates of total knee arthroplasty and total hip arthroplasty in 2003-2007 did not decrease in patients aged ≥ 60 years but increased by 4% ($P = 0.19$) and 26% ($P < 0.0001$), respectively. Similar trends were observed in the general population. Compared with rates of ankle and wrist surgery in the mid-1980s, rates in the mid-2000s decreased significantly in both age groups. For all four procedures, trends were similar in men and women.

Table. Age-, sex-, and race-adjusted rates of joint surgery among 100,000 persons with rheumatoid arthritis from 1983-2007

	1983-1987	**1988-1992**	**1993-1997**	**1998-2002**	**2003-2007**

Total					
Total knee arthroplasty	478.3	486.9	524.1	444.3	460.4
Total hip arthroplasty	311.6	377.3	417.4	363.4	323.5
Ankle surgery	39.8	47.2	48.2	32.7	23.7
Wrist surgery	7.8	15.1	12.8	8.2	3.1
Age 40-59 years					
Total knee arthroplasty	381.6	366.6	381.2	301.9	309.3
Total hip arthroplasty	286.4	276.9	268.1	223.6	172.0
Ankle surgery	52.3	56.9	52.5	33.1	20.8
Wrist surgery	8.3	15.4	10.4	8.0	3.5
Age ≥ 60 years					
Total knee arthroplasty	553.9	581.2	636.0	555.2	577.8
Total hip arthroplasty	331.5	456.2	534.0	472.4	441.3
Ankle surgery	30.2	39.8	44.9	32.4	25.9
Wrist surgery	7.4	15.0	14.6	8.5	2.7

Conclusion: Rates of joint surgery in patients with RA peaked in the 1990s and have declined thereafter, suggesting that long-term outcomes of RA are improving.

Disclosure: G. H. Louie, None; **M. M. Ward**, None.

1249

Decrease of Hip Replacement Surgery in Patients with Rheumatoid Arthritis - Results From a Well Defined Population in Southern Sweden. Korosh Hekmat[1], Lennart TH Jacobsson[1], Jan-Åke Nilsson[1], Ingemar F. Petersson[2], Otto Robertsson[2], Göran Garellick[3] and Carl Turesson[1], [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Orthopedics, Department of Clinical Sciences, Lund, Lund University, Lund, Sweden, [3]Department of Orthopaedics, Swedish Hip Arthroplasty Register, Institute of Clinical Sciences at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Purpose: Major joint arthroplasty is used effectively in many patients with severe rheumatoid arthritis. The aim of modern pharmacologic treatment is to prevent joint destruction and reduce the need for orthopedic surgery. The purpose of our study was to investigate trends in the incidence of primary total hip and knee replacements in a well defined sample of patients with RA.

Method: Patients were recruited from a community based register established in 1997, which includes patients from a single University Clinic and collaborating private practitioners. Prevalent cases of RA in 1997 and incident cases 1997-2007 were included. Based on a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria, and the year of RA diagnosis was noted. The incidence of major joint arthroplasty was estimated based on linkage of this cohort with the Swedish

National Hip Arthroplasty (through December 2006) and the Swedish Knee Arthroplasty Register (through October 2007). During the study period, indications for joint replacement in Sweden were based on objective clinical and radiographic findings and were relatively stable across different clinics, although minor changes over time can not be excluded. Patients with a registered hip or knee arthroplasty before 1997 or before RA diagnosis were excluded. The incidence rate for the period at and just after the time of the introduction of TNF inhibitors (1998-2001) was compared to the period when biologics were part of the established treatment for severe RA (2002-2006 for hip replacements and 2002-2007 for knee replacements).

Results: There were 2164 patients in the cohort (1545 women, 619 men; mean age at diagnosis 51 years). During the study period, a primary hip arthroplasty was registered for 115 patients and a primary knee arthroplasty for 85 patients. The incidence of primary hip arthroplasties decreased from the period 1998-2001 [12.6/1000 person-years(pyr)] to 2002-2006 (6.6/1000 pyr) [rate ratio (RR) 0.52; 95% confidence interval (CI) 0.35-0.76 for 2002-2006 vs. 1998-2001] There was a trend towards an increase of the incidence of primary knee arthroplasty (4.8/1000 pyr 1998-2001 vs. 6.8/1000 pyr 2002-2007 – RR 1.43; 95% CI 0.89-2.31).

Conclusion: Our investigation shows a significant decrease in hip replacement surgery in patients with RA after 2001. Possible explanations include an effect on joint damage from more aggressive treatment with DMARDs and biologics. The trend towards an increase of knee arthroplasty may be due to changing indications for surgery. Alternatively, destruction of hip and knee joints in RA may be partly due to distinct mechanisms.

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ACR Concurrent Abstract Sessions

Reproductive Issues in Systemic Lupus Erythematosus

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1250

Importance of Cutaneous Manifestations of Neonatal Lupus as a Risk Factor for Subsequent Congenital Heart Block. Peter M. Izmirly, Carolina Llanos and Jill P. Buyon, New York University School of Medicine, New York, NY

Purpose: The cutaneous manifestations associated with placental transport of maternal anti-Ro/La antibodies are generally transient and inconsequential. However, the impact of this manifestation of neonatal lupus on the risk of cardiac disease in a future pregnancy is critical for family counseling and powering of preventive trials.

Methods: Of the 380 families enrolled in the Research Registry for Neonatal Lupus (RRNL) 57 met the following inclusion criteria: a) maternal anti-Ro or La antibodies, b) a child with classic annular or elliptical lesions on the face, scalp, trunk, or extremities which was verified by medical records and/or photographs, c) information on pregnancies subsequent to the child with rash. Maternal risk factors evaluated for recurrence of rash or emergence of cardiac manifestations included: age, race/ethnicity, antibody status, diagnosis, and use of non-fluorinated steroids during pregnancy. The following risk factors were also evaluated: gender of the child, season of birth, latitude of the city at birth, and breast feeding.

Results: The majority (77%) of the 57 mothers were Caucasian. Of the 76 pregnancies following a child with rash, the overall recurrence rate for any manifestation of neonatal lupus was 50%. Specifically 14 (18%) were complicated by congenital heart block (CHB) (all 2nd/3rd degree, 9 accompanied by a rash and 2 with associated liver/hematological abnormalities), a nearly tenfold risk over the 2% rate reported without a previously affected child. Twenty-three (30%) of the subsequent children had a rash (3 accompanied by hematological and/or liver abnormalities). One child (1%) had isolated liver/hematological abnormalities and one neonate (1%) died of unknown reasons. Thirty-seven (49%) were healthy. In an attempt to limit potential referral bias of families with multiple affected children, a subset analysis was restricted to the 45 children who were born prospectively after the initial child was enrolled in the RRNL. In this analysis, the overall recurrence rate for neonatal lupus was 36%. Specifically, 5 (11%) developed CHB (a 6-fold higher risk for CHB), 10 (22%) developed a rash and one child (2%) developed isolated liver/hematological abnormalities. There were no significant differences in the following maternal risk factors for a having a subsequent child with either CHB or rash: age, race/ethnicity, anti-La status, diagnosis or use of non-fluorinated steroids during

pregnancy. Fetal gender of the subsequent child did not influence the development of CHB or rash. Specifically with regard to the development of rash in a subsequent child, breast feeding, season of birth, or latitude of the city at birth did not affect risk.

Conclusion: Based on data from this large cohort, the identification of cutaneous disease in an anti-Ro exposed infant is particularly important since it predicts increased risk for a subsequent child with CHB.

Disclosure: P. M. Izmirly, SLE Foundation, Inc., 2 ; **C. Llanos**, SLE Foundation, Inc., 2 ; **J. P. Buyon**, NIH Contract NO1-AR-4-2220 (Research Registry for Neonatal Lupus), 2 .

1251

Preventive IVIG Therapy for Congenital Heart Block (PITCH). Deborah M. Friedman[1], Carolina Llanos[2], Peter M. Izmirly[2], Mimi Y. Kim[3] and Jill P. Buyon[2], [1]New York Medical College, Valhalla, NY, [2]NYU School of Medicine, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NY

Background: The recurrence rate of anti-SSA/Ro associated congenital heart block (CHB) is 17%. Reversal of 3rd degree block has never been achieved. Prophylactic IVIG was considered based on two presumed mechanisms of efficacy, a) saturation of FcRn to accelerate maternal IgG catabolism and decrease placental transport b) elevation of macrophage FcγRIIB expression to attenuate inflammatory fetal responses.

Purpose: To evaluate IVIG efficacy and safety as a preventive therapy for CHB.

Methods: A multicenter open-label study based on Simon's 2-stage optimal design was initiated. Enrollment criteria included: maternal anti-SSA/Ro antibody, a previous child with CHB/rash,nd or 3 rd degree CHB in three fetuses.

Results: Twenty mothers were enrolled. Sixteen children had normal PR intervals throughout the study and no manifestations of neonatal lupus. One child developed a transient rash consistent with neonatal lupus and had normal PR intervals during pregnancy and normal EKG at birth. However, the pre-determined stopping rule was reached. CHB was detected in three fetuses, at 19, 20 and 25 weeks; none followed an abnormal PR interval. One of these mothers had two previous children with CHB. Antibody titers assessed before every IVIG infusion, and at 28 wks, 34 wks and delivery were compared with values obtained at baseline. No significant changes in maternal antibody titers to SSA/Ro, SSB/La, or Ro52 were detected over the course of therapy or at delivery ($P>0.05$ for all comparisons). There were no changes in maternal blood pressure, severe headaches, rashes, fever or any other adverse effects related to the infusions. Neonatal weight, height, and head circumference were derived from gestational age -specific growth curves to correct for prematurity when necessary. Four (21%) of the newborns, two with CHB and two healthy, were small for gestational age (<10th centile) and 3 healthy babies (16%) were born prematurely (<37 weeks of gestation).

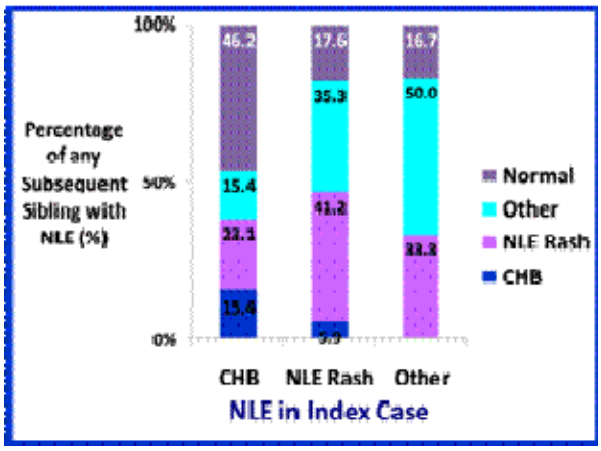
Conclusion: IVIG at doses consistent with replacement does not prevent the recurrence of CHB or reduce maternal antibody titers. Having established safety with this protocol and feasibility of patient enrollment, subsequent studies should address the efficacy of IVIG at higher doses to exploit an anti-inflammatory effect.

Disclosure: D. M. Friedman, MedImmune, 8 ; **C. Llanos**, SLE Foundation Inc., NY., 2 ; **P. M. Izmirly**, SLE Foundation Inc, NY., 2 ; **M. Y. Kim**, None; **J. P. Buyon**, Alliance for Lupus Research , 2 .

1252

Recurrence of Neonatal Lupus Erythematosus in Siblings. KC Danayan[1], E. Jaeggi[1], PN Tyrrell[2], A. Rogers[1] and ED. Silverman[3], [1]Hospital for Sick Children, Toronto, ON, [2]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, [3]Hospital for Sick Children and University of Toronto, Toronto, ON

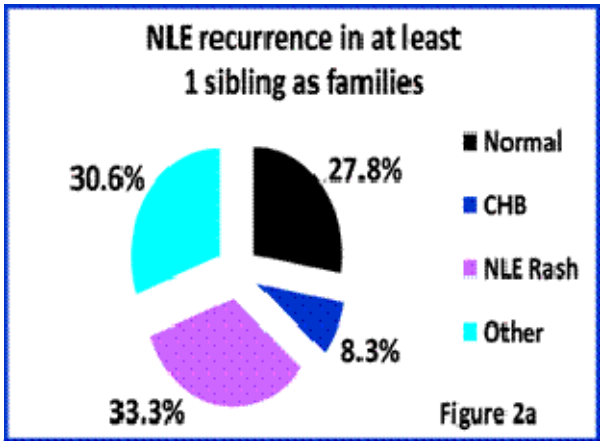
Purpose: Neonatal lupus erythematosus (NLE) is a model of passively acquired autoimmunity due to in utero exposure to maternal anti-Ro and/or anti-La antibodies. Manifestations of NLE include: congenital heart block (CHB), rash, hepatic or haematologic abnormalities, and macrocephaly. Much of the research to date has focused on the cardiac manifestations of NLE with little information on the risk of recurrence of NLE in subsequent pregnancies. The literature suggests a 15% recurrence risk of CHB developing in the subsequent sibling



following the delivery of a child with CHB related to NLE. However, this recurrence rate is based on very few studies and none examined the risk of recurrence of any NLE manifestation following an index case with NLE. Our study was designed to address this clinical question.

Method: A retrospective cohort study of 36 patients with confirmed NLE (index cases) and all 42 of their subsequent siblings followed at a tertiary paediatric hospital from March 1984 to April 2009. Detailed patient and maternal medical information was extracted from a rheumatology database and validated by chart review. The study cohort consisted of 42 consecutive children born to 36 anti-Ro and/or anti-La positive women. The women were identified following the delivery of a first-born child with confirmed NLE and all subsequent pregnancies were followed prospectively for the presence of fetal or neonatal manifestations of NLE. Patients were excluded if the NLE diagnosis was made retrospectively, essential patient information was missing, or the index NLE case was not seen initially at our institution.

Results: Recurrence of NLE in a subsequent sibling after an index case of confirmed NLE occurred in 72.2% of families (26 out of 36 families) and 64.3% of subsequent siblings (27 out of 42 siblings). The outcome of NLE manifestations in index cases compared to any subsequent sibling is illustrated below. The rate of occurrence of CHB was 8.3% in families and 7.1% of all subsequent siblings after an index case of NLE, but 15.4% if the index case had CHB and 0% if the index case did not have CHB or rash as their NLE manifestation.



Conclusion: NLE recurred in at least one subsequent sibling in over two-thirds of families and the majority of subsequent siblings following an index case of NLE - however, it mainly presented as benign and transient non-cardiac features. Interestingly, when an index case had CHB, the risk of CHB in any subsequent sibling was higher (15.4%) compared to families where an index case presented with non-cardiac manifestations of NLE, similar to previously published recurrence rates. Further studies are needed to identify predictors of NLE recurrence of congenital heart block in order to help guide prospective monitoring of future pregnancies and siblings.

Disclosure: K. Danayan, None; **E. Jaeggi**, None; **P. Tyrrell**, None; **A. Rogers**, None; **E. Silverman**, None.

1253

High Prevalence of Thyroid Disease in Pregnant Women with Systemic Lupus Erythematosus. Ehtisham Akhter[1], Alex Stagnaro-Green[2], Chang Yim[3], Terry F. Davies[3] and Michelle Petri[4], [1]Johns Hopkins University, Baltimore, MD, [2]Touro University College of Medicine, Hackensack, NJ, [3]Mount Sinai School of Medicine, New York, NY, [4]Johns Hopkins Univ, Baltimore, MD

Purpose: Postpartum thyroiditis (PPT) occurs in 5-10% of all women. Individuals with systemic lupus erythematosus (SLE), a systemic autoimmune disorder, have an increased incidence of autoimmune thyroid disease. The goal of the present study is to determine the incidence of thyroid disease during pregnancy and postpartum in women with SLE.

Method: Sixty-three women who participated in the Hopkins Lupus Cohort and who had sera frozen during pregnancy and/or the first year postpartum were included in the study. All samples were assayed for TSH, thyroid peroxidase and thyroglobulin antibodies. Demographic and laboratory data were available for analysis.

Results: Twenty-four percent of the 63 women were positive for thyroid antibodies. Eight of the 63 women (13%) were on levothyroxine prior to pregnancy. Six of the remaining 55 women (11%) were hypothyroid based on their first pregnancy sample. Six of the remaining 49 women had a serum sample available only during pregnancy, leaving 43 women who were evaluated for PPT. On average, each woman had 2 postpartum samples available for analysis. The incidence of PPT was 14% (6/43). Only one of the women who developed PPT was thyroid antibody positive. Analysis of demographic and laboratory data revealed no correlation with the presence of thyroid disease.

Conclusion: The percentage of women with SLE who either had levothyroxine treated thyroid disease prior to pregnancy, who were diagnosed with hypothyroidism during pregnancy, or who developed PPT was 38%. Women with SLE have a marked increased incidence of autoimmune thyroid disease. Antithyroid antibodies did not predict postpartum thyroiditis. It is recommended that all women with SLE should have a TSH and thyroid antibodies performed prior to pregnancy, as this study showed that the clinical diagnosis was frequently missed, with implications in terms of fetal growth and development and pregnancy outcomes

Disclosure: E. Akhter, None; **A. Stagnaro-Green**, None; **C. Yim**, None; **T. F. Davies**, None; **M. Petri**, None.

1254

Cervical Neoplasia and HPV Genetics in Systemic Lupus Erythematosus. J. P Dhar[1], L. Gregoire[1], W. Lancaster[1], A. Stark[2], A. Schwartz[1], D. Schultz[3], L. Essenmacher[1], J. Ager[1], L. Chiodo[1], M. Husain[4] and R. J. Sokol[1], [1]Wayne State University School of Medicine, Detroit, MI, [2]Geisenger Health Systems, Danville, PA, [3]Henry Ford Health Systems, Detroit, MI, [4]Detroit Medical Center, Detroit, MI

Purpose: To determine the frequency of high risk human papilloma virus (HPV), transcription activity, and viral genome integration in neoplastic cervical tissue of women with systemic lupus erythematosus (SLE), an immunosuppressed population with increased risk for cervical neoplasia.

Methods: The presence of high risk HPV types 16 and 18 were assayed in archived cervical biopsies obtained from 124 SLE patients with an abnormal pap smear from two large urban medical centers. DNA was extracted from paraffin blocks for polymerase chain reaction (PCR) All samples were positive for GAPDH amplification and amplified using primers specific for HPV 16 and HPV 18. RNA was extracted from formalin fixed tissues, reverse transcribed, and evaluated by real-time PCR using primers specific for HPV 16 and 18 open reading frames E7, E5, and E2. The presence of viral RNA indicated active transcription of the viral genome. Integration of viral DNA into host genome was determined by reduction of E5 and/or E2 relative to E7. Clinical data were abstracted from medical records; histologic diagnoses were confirmed for this study.

Results: Of the 124 SLE patients 77% were African American, 19% Caucasian, 4% other; mean age=48.1 yrs, mean age at time of biopsy=38.5 yrs. The results are summarized below in TABLE 1. HPV 16 was present in 16.9% (21/124) of biopsies; 7% (9/124) had HPV 18; 0.8% (1/124) had both HPV 16 and 18. Active transcription of the viral genome was present in only 14.3% of low grade lesions indicating most lesions had transcriptionally inactive HPV DNA (latent infection). RNA transcription was seen in the majority of high grade lesions indicating an active infection. However, integration of the viral genome into the host genome was infrequent.

TABLE I: CIN* histology vs. HPV DNA, RNA, integration

Histology	N	HPV 16 DNA	HPV 18 DNA	HPV 16 RNA #active/total present	HPV 18 RNA #active/total present	Integration 16	Integration 18
CIN I	63	7 (11.1%)	4 (6.3%)	1/7 (14.3%)	2/4 (50.0%)	1	0
CIN II	31	7 (22.6%)	2(6.5%)	6/7 (85.6%)	0/2 (0.0%)	2	0
CIN III	21	5 (23.8%)	2 (9.5%)	3/5 (60.0%)	2/2 (100%)	0	1
CIS*	3	1 (33.3%)	0 (0.0%)	1/1 (100%)	0/0 (0.0%)	0	0
Invasive	1	0 (0.0%)	0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0	0
Ad.sq.ca*	2	0 (0.0%)	1 (50.0%)	0/0 (0.0%)	1/1 (100%)	0	1
Abnormal - Unclassified	3	0 (0.0%)	0 (0.0%)	0/3 (0.0%)	0/3 (0.0%)	0	0
TOTAL	124	21 (16.9%)	9 (7.3%)	11/21(52.4%)	5/9 (55.5%)	3	2

*CIN:cervical intraepithelial neoplasia, CIS:carcinoma in situ, Ad. sq. ca: adenosquamous carcinoma

Conclusion: This is the first series of SLE patients with data on integration and active transcription of HPV in dysplastic/neoplastic cervical tissue. The presence of high risk HPV types 16 and 18 reported in this study may explain the increased rate of cervical dysplasia seen in lupus. In most low grade lesions, the viral genome was transcriptionally inactive indicating a latent form of HPV. Transcription was lower than the expected overall as was integration in high grade lesions. This data suggests that immunosuppression affects HPV persistence and viral integration in women with SLE.

Disclosure: J. P. Dhar, None; **L. Gregoire**, None; **W. Lancaster**, None; **A. Stark**, None; **A. Schwartz**, None; **D. Schultz**, None; **L. Essenmacher**, None; **J. Ager**, None; **L. Chiodo**, None; **M. Husain**, None; **R. J. Sokol**, None.

1255

Risk Factors for Squamous Intraepithelial Lesions in Systemic Lupus Erythematosus- A Prospective Cohort Study. Lai-Shan Tam[1], Paul K. Chan[2], Suzanne C. Ho[2], May M. Yu[1], So-Fan Yim[1], Tak-Hong Cheung[1], Martin C. Wong[1] and Edmund K. Li[1], [1]The Chinese University of Hong Kong, Hong Kong, China, [2]The Stanley Ho Centre for Emerging Infectious Diseases, Hong Kong, China

Purpose: In patients with systemic lupus erythematosus (SLE), association between cervical diseases and cyclophosphamide (CY) was controversial. SLE patients with a high human papillomavirus (HPV)-16 viral load more frequently had squamous intraepithelial lesions (SIL). However, the role of other high risk HPV types has not been addressed. We undertook a prospective cohort study to ascertain the risk factors for the development of SIL in patients with SLE.

Method: One hundred and thirty-seven SLE patients with normal pap smear at baseline were evaluated at six-month intervals for up to three years. At each visit, a Pap test, a test for HPV DNA and clinical assessment were performed. HPV DNA detection was performed using the PGMY PCR targeting the consensus region of the HPV L1 gene. HPV typing was done using the Linear Array HPV Genotyping Test that can detect 37 HPV types. Baseline risk factors for development of SIL included sociodemographic, lifestyle, reproductive and gynecologic variables, disease related variables, the use of immunosuppressants and HPV status.

Results: The mean age was 41 +/- 9 years and 55 (36.7%) were postmenopausal. The mean disease duration was 8.6 (4.6-14.4) years. The total follow up duration was 4,066 patient months. Eleven out of 137 (8.0%) patients developed at least one episode of SIL. Amongst the 30 patients with HPV infection detectable by DNA testing at baseline or during follow-up, 9/30 (30%) developed SIL. Univariate analysis showed that the development of incident SIL was associated with the use of azathioprine and cyclophosphamide (CY) (oral, intravenous (IV) or combined) ever, current use of IVCY; HPV infection (pre-existing, incident and ever), multiple HPV infection (pre-existing, during first incident infection and ever), high risk HPV infection (baseline and ever), any persistent HPV infection (since baseline or ever) and persistent

high risk HPV infection (ever); previous treatment of cervical lesions, age at first sexual intercourse </=22. Other demographic and clinical parameters, and the use of immunosuppressants were not associated with the development of SIL. All these variables were analyzed using regression analysis. The independent risk factor for the incident SIL in this group of SLE patients included the use of CY ever (p=0.021, OR 3.5, 95% CI 12.2-10.2), persistent high risk HPV infection (p=0.007, OR 12.9, 95% CI 2.0-80.9), and previous treatment of cervical lesions (p=0.028, OR 10.0, 95% CI 1.3-77.9).

Conclusion: Persistent high risk HPV infection, previous treatment of cervical lesions and the use of CY were independent risk factors associated with the development of SIL in SLE patients.

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Disclosure: L. S. Tam, None; **P. K. Chan**, None; **S. C. Ho**, None; **M. M. Yu**, None; **S. F. Yim**, None; **T. H. Cheung**, None; **M. C. Wong**, None; **E. K. Li**, None.

ACR Concurrent Abstract Sessions

Spondyloarthritis: Treatment

Monday, October 19, 2009, 4:30 PM - 6:00 PM

1256

Infliximab Plus Methotrexate Significantly Improves Rates of Remission for Methotrexate Naïve Psoriatic Arthritis (PsA) Patients Compared to Methotrexate Alone: The RESPOND† Trial. H. Raffayova[1], N. Kungurov[2], A. Kubanova[3], A. Baranauskaite[4], A. Venalis[5], L. Helmle[6], S. Srinivasan[7] and E. Nasonov[8], [1]National Institute for Rheumatology Diseases, Piestany, Slovak Republic, [2]Urals Dermato-venerology Inst., Yekaterinburg, Russia, [3]Central DermatoVenerology Inst., Moscow, Russia, [4]Kaunas Medical Univ. Hospital, Kaunas, Lithuania, [5]Vilnius Univ. Hospital, Vilnius, Lithuania, [6]Schering-Plough Corp., Budapest, Hungary, [7]Kenilworth, NJ, [8]Institute of Rheumatology, Moscow, Russia

Purpose: To assess the effect of infliximab (IFX) + methotrexate (MTX) vs MTX alone on the rate of remission (DAS28 < 2.6) in MTX naïve patients with active, polyarticular PsA. This study is the first to assess anti-TNF + MTX vs MTX alone in early, MTX-naïve active polyarticular PsA.

Method: Patients ≥18 years of age with active PsA (≥5 swollen and tender joints, + one of the following; ESR≥28 mm/hr, CRP≥15 mg/L, morning stiffness≥45 min) were included in this randomized, prospective, open-label, multi-center, multi-national study. Patients were naïve to MTX, anti-TNF agents, and could not be on DMARDs. Patients were randomized (1:1) to IFX (5 mg/kg) intravenous at week 0, 2, 6, and 14 + MTX (15 mg/week) or MTX (15 mg/week) alone. Study visits were at week 0, 2, 6, 14, and 16. The primary assessment was the proportion of ACR20 improvement at week 16. The study complied with Good Clinical Practices.

Results: 57 patients were randomized in the IFX + MTX group (48.2% male, mean age 40.1 years, mean disease duration 2.8 years)‡ and 58 in the MTX group (61.1% male, mean age 42.3 years, mean disease duration 3.7 years) ‡. Baseline conditions indicated severe disease: mean swollen and tender joint counts of > 14 and 20 respectively, mean CRP > 25 mg/dL, and mean PASI scores > 8 with more then 2/3 patients having a baseline PASI of at least 2.5. Rates of DAS28 remission by visit are summarized in the table. Also, 57% and 25% of patients had 0 swollen joints, 31% and 8% had 0 tender joints, 78% and 38% had a normal CRP level, and 71% and 29% had a PASI90 response at week 16 in the IFX+MTX and MTX groups respectively.

Visit	IFX + MTX (n=56)	MTX (n=54)	*p*-value
Week 2	12/56 (21%)	1/54 (2%)	0.0015
Week 6	24/52 (46%)	7/49 (14%)	0.0005
Week 14	29/50 (58%)	12/46 (26%)	0.0016

Week 16	35/51 (69%)	14/48 (29%)	<0.0001
Last Visit	37/56 (66%)	14/54 (26%)	<0.0001

The most commonly reported adverse event was increased levels of alanine aminotransferase (~10% in both groups). There were 2 serious adverse events in the IFX+MTX group, 1 infusion reaction with dyspnoea and erythema and 1 latent tuberculosis reactivation.

Conclusion: Early MTX naïve PsA patients with active disease achieved significantly greater remission rates when treated with IFX + MTX compared to MTX alone at every time point in the study. †(**RE**micade **S**tudy in **P**sA patients **O**f methotrexate-**N**aive **D**isease) ‡ITT analysis set.

Disclosure: H. Raffayova, None; **N. Kungurov**, None; **A. Kubanova**, Schering-Plough, 8 ; **A. Baranauskaite**, None; **A. Venalis**, None; **L. Helmle**, Schering-Plough, 3 ; **S. Srinivasan**, Schering-Plough, 3 ; **E. Nasonov**, Schering-Plough, 8 .

1257

Resolution of Inflammation Following Treatment of Ankylosing Spondylitis with Anti-TNF Agents Is Associated with New Bone Formation. Praveena Chiowchanwisawakit[1], Susanne J. Pedersen[2], Robert GW Lambert[3], Mikkel Ostergaard[2] and Walter P. Maksymowych[3], [1]Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Copenhagen University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB

Purpose: A previous study of patients with ankylosing spondylitis (AS) receiving anti-TNF agents in clinical trials showed that new bone formation was more likely to occur at those vertebral corners (VC) where inflammation had resolved following institution of anti-TNF therapy. A "release of TNF brake" hypothesis has been proposed whereby decreased TNF downregulates Dickkopf-1 allowing new bone formation through signalling by Wnt and other bone growth factors. However, data supporting the association between development of a new syndesmophyte and resolution of a vertebral corner inflammatory lesion (CIL) remain scarce. We aimed to test the hypothesis that a CIL visible on MRI that resolves following treatment is more likely to develop into a *de novo* syndesmophyte visible on plain x-ray than a vertebral corner with no prior CIL visible on MRI.

Method: We studied 51 AS patients (28 on standard and 23 on Anti-TNF treatment) followed prospectively who had MRI at baseline and at follow up (mean of 17.9 months), and radiography of the cervical and lumbar spine at baseline and 2 years. A persistent CIL was defined as being present on both MRI scans whilst a resolved CIL was defined as present at baseline MRI and completely disappeared at follow up MRI. The anterior vertebral corners on anonymised MRI were assessed independently and blinded to patient, treatment, and radiography by 2 readers. We conducted the following comparisons:1. proportion of new syndesmophytes developing at each anterior VC from a *resolved* inflammatory lesion at the corresponding VC; 2. the proportion of new syndesmophytes developing at each anterior VC from a *persistent* inflammatory lesion at the corresponding VC; 3. proportion of new syndesmophytes developing at each anterior VC where there is *no prior* inflammatory lesion. Proportions were compared by the Pearson chi-square analysis of the reader concordant data and discordant data was not included in this analysis.

Results: For patients receiving anti-TNF therapy, new syndesmophytes developed significantly more frequently in those vertebral corners with inflammation on MRI at baseline (10.3%) as compared to those that were normal on MRI (1.4%) ($p = 0.001$). For patients receiving standard treatment, new syndesmophytes developed in 12.5% of vertebral corners with inflammation at baseline as compared to 2.9% of those without ($p = 0.01$). New syndesmophytes developed in an even higher percentage of CIL that resolved following anti-TNF therapy (27.3%).

New syndesmophyte	Treatment	Resolved CIL	Persistent CIL	Normal VC	P value
Yes	Anti-TNF	3 (27.3)	0	5 (1.7)	<0.0001
No		8 (72.7)	3	282 (98.3)	
Yes	Standard	1 (16.7)	0	16 (3.3)	NS
No		5 (83.3)	10	463 (96.7)	

Conclusion: This study of AS spines documents that MRI findings predict subsequent damage on X-ray. Further, the demonstration of an increased likelihood of developing new bone following resolution of inflammation offers strong support for the "TNF brake hypothesis".

Disclosure: P. Chiowchanwisawakit, None; **S. J. Pedersen**, None; **R. G. Lambert**, None; **M. Ostergaard**, None; **W. P. Maksymowych**, None.

1258

Apremilast Is Active in the Treatment of Psoriatic Arthritis (PsA). Georg Schett[1], J. Wollenhaupt[2], Kim Papp[3], Rik Joos[4], Kurt L. De Vlam[5], Jude F. Rodrigues[6], Adele Vessey[7], Angela Hu[7], Wei Zhu[7] and Victor S. Sloan[7], [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Klinikum Eilbek, Hamburg, Germany, [3]Probity Medical Research, Waterloo, ON, [4]ZNA Rheumatology Department, Merksen, Belgium, [5]University Hospitals Leuven, Leuven, Belgium, [6]Clinical Research and Arthritis Centre, Windsor, ON, [7]Celgene Corporation, Summit, NJ

Purpose: Apremilast (APL) is a novel oral phosphodiesterase-4 inhibitor that suppresses multiple pro-inflammatory mediators and cytokines implicated in the pathogenesis of PsA.

Method: This was a phase II randomized, double-blind, placebo (PBO) controlled, multicenter study conducted in North America and Europe. Subjects with joint involvement of ≥6 months' duration, and with PsA satisfying Moll & Wright criteria with ≥3 tender joints (TJ) and swollen joints (SJ) were randomized to APL 20mg BID, APL 40mg QD, or PBO for 12 weeks' treatment. Stable doses of NSAIDs, corticosteroids (≤10 mg/day prednisone or equivalent), and methotrexate were allowed. A total of 126 subjects were then treated in an active-drug extension for 12 weeks (24 weeks total) including 40 PBO subjects who received the two dose regimens of APL in a 1:1 ratio.

Results: Two hundred four subjects were enrolled [53% M, 47% F; mean age 51 (21-81)]. Mean duration of PsA was 7.8 years; mean TJ count of 22, mean SJ count of 10 at baseline. Baseline characteristics were well-balanced between treatment groups. One hundred sixty eight subjects completed the 12 week treatment phase. Primary endpoint, ACR20 at 12 weeks, was met by APL 20 mg BID and 40 mg QD. Efficacy results are given in the table below. In evaluable subjects, response was maintained at 24 weeks (ACR20 40% and 39.1% for 20 mg BID and 40 mg QD, respectively). PBO subjects switched to APL in the extension achieved similar responses at 24 weeks to subjects originally allocated to APL (ACR20 35% and 40% for PBO to 20 mg BID and PBO to 40 mg QD, respectively).

Treatment Group	**(N)**	**Placebo**	**APL 20mg BID**	**APL 40mg QD**
		(68)	**(69)**	**(67)**
ACR20 (%)		11.8	43.5*	35.8**
ACR50 (%)		2.9	17.4***	13.4
ACR70 (%)		1.5	5.8	7.5

* $p<0.0001$ ** $p = 0.002$ *** $p=0.012$

The 5 most common adverse events (AEs) were nausea, diarrhea, headache, nasopharyngitis, and fatigue. Discontinuations due to AEs were 9% and 6% of APL subjects (20 mg BID, 40 mg QD, respectively), vs 3% in PBO group. Discontinuations due to lack of efficacy were 7 and 0% of APL subjects (20 mg BID, 40 mg QD, respectively), vs 15% in the PBO group. Eight subjects reported a serious AE (SAE) during the 12 week study period (4 in 20 mg BID, 0 in 40 mg QD, 4 in PBO); 7 subjects reported an SAE in the extension. There was no obvious difference in infections between APL and PBO groups and there were no deaths.

Conclusion: APL significantly improved signs and symptoms of PsA in this study. The majority of the AEs were mild to moderate and did not lead to discontinuation. Larger, longer-term studies are needed to characterize the optimum dose, efficacy and safety of APL for treatment of PsA.

Disclosure: G. Schett, Celgene Corporation, 2 ; **J. Wollenhaupt**, Celgene Corporation, 2 ; **K. Papp**, Celgene Corporation, 2 ; **R. Joos**, Celgene Corporation, 2 ; **K. L. De Vlam**, Celgene Corporation, 2 ; **J. F. Rodrigues**, Celgene Corporation, 2 ; **A. Vessey**, Celgene Corporation, 1, Celgene Corporation, 3 ; **A. Hu**, Celgene Corporation, 3, Celgene Corporation, 1 ; **W. Zhu**, Celgene Corporation, 1, Celgene Corporation, 3 ; **V. S. Sloan**, Celgene Corporation, 1, Celgene Corporation, 3 .

1259

Golimumab, a New, Human, TNF-α antibody Administered Subcutaneously Every 4 Weeks, in Ankylosing Spondylitis (AS): 104-Week Efficacy and Safety Results of the Randomized, Placebo-Controlled GO-RAISE Study. J. Braun[1], Désirée M.F.M. van der Heijde[2], Atul A. Deodhar[3], L. Diekman[4], J. Sieper[5], S.I. Kim[6], A. Beutler[7], M. Mack[7], S. Xu[7], J. Zrubek[7], B. Hsu[7] and R. D. Inman[8], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Oregon Health & Science University, Portland, OR, [4]University of Texas Medical School, Houston, TX, [5]Charite Hospital, Berlin, Germany, [6]Pusan National University Hospital, Busan, South Korea, [7]Centocor R&D, Inc, Malvern, PA, [8]University of Toronto, Toronto, ON

Purpose: To assess golimumab (GLM) efficacy/safety in pts with active ankylosing spondylitis (AS).

Methods: 356 pts were randomized (1.8:1.8:1 ratio) to SC GLM 50 or 100mg or PBO q4wks. Eligible pts had definite AS (modified NY criteria), BASDAI ≥4, and a back pain score of ≥4. At wk16, PBO or GLM 50 mg pts with <20% improvement in total back pain and morning stiffness entered early escape (EE) to GLM 50 and 100mg q4wks, resp (double-blind). At wk24, pts still receiving PBO crossed over to blinded GLM 50mg SC injections q4wks; others continued regimen through wk100, with evaluation 4 wks later. Key data summaries are based on randomized treatment groups with no statistical comparisons; other summaries show observed data only by regimen followed.

Results: As reported previously, the primary endpoint (proportion of pts with ASAS20 at wk14), was achieved. Benefit seen at wks 14&24 was maintained through wk104 (Table). BASMI linear scores improved from baseline to wk52; improvements were also maintained through wk104, as were improvements in SF-36 MCS & PCS scores. Pts not responsive to GLM 50mg who increased to 100mg had lower rates of ASAS response and less improvement in other parameters vs other GLM-treated pts (Table). AEs through wk104 were reported for 94% of GLM pts (little variation across GLM doses). Through wk104, 11% of GLM pts had a serious AE; the rate of GLM injection-site reactions was 1.4% (106/7705 inj) through wk104. There were no deaths.

Table:

	Placebo	GLM50mg	GLM100mg
Pts randomized	78**	138	140
ASAS 20[+]	30 (38.5%)	83 (60.1%)	100 (75.6%)
ASAS 40[+]	30 (38.5%)	77 (55.8%)	76 (54.3%)
ASAS partial remission[+]	17 (21.8%)	44 (31.9%)	43 (30.7%)
BASDAI[++]	6.02 (1.36,7.79)	2.65 (0.84, 6.08)	2.73 (1.08,5.34)
BASFI[++]	4.93 (0.98, 7.07)	2.22 (0.52,5.80)	1.77 (0.49, 4.79)

Table footnotes:

*Intent-to-treat analysis

+n in response, (%)

++median, (interquartile range)

**Includes 35 pts who did not meet EE criteria at wk16 and 41 pts who did

Conclusion: Clinical improvements in AS pts previously seen at wk24 were maintained through wk104, with no major differences in efficacy/safety between GLM doses. GLM was generally well tolerated through 2yrs of this 5yr study.

Disclosure: J. Braun, Centocor Research and Development, Inc, 9 ; **D. M. F. M. van der Heijde**, Abbott Laboratories, Amgen, Centocor Research and Development, Inc, Schering-Plough, UCB, Wyeth, 5 ; **A. A. Deodhar**, Centocor, Inc., 8 ; **L. Diekman**, None; **J. Sieper**, Centocor Research and Development, Inc, 9 ; **S. I. Kim**, Centocor Research and Development, Inc, 9 ; **A. Beutler**, Centocor, Inc., 3 ; **M. Mack**, Centocor Research and Development, Inc, 3 ; **S. Xu**, Centocor Research and Development, Inc, 3 ; **J. Zrubek**, Centocor Research and Development, Inc, 3 ; **B. Hsu**, Centocor Research and Development, Inc, 3 ; **R. D. Inman**, Centocor Research and Development, Inc, 9 .

1260

Abatacept in Psoriatic Arthritis: Results of a Phase II Study. P. Mease[1], M. Genovese[2], C. Ritchlin[3], J. Wollenhaupt[4], Paul P. Tak[5], A. Kivitz[6], G. Gladstein[7], O. Bahary[8], S. Kelly[8], J. Teng[8], J.-C. Becker[8] and D. Gladman[9], [1]Swedish Medical Ctr/Univ. of Washington, Seattle, WA, [2]Stanford Univ., Palo Alto, CA, [3]Univ. of Rochester, Rochester, NY, [4]Klinikum Eilbek, Hamburg, Germany, [5]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]New England Research Assoc, Trumbull, CT, [8]Bristol-Myers Squibb, Princeton, NJ, [9]Univ. of Toronto, Toronto, ON

Purpose: Abatacept (ABA) is a selective co-stimulation modulator approved for the treatment of RA and juvenile idiopathic arthritis. Here we assess the efficacy of ABA in patients (pts) with psoriatic arthritis (PsA) previously exposed to DMARDs in a phase II study.

Method: In this double-blind study, PsA pts with a target lesion (TL) ≥ 2 cm were randomized (1:1:1:1) to placebo (PBO) and ABA at 3, 10, and 30/10 (30 x 2 followed by 10) mg/kg (mpk). Treatments were administered on Days 1, 15, 29, and then once every 28 days. The primary endpoint was ACR20 at Day 169. Secondary endpoints were Health Assessment Questionnaire (HAQ), Short Form-36 (SF-36), investigator global assessment (IGA), TL score at Day 169, and safety. Psoriasis area and severity index (PASI) and magnetic resonance imaging (MRI) score of the joints at Day 169 were exploratory.

Results: Baseline characteristics were similar among groups except for more pts being previously exposed to anti-TNF therapies in the 30/10 mpk arm (51%) than other arms (29-36%). Of 170 pts treated, 147 completed first 6 months of treatment; 23 pts discontinued (7 for AEs and 10 for lack of efficacy). Significant number of pts achieved ACR20 with ABA (10 and 30/10 mpk) compared to PBO (**table**). Improvements in HAQ, physical component summary (PCS) and MRI score were also seen with ABA compared to PBO. The skin response in terms of TL and PASI showed a separation between PBO and ABA arms, with the 3 mpk dose showing the most separation; an improved IGA response was seen only with 3 mpk. Improvements in ACR20 and TL were greater in anti-TNF-naive pts than in pts pre-exposed to anti-TNF therapies. The safety profiles were similar among arms.

Response	ABA			PBO
	30/10 mpk* n = 43	10 mpk n = 40	3 mpk N = 45	n = 42
Joint				
ACR20†	42 (27, 57)	48 (32, 63)	33 (20, 47)	19 (7, 31)
p vs. PBO	0.022	0.006	0.121	NA
Pre-exposed to anti-TNF therapy				
No, n	21	27	29	30
ACR20†	48 (26, 69)	56 (37, 74)	35 (17, 52)	20 (6, 34)
Yes, n	22	13	16	12
ACR20†	36 (16, 57)	31 (6, 56)	31 (9, 54)	17 (-4, 38)
MRI of joints‡				
Erosion	0.3 (3.5)	-0.6 (4.2)	0.5 (2.4)	1.5 (7.4)
Synovitis	-0.8 (3.1)	-1.4 (3.0)	-0.2 (2.9)	0.8 (4.3)
Edema	-0.5 (1.9)	-1.1 (2.6)	-0.3 (1.7)	0.4 (3.3)
Skin				
TL50†	30 (17, 44)	33 (18, 47)	36 (22, 50)	17 (5, 28)

TL75†	16 (5, 27)	10 (1, 19)	29 (16, 42)	10 (1, 18)
Patient-reported outcomes				
HAQ§†	35 (21, 49)	45 (30, 60)	36 (22, 50)	19 (7, 31)
PCS‡	7.3 (1.9)	9.3 (1.9)	6.3 (1.8)	0.2 (1.9)
*30 mpk followed by 10 mpk; †% pts with 95% CI; ‡Adjusted mean (± SE) change from baseline; §Improvement of ≥ 0.3 unit from baseline				

Conclusion: ABA at 10 mpk significantly improved ACR20 and physical function in PsA pts, consistent with previous trials in RA. ABA treatment also resulted in less joint damage by MRI evaluation. All doses showed improvement in TL score with the 3 mpk dose showing the most.

Disclosure: P. Mease, Bristol-Myers Squibb, 8, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2 ; **M. Genovese**, BMS, 5, BMS, 2, BMS, 8 ; **C. Ritchlin**, Bristol-Myers Squibb, 5, Wyeth Pharmaceuticals, 5, Amgen, Roche, Sanofi, Centocor, 5, Centocor, Inc., 2 ; **J. Wollenhaupt**, None; **P. P. Tak**, BMS, 2 ; **A. Kivitz**, Amgen, 8, takeda, novartis, roche, 8 ; **G. Gladstein**, Pfizer Inc, Genentech, BMS, Roche, Forest, Cephalon, Regeneron, Centocor, 2, Bristol-Myers Squibb, 8 ; **O. Bahary**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **S. Kelly**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **J. Teng**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **J. -. C. Becker**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **D. Gladman**, Abbott, Amgen, Centocor, Schering, Wyeth, Roche, UCB, 5 .

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Golimumab Administered Subcutaneously Every 4 Weeks in Psoriatic Arthritis Patients: 52-Week Health-Related Quality of Life, Physical Function and Health Economic Results of the Randomized, Placebo-Controlled GO-REVEAL Study. A. Kavanaugh[1], D. Gladman[2], P. Mease[3], Iain B. McInnes[4], A. Beutler[5], J. Zrubek[5], J. Buchanan[6], S. Parasuraman[6], M. Mack[5] and G.G. Krueger[7], [1]U of Calif San Diego, San Diego, CA, [2]Toronto Western Hosp, Toronto, ON, [3]Seattle Rheum Assoc, Seattle, WA, [4]University of Glasgow, Glasgow, United Kingdom, [5]Centocor R&D, Inc, Malvern, PA, [6]J&J Pharm Services, Malvern, PA, [7]U of Utah Hlth Sciences Ctr, Salt Lake City, UT

Purpose: The impact of GLM on physical function, self-reported productivity, health-related quality of life (HRQoL), healthcare resource utilization, employability and time lost from work were assessed.

Methods: Adult PsA pts (n=405) with ≥3 SJC & ≥3 TJC were randomized to SC PBO or GLM (50 or 100 mg) q4wks. At wk16, pts with inadequate arthritis response entered early escape (EE). All pts on PBO received GLM50mg from wk24. Wk24 comparisons were between GLM and PBO groups using ANOVA on van der Waerden normal scores for continuous outcomes. At wk52, response was determined using observed data.

Results: Mean age was 46-48yrs, median SJC/TJCs were 12-14/22-24, HAQ scores were 1.0-1.1, and PASI scores were 8.4-11.1. GLM was significantly better than PBO in improving physical function, HRQoL, self-reported productivity and reducing time lost from work for caregivers at wk24 ($p<0.05$, for all endpoints). Through wk24 there were no statistically significant effects on healthcare resource utilization, employability, or pt time lost from work. Improvements in HRQoL, physical function and self-reported productivity continued through wk 52. GLM-treated pts showed improvements in resource utilization, employability, and in caregiver and pt time lost from work at wk 52.

Table:

	PBO	**GLM 50mg**	**GLM 100mg**
	n=113	**n=146**	**n=146**
Wk 24+			
HAQ ≥0.3[a]	22.1%	43.2%*	51.7%*
PCS/MCS,mean±SD	0.67±8.7/-0.60±12.1	7.42±9.2*/3.37±10.6**	8.22±9.6*/4.29±11.0**

improv			
Productivity,mean±SD improv[b]	-0.08±2.6	-1.9±2.7*	-2.6±3.0*
Caregiver/Pt[c]time lost frm work,mean±SDdays	1.1±4.0/0.4±1.1	0.2±1.0**/1.6±10.0	0.2±1.3**/2.3±17.6
Week 52[#,^]	-	n=118[d]	n=146[d]
HAQ ≥0.3[a]	-	55.0%	57.1%
PCS/MCS,mean±SD improv	-	11.65±8.9/3.91±12.3	9.97±10.2/5.25±11.4
Productivity,mean±SD improv[b]	-	-2.8±2.6	-2.9±3.1
Caregiver/Pt[c]time lost frm work,mean±SDdays	-	0.03±0.3/0.04±0.2	0.00±0.0/0.08±0.3
#physician visits, mean±SD,BL/Wk52	-	2.8±3.1/0.5±1.05	2.7±3.3/0.7±2.6
#pts employable,Wk52 (among unemployed@BL)	-	8/11(72.7%)	5/13(38.5%)

*+ For comparisons at wk 24 *p<0.001 vs PBO, **p < 0.05 vs PBO; # GLM 50mg only: Wk 24 all pts randomized to GLM 50 mg included; Wk 52, only pts randomized to GLM 50 mg and did not enter EE included. ^GLM 100mg: Wk 24 and 52 all pts randomized to GLM100 mg regardless of whether they entered EE included; a: number(%) of pts with ≥0.3 improvement from BL; b: Negative change for productivity is improvement; c: Randomized pts<65yrs and full-time employed at BL; d:randomized pts: outcomes in evaluable population*

Conclusion: GLM50 and 100mg SC q4wks improved physical function, HRQoL, resource utilization, employability and self-reported productivity of pts with active PsA through wk52.

Disclosure: A. Kavanaugh, Centocor Research and Development, Inc ; **D. Gladman**, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Research and Development, Inc., Schering-Plough, Wyeth Pharmaceuticals , 5 ; **P. Mease**, Centocor Research and Development, Inc, 9 ; **I. B. McInnes**, Centocor Research and Development, Inc, 9 ; **A. Beutler**, Centocor, Inc., 3 ; **J. Zrubek**, Centocor Research and Development, Inc, 3 ; **J. Buchanan**, JJPS, LLC, 3 ; **S. Parasuraman**, JJPS, LLC, 3 ; **M. Mack**, Centocor Research and Development, Inc, 3 ; **G. G. Krueger**, Centocor Research and Development, Inc, 9 .

ACR Concurrent Abstract Sessions

Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Pathogenesis, Animal Models and Genetics

Monday, October 19, 2009, 4:30 PM - 6:00 PM

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Genome-Wide Association Scan in Systemic Sclerosis Identifies MHC Region and Two Additional Susceptibility Loci On 2q32 and 7q32. Timothy RDJ Radstake[1], Behrooz Z. Alizadeh[2], Rogelio Palomino-Morales[3], Jasper C. A. Broen[4], Jose-Ezequiel Martin[5], Ruben 'T slot[6], Carmen Simeon[7], Lorenzo Beretta[8], Norberto Ortego-Centeno[9], P. Airo[10], Gabriela Riemekasten[11], Miguel A. Gonzalez-Gay[12], N. Hunzelmann[13], Anna Pros[7], MC Vonk[1], Marieke Coenen[1], J.M. van Laar[14], Ariane L. Herrick[15], R. Hesselstrand[16], Vanessa Smith[17], Filip de Keyser[18], F. Houssiau[19], Mayte Camps[7], Patricia E. Carreira[20], Bernardino Diaz[7], Paloma de la Peña[7], Esther F. Vicente[21], L. Rodriguez-Rodriguez[22], Jose Román-Ivorra[7], Antonio Fernández-Nebro[23], Vicent Fonollosa[7], Francisca Gonzalez-Escribano[24], Meng May Chee[25], Rajan Madhok[26], Paul Shiels[27], Rene Westhovens[28], Wilfride de Baere[29], Torsten Witte[30], L. Padyukov[31], L. Klareskog[31], J. Worthington[32], Blanca Rueda[33], Bobby PC Koeleman[34] and Javier Martin[3], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University of Groningen, Groningen, Netherlands, [3]Instituto de Biomedicina y Parasitología López-Neyra, Granada, Spain, [4]Radboud University Medical Center, Nijmegen, Netherlands, [5]Researcher, Granada, Spain, [6]Research Technician, Utrecht, Netherlands, [7]Rheumatologist, Granada, Spain, [8]Fondazione IRCCS policlinico mangiagalli Regina Elena and University of Milan, Italy, Milan, Italy, [9]Hospital Clinico San Cecilio, Granada, Spain, [10]Clinica Spedali Civili, Brescia, Italy, [11]Rheumatologist, Berlin, Germany, [12]Hospital Xeral-Calde, Lugo, Spain, [13]Dermatology, Cologne, Germany, [14]Newcastle University, Newcastle, United Kingdom, [15]University of Manchester, Manchester, UK, United Kingdom, [16]Rheumatology, Lund, Sweden, [17]Rheumatologist, Gent, Belgium, [18]Rheumatologist, Ghent, Belgium, [19]Universite Catholique Louvain, Brussels, Belgium, [20]Hospital 12 de Octubre, Madrid, Spain, [21]Hospital de la Princesa, Madrid, Spain, [22]Rheumatology Service, Hospital Clinico San Carlos, Madrid, Spain, [23]Hospital regional Universitario Carlos Haya, Malaga, Spain, [24]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [25]Rheumatologist, Glasgow, United Kingdom, [26]Glasgow Royal Infirmary, Glasgow, [27]Biologist, Glasgow, United Kingdom, [28]UZ Gasthuisberg, Leuven, Belgium, [29]Pediatrician, Ghent, Belgium, [30]Hannover Medical School, Hannover, Germany, [31]Karolinska Institute, Stockholm, Sweden, [32]arc Epidemiology Unit, Manchester, United Kingdom, [33]CSIC, Granada, Spain, [34]University Medical Centre Utrecht, Utrecht, Netherlands

Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs that leads to profound disability and premature death. Accumulating evidence point to a strong genetic component that is underlying the susceptibility of SSc. Here we aimed to identify the genetic factors that underly SSc.

Method & Results: To identify the genetic traits for SSc, we performed a genome-wide association study comparing 842 European Caucasian SSc cases with 1711 European Caucasian controls exploiting the Illumina human BeadChip. Using a replication cohort comprising 1640 European Caucasian SSc cases and 1700 controls matched for country of origin we aimed to replicate the 11 most strongly non-MHC associated SNPs in the GWAS and replicated the association of STAT4 (P = 4.03E-10). After stratification for SSc phenotype, significant association (P<5.0E-08) was reached for ten SNPs in 3 loci (STAT4 in limited disease, MHC region in diffuse disease and CXCR4 region in female subjects). These results replicate the previous published associations to the MHC region and the STAT4 gene with SSc [1-3]. In addition, SNPs in three loci were found to be associated in both our study and the independent US screen (Gorlova et al.) These regions included the MHC, the STAT4, and the TNPO3 genes that when combined reach genome wide significance respectively (P<5.0E-08), further confirming these loci as risk factors for SSc. Finally, one SNP in the CD3Z gene showed association in both the US and EU cohorts (P=1.4E-07)

Conclusion: To date this is the first GWAS performed in SSc in a European population. Apart from the MHC region, two non-MHC loci, STAT4, TNPO3 were confirmed as susceptibility factors for SSc. The identification of these loci underscore a strong role for immune deregulation in the pathogenesis of SSc.

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Tyrosine Kinase Inhibitors (TKI) Are Promising Therapeutic Agents for the Proliferative Vasculopathy in SSc. Britta Maurer[1], Nicole Busch[2], Astrid Jüngel[1], Renate E. Gay[1], Georg Schett[3], Beat A. Michel[1], Steffen Gay[1], Jörg HW Distler[2] and Oliver Distler[1], [1]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [2]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: Proliferative vasculopathy such as pulmonary arterial hypertension (PAH) and fibrosis are the leading causes of death in SSc patients. Herein, we analyzed the effects of TKI on the proliferative vasculopathy in the novel vascular SSc model of Fra-2 tg mice, and examined the activation of TKI targets in the skin of SSc patients and fibrotic animal models of SSc.

Method: Fra-2 tg mice (n=12; Bl6), wt littermates (n=3) and bleomycin treated mice (n=3; C3H/HeJ) were analyzed. Subgroups of Fra-2 tg mice (n=6) were treated with the TKI nilotinib at 2 x 35mg/d p. o. from 8 weeks of age. In addition, skin sections from SSc patients (n=5) were examined.

Results: Untreated Fra-2 tg mice developed a strong proliferative vasculopathy in the lungs resembling PAH. Vascular remodelling of small arteries was characterized by proliferation (PCNA staining) of vascular smooth muscle cells (SM22α, double staining) and myofibroblasts/pericytes (α-SMA and Thy). The expression of the phosphorylated and thus activated TKI targets p(phospho)-c-abl and p-PDGFRβ was significantly increased in the pulmonary vessels of untreated Fra-2 tg mice. Accordingly, nilotinib improved the proliferative vasculopathy in the lungs of treated (vessel wall diameter, mean ± SEM 30.6 ± 1.3 μm) compared to the untreated Fra-2 tg mice (43.3 ± 1.4 μm, $p<0.05$) and significantly decreased the numbers of proliferating vascular cells. Interstitial lung fibroblasts did not express activated TKI targets, and thus, perivascular pulmonary fibrosis was not reduced. However, in the skin, the expression of p-PDGFRβ was prominent both in vascular structures and fibroblast-like cells (4.9 ± 0.7 cells/HPF). In accordance, nilotinib prevented the development of skin fibrosis in treated compared to untreated Fra-2 tg mice (skin thickness 290 ± 10 μm vs. 324 ± 10.4 μm ; $p<0.05$). Next, we analyzed the expression of activated TKI targets in the skin of the bleomycin model. P-c-abl (5.9 ± 0.08 cells/HPF) and p-PDGFRβ (6.4 ± 1.5 cells/HPF) were abundantly expressed in all cells including fibroblasts, consistent with the strong antifibrotic effects for TKI seen in this model. Most interestingly, in skin sections of SSc patients, the expression of p-c-abl (1.5 ± 0.8 cells/HPF) and p-PDGFRβ (3.0 ± 1.1 cells/HPF) was largely limited to vascular structures.

Conclusion: Our study suggests that differences in the expression pattern and activation status of TKI targets between animal models and SSc may account for the relatively minor anti-fibrotic effects in humans. However, based on the vascular predominance of TKI targets in human SSc and the effects on vascular remodelling in the vascular Fra-2 tg model, our data suggest TKI as novel promising drugs to treat proliferative vasculopathies such as SSc-PAH. This is supported by preliminary data from human phase II studies with imatinib in PAH.

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Hedgehog Signaling Plays a Crucial Role for Fibroblast Activation and Tissue Fibrosis in Systemic Sclerosis. Angelika Horn[1], Clara Dees[1], Alfiya Akhmetshina[1], Nicole Busch[1], Jürgen Beer[1], Oliver Distler[2], Georg Schett[3] and Jörg HW Distler[1], [1]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [2]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [3]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: The Hedgehog (Hh) pathway plays important roles in embryonic tissue development, in the pathogenesis of various tumors and in hepatic fibrosis. The ligand Sonic Hedgehog (Shh) binds to the transmembrane receptor Patched (Ptch), which releases the membrane protein Smoothened (Smo) from its repression. As a result, Smo activates the transcription factor Gli-2 for further activation of several target genes. The aim of the present study was to investigate the role of Hh in SSc.

Method: The expression of Shh, Smo and Gli-2 was analyzed by immunohistochemistry. Hedgehog signaling was activated by recombinant Shh or adenoviral expression of Shh. Two different animal models of SSc, bleomycin-induced dermal fibrosis and tight-skin (tsk-1) mice were used to assess the role of Hh signaling in experimental fibrosis and evaluate the anti-fibrotic potential of the selective Hh inhibitor LDE223.

Results: The expression of Shh and its downstream target Gli-2 was significantly elevated in skin sections of SSc patients compared to healthy controls. Hh signaling was also activated in different models of experimental fibrosis. Stimulation of healthy dermal fibroblasts with recombinant Shh induced an SSc-like phenotype and stimulated the release of collagen dose-dependently by up to 4.4 ± 0.2 fold. This effect was mediated by higher mRNA stability. Adenoviral overexpression of Shh induced dermal fibrosis in mice with dermal thickening, increased accumulation of collagen and myofibroblast differentiation. In addition, mice lacking one allele of the inhibitory receptor Ptch were more sensitive to experimental fibrosis. Next, we evaluated the therapeutic potential of the Hh inhibitor LDE223. Dermal thickening was reduced by 72 ± 2 % in the mouse model of bleomycin-induced fibrosis upon treatment with LDE223. Consistent with the reduced dermal thickening, LDE223 treated mice showed significantly decreased myofibroblast counts and the amount of collagen in the lesional skin was reduced by 67 ± 17 %. LDE223 was also effective in the tight skin 1 mouse model, a non-inflammatory model of SSc. Treatment of tight skin 1 mice with LDE223 reduced hypodermal thickening by up to 78 ± 5 % and completely prevented myofibroblast differentiation.

Conclusion: The Hh pathway is activated in experimental fibrosis and in SSc patients. We demonstrate that activation of Hh activates cultured fibroblasts in vitro and induces fibrosis in vivo. Inhibition of Hedgehog signaling by selective inhibition of Smo exerts potent anti-fibrotic effects in different models of experimental fibrosis. Thus, the hedgehog pathway could be an interesting novel target for the treatment of SSc.

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Tgfß Stimulates Promoter Hypermethylation and Subsequent Silencing of the Anti-Fibrotic Gene Socs-3. Clara Dees[1], Alfiya Akhmetshina[1], Nicole Busch[1], Angelika Horn[2], Johannes Gusinde[1], Astrid Jüngel[3], Steffen Gay[3], Oliver Distler[3], Georg Schett[4] and Jörg HW Distler[1], [1]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [2]Dept Int Med 3, Univ Erlangen, Germany, Erlangen, Germany, [3]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [4]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: Tissue fibrosis caused by a pathological activation of SSc fibroblasts is a major hallmark of systemic sclerosis (SSc). TGFβ is a major mediator of fibrosis and has been identified as key-player in the pathogenesis of SSc. Alterations in DNA methylation and subsequent changes in gene transcription have been implicated in the pathogenesis of SSc. The aim of the present study was to investigate whether TGFβ induces DNA methylation.

Method: The methylation status of suppressor of cytokine signaling 3 (socs-3) in fibroblasts was evaluated by methylation-specific PCR. The expression of socs-3 was analyzed by real-time PCR and immunohistochemistry. The expression of socs-3 was specifically targeted by siRNA. The anti-fibrotic potential of 5-aza, a potent inhibitor of DNA methyltransferases, for prevention and treatment of established fibrosis was analyzed in the mouse model of bleomycin-induced skin fibrosis.

Results: Socs-3 potently regulated the release of collagen in fibroblasts. Knockdown of socs-3 by siRNA in healthy fibroblasts increased mRNA and protein levels of col 1a1 and col 1a2 by up to 85 ± 36 % ($p < 0.05$). The expression of socs-3 was strongly reduced in SSc fibroblasts and in the skin of SSc patients. The promoter of socs-3 was heavily hypermethylated in SSc fibroblasts. Incubation with 5-aza reactivated the expression of socs-3 in SSc fibroblasts, but had no effects in control fibroblasts. The hypermethylation of socs-3 in SSc might be mediated by TGFβ. TGFβ induced hypermethylation of the promoter of socs-3 in healthy fibroblasts similar to SSc fibroblasts and reduced the expression of socs-3 by 69 ± 8 % ($p < 0.05$). The increased DNA methylation was mediated by TGFβ dependent induction of the DNA methyltransferase 3a. Coincubation with 5-aza prevented not only the inhibitory effects of TGFβ on the expression of socs-3, but also reduced the TGFβ induced stimulation of the collagen synthesis by 68 ± 6 % ($p < 0.05$). 5-aza also exerted anti-fibrotic effects in vivo. 5-aza reduced dermal thickening upon challenge with bleomycin by 89 ± 9 % ($p < 0.05$). In addition, 5-aza induced regression of pre-established fibrosis with a decrease in dermal thickening of 44 ± 3 % below pre-treatment levels ($p < 0.05$).

Conclusion: We demonstrate that TGFβ induces silencing of the anti-fibrotic gene socs-3 via DNA methyltransferase 3a dependent promoter hypermethylation. Inhibition of the TGFβ induced silencing of socs-3 by 5-aza reduced the stimulatory effects of TGFβ on the collagen synthesis in vitro and exerted potent anti-fibrotic effects in vivo. Thus, we identify inhibitors of DNA methyltransferases as novel anti-fibrotic drugs and provide a novel mechanism for the pro-fibrotic effects of TGFβ.

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The Role of GATA-6 in Pulmonary Arterial Hypertension in Scleroderma Patients. Angela V. Ghatnekar, Lukasz Stawski, Elaine Wirrig, Malgorzata Markiewicz, Yoshihide Asano, Russel Harley and Maria Trojanowska, Medical University of South Carolina, Charleston, SC

Purpose: Pulmonary arterial hypertension (PAH) is an increase in blood pressure in the pulmonary artery or lung vasculature and in severe cases can lead to right ventricular heart failure and death. PAH can be idiopathic (cause unknown), familial (genetic), or associated with a variety of other conditions, such as connective tissue diseases like systemic sclerosis (SSc). The key features of this disease are vasoconstriction, followed by intimal proliferation and fibrosis, in-situ thrombosis, and plexogenic changes. Several factors are known to be perturbed in endothelial cells (ECs) during PAH: TGF-β/Bone Morphogenetic Protein (BMP) components, nitric oxide (NO), and endothelin-1 (ET-1). GATA-6 is a zinc finger transcription factor that is indispensable for embryogenesis and subsequent tissue-specific gene regulation. Recent studies have demonstrated that GATA-6 is downregulated in both intramyocardial arteries from spontaneously hypertensive rats and rat carotid arteries following balloon-mediated injury. The goal of this work was to evaluate the potential role of GATA-6 as a novel regulator of gene programs altered in PAH.

Method: The protein levels of GATA-6 were assessed by immunostaining of lung specimens from 9 patients with SSc-PAH and 4 healthy controls. To identify genes regulated by GATA-6 in microvascular ECs, we performed a microarray analysis after AdsiRNA-mediated GATA-6 knockdown, and subsequently validated putative target genes using commercial siRNA oligos followed qRT-PCR and western blotting. To investigate if GATA-6 is a direct transcriptional regulator of these genes, we performed chromatin immunoprecipitation (ChIP) analysis. The mRNA and protein levels of GATA-6 and its potential targets were also examined in the lungs of the monocrotaline (MCT) rat model of PAH by using qRT-PCR and western blot.

Results: The immunostaining revealed that GATA-6 protein levels are dramatically reduced in ECs (e.g. 15% arterioles stained positive in SSc-PAH versus 85% in controls) within occluded and non-occluded vessels of patients. Genes altered in endothelial cells after suppression of GATA-6 included components of the BMP pathway, endothelial cell markers and matrix remodeling proteins. Silencing of GATA-6 with siRNA oligos in ECs confirmed that GATA-6 might be a negative regulator of MMP1 and MMP10 and a positive regulator of eNOS, VE-cadherin and BAMBI gene expression. ChIP analysis demonstrated that GATA-6 is a direct transcriptional regulator of BAMBI, eNOS, MMP1 and MMP10. We also found significant reductions in GATA-6 expression as well as decreased mRNA levels of its putative targets, BAMBI, eNOS and VE-cadherin at both early and late stages of disease in the MCT rat model.

Conclusion: These findings suggest that GATA-6 reduction occurs before vessel occlusion and may reflect an initial phase of EC activation and/or dysfunction and, therefore, may play a critical role in development of PAH by regulating genes associated with vascular remodeling.

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1267

Molecular Profiling of Lung Tissues From Patients with Systemic Sclerosis. Eileen Hsu and Carol A. Feghali-Bostwick, University of Pittsburgh, Pittsburgh, PA

Purpose: Pulmonary involvement in systemic sclerosis (SSc) includes pulmonary fibrosis (PF) and pulmonary arterial hypertension (PAH) and is the leading cause of SSc-related mortality. To gain a better understanding of the pathogenesis of SSc-associated PF and PAH, we used microarray analysis to identify the molecular fingerprints of SSc lung tissues and compared them to those of patients with idiopathic pulmonary fibrosis (IPF) and idiopathic pulmonary arterial hypertension (IPAH).

Methods: Lung tissues were obtained from patients who underwent lung transplantation or from normal donors (n=9) whose lungs were not used for transplant surgery. SSc patients were identified as having severe PF (n=9) or PAH (n=9). All SSc-PF patients had severe restrictive

lung disease with FVC <55% of predicted without evidence of PAH. All SSc-PAH patients had mean PA pressure >25mmHg with mild restriction or normal spirometry. IPF patients (n=10) had CT scan or lung biopsy findings consistent with usual interstitial pneumonia without evidence of connective tissue disease or other known exposures. IPAH (n=6) patients had pulmonary arterial hypertension of unknown etiology. Total RNA was extracted from frozen lung tissues. Microarray analysis was done using Illumina HumanRef-8v3.0 Bead Chips. Consensus efficiency analysis was used to determine optimal method of data processing and differentially expressed genes. Ingenuity Pathway Analysis and Gene Ontology Tree Machine software identified the enriched functional groups. Microarray results were confirmed using real-time PCR.

Results: Efficiency analysis of microarray data of SSc, IPF and IPAH whole lung tissues identified 242 genes that were differentially expressed compared to normal lungs. In SSc-PF and SSc-PAH lungs, 73 and 83 genes, respectively, were differentially expressed compared to normal lungs. In IPF and IPAH lungs, 73 and 85 genes, respectively, were differentially expressed compared to normal lungs. Functional groups that were enriched in SSc-PF and SSc-PAH lungs, but not IPF or IPAH, included leukocyte chemotaxis and pepsin A activity. Enriched functional categories shared by SSc-PF and IPF lungs included insulin-like growth factor signaling, caveolar-mediated endocytosis and hepatic fibrosis. Genes shared by SSc-PAH and IPAH lungs included genes involved in IL-17 signaling, antigen presentation, chemokine activity, and transition metal ion binding.

Conclusion: Lung tissues of patients with SSc-associated lung disease exhibit unique molecular profiles compared to idiopathic forms of lung disease. Furthermore, gene expression profiles of SSc-PF and SSc-PAH lungs are distinct. In summary, using lung tissues, we identified novel genes that may play a role in the pathogenesis of SSc-PF and SSc-PAH. We generated unique molecular signatures that are disease (SSc) and phenotype (PF vs PAH)-specific. The identified differentially expressed genes provide new targets for the development of therapies targ

Disclosure: E. Hsu, None; **C. A. Feghali-Bostwick**, None.

ACR/ARHP Poster Session C

Antiphospholipid Syndrome: Pathogenesis and Clinical Aspects
Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Vitamin D: An Instrumental Factor in the Anti-Phospholipids Syndrome - Inhibiting Tissue Factor Expression. Nancy Agmon-Levin[1], Maya Glazer[1], Howard Amital[2], Gisele Zandman-Goddard[3], Hedi C. Orbach[3], Shlomo Berliner[4], Pierluigi Meroni[5], Angela Tincani[6], Andrea Doria[7], Ricard Cervera[8], Wolfgang Miesbach[9], Ljudmila Stoyanovich[10], Vivian Barak[11], Bat-Sheva Porat katz[12], Miri Blank[1] and Yehuda Shoenfeld[13], [1]Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan, Israel, [2]Meir Medical Center, Kfar-Saba, Israel, [3]Wolfson Medical Center, Holon, Israel, [4]Sourasky Medical Center, Tel aviv, Israel, [5]University of Milan, Milan, Italy, [6]University of Brescia, Brescia, Italy, [7]University of Padova, Padova, Italy, [8]Autoimmune Diseases. Hospital Clínic, Barcelona, Spain, [9]Johann Wolfgang Goethe-University, Germany, [10]"Bezhanijska Kosa" University Medical Center, Belgrade, Serbia and Montenegro, [11]Department of Oncology, Hadassah University Hospital, Jerusalem, Israel, [12]Faculty of Agricultural, The Hebrew University, Jerusalem, Israel, [13]Center for Autoimmune Diseases, Sheba Medical Center, Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

Purpose: Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent thrombotic events and elevated titers of antiphospholipid antibodies (Abs) including anti- beta 2 glycoprotein-I (β2GPI) Abs. Anti-β2GPI-Abs may induce thrombosis *via* induction of tissue factor (TF) expression, which triggers the coagulation cascade. One of the recently suggested novel roles of Vitamin-D entails immunomodulation and anti-thrombotic mechanisms. Therefore, in a large cohort of APS patients we evaluated vitamin-D levels and its effect in an *in vitro* model of thrombosis utilizing an anti-β2GPI–mediated TF expression system.

Methods: Patients: Serum concentrations of Vitamin-D were measured in 337 European APS patients with clinically diagnosed thrombotic events (i.e. venous or arterial).. We used the Liaison chemiluminescent immunoassay method (DiaSorin - Italy).

Experimental model: We purified anti- β2GPI antibodies from 3 patients with APS and utilized them to activate human endothelial cells (HUVEC) to expresses TF. Vitamin D (1,25-dihydroxyvitamin D, 10nM) was added to starved HUVEC in the presence of anti-β2GPI Abs. TF expression was analyzed by immunoblot utilizing mouse anti-human-TF.

Results: The prevalence of vitamin-D deficiency (≤15ng/ml) was documented in 63% of our APS patients. An increased prevalence of thrombotic events (58% *vs*. 41%) were documented in patients with vitamin-D deficiency compared to those with higher levels of vitamin-D ($P<0.05$).

In our experimental model the addition of vitamin-D to endothelial cells significantly inhibited the expression of TF induced by anti- β2GPI Abs purified from the patients.

Conclusion: Vitamin-D deficiency is common among APS patients and associated with clinically diagnosed thrombotic events. Vitamin-D inhibited anti- β2GPI mediated TF expression in an *in vitro* model. Thus, low levels of Vitamin-D may be associated with decreased inhibition of TF expression and thus increased coagulation in APS.

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The Phosphatidylserine-Dependent Monoclonal Antiprothrombin Antibody with Lupus Anticoagulant Activity Induces Platelet Activation with Over-Expression of Surface Antigen. Kenji Oku, Tatsuya Atsumi, Olga Amengual, Yuichiro Fujieda, Kotaro Otomo, Masaru Kato, Hiroshi Kataoka, Tetsuya Horita, Shinsuke Yasuda and Takao Koike, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: We previously showed that monoclonal phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) induced tissue factor (TF) mRNA expression on procoagulant cells (ACR Abstract 1406 in 2007 and 645 in 2008). Increased thrombin generation in vivo would be due to up-regulation of TF expression, presumably correlated with venous thrombosis. In contrast, platelet activation and aggregation is crucial procedures in the development of arterial thrombosis. There have been, however, only little data available to link arterial events / platelet activation and aPS/PT. In this study, we compared the events of arterial thrombosis and aPS/PT in a large cohort of patients with autoimmune diseases. In addition, to explore the pathogenesis of aPS/PT in the arterial disease, we treated platelets with monoclonal aPS/PT and investigated their behavior in vitro.

Methods and Patients**:** This study comprised 500 patients who visited our autoimmune disease clinic (423 female, age 48(15-89) years; 196 systemic lupus erythematosus, 107 primary antiphospholipid syndrome, 48 rheumatoid arthritis, 28 scleroderma, 149 other autoimmune diseases). The arterial thrombosis was found in 70 patients (14%), all confirmed by at least one of CT scan, MRI or angiography. A monoclonal aPS/PT, 231D, that shared the properties with autoimmune aPS/PT (Arthritis Rheum, in press) was used for the following in vitro experiments. Normal platelets were treated with 231D in the presence of prothrombin(PT). Positive ratio of CD62P(P-selectin), a surface marker of activated platelets, was detected by two-colored flow-cytometry. Conventional ADP or collagen induced platelet aggregation assay was performed using 231D-spiked platelet rich plasma (PRP) by turbidimetric method.

Results: IgG aPS/PT were found in 81 patients (16%), and the prevalence of IgG aPS/PT was significantly higher in patients with arterial events than in those without (OR 8.2 95%CI(4.6-14.3)). Positive rate of CD62P was significantly increased on platelet treated with 231D in the presence of prothrombin (PT+231D vs base line, 231D alone, PT+control IgG:0.91+/-0.07 vs 0.78+/-0.06, 0.81+/-0.03 ;all $p<0.005$). PRP spiked with 231D (5,10,20ug/ml) inhibited primary and secondary aggregation induced by ADP. Collagen induced platelets aggregation was not affected by 231D.

Conclusion: The presence of IgG aPS/PT was a strong risk to have arterial events in patients with autoimmune diseases. Platelets were activated by monoclonal aPS/PT, thus aPS/PT may be involved in the pathogenesis of arterial diseases in such patients. However, ADP induced platelet aggregation was inhibited by 231D, suggesting that the *in vitro* behavior of aPS/PT-treated platelets is complex and paradoxical. Further studies will promise to unveil the enigmatic role of aPS/PT in the development of arterial disease in the affected patients.

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Association of Anti-oxLDL/ß2 GP1 Immune Complex and Accelerated Atherosclerosis in Patients with Primary Antiphospholipid Syndrome. Antonio Barrera[1], Claudia Hernandez[2], Gabriela Medina[3], Miguel Saavedra[4] and Luis Javier Jara[3], [1]Hospital de Especialidades Centro Medico La Raza IMSS, Mexico Distrito federal, Mexico, [2]Hospital de Especialidades Centro Medico La Raza IMSS, Mexico, Mexico, [3]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico, [4]Hospital Angeles Metropolitano, Mexico DF, Mexico

Purpose: Autoantibodies against oxLDL/ß2 GP1 complexes occur in patients with antiphospholipid syndrome (APS) and significantly correlate with arterial thrombosis, but their exact clinical significance in primary antiphospholipid syndrome (PAPS) and accelerated atherosclerosis remains unclear

Method: We included 40 PAPS patients and 40 controls matched by age and gender. Demographic and clinical data were obtained by direct interview, chart review, and physical examination. Cardiovascular risk factors for atherosclerosis were registered. Blood samples from patients and controls were taken for serum determination of IgG, and IgM anti-oxLDL/b2GP1 antibodies (ELISA test, Immunomex commercial kit, normal values: < 20 IU). Atherosclerosis was defined as a carotid intima-media thickness (IMT) greater than 0.8 mm. measured by high resolution B mode ultrasound.

Results: The mean age of patients and controls was 41 ± 6 years with a female predominance (93%), disease duration was 10 ± 5 years. The principal clinical manifestations of PAPS patients were deep venous thrombosis (50%) and cerebral vascular disease (36%). Traditional cardiovascular risk factors were similar in patients and controls. Patients with PAPS had a significant IMT in comparison with controls (0.75 ± .09 mm vs. 0.64 ± 0.09 mm, $p < 0.001$) and they had higher titers of anti-oxLDL/b2GP1 IgG in comparison with controls (67.62 ± 10.50 vs. 14.97 ± 18.01, $p=0.005$). In the group of patients with PAPS, there was not correlation between IgG anti-oxLDL/b2GP1 titers and IMT ($r=-.182$)

Conclusion: Our study suggests that autoantibodies against oxLDL/b2GP1 complexes ocurr in patients with PAPS. However, there was not correlation between IgG anti-oxLDL/b2GP1 titers and IMT. Further prospective clinical studies are necessary to determine its role on aterosclerosis

Disclosure: A. Barrera, None; **C. Hernandez**, None; **G. Medina**, None; **M. Saavedra**, None; **L. J. Jara**, None.

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Association Between CD36 Single Nucleotide Polymorphism and Antiphospholipid Syndrome. Masaru Kato, Tetsuya Horita, Tatsuya Atsumi, Olga Amengual, Hisako Nakagawa, Yuichiro Fujieda, Kotaro Otomo, Kenji Oku, Hiroshi Kataoka, Shinsuke Yasuda and Takao Koike, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: CD36, known as a scavenger receptor, is a transmembrane glycoprotein expressed on monocytes, macrophages, platelets and capillary endothelial cells. CD36 recognizes multiple ligands, including phosphatidyl serine, and is a mediator of both atherogenesis and thrombosis. Some reports indicated that CD36-null mice were resistant for thrombus formation. Human CD36 deficiency was first described in 1989 as refractory to HLA-matched platelet transfusions, and is found in 4 to 10 % of Asian or African population. There has been, however, no report of the correlation between CD36 gene polymorphism and thrombotic diseases. The purpose of this study is to investigate the association between CD36 gene polymorphisms and antiphospholipid syndrome (APS).

Methods: This study comprised a total of 795 Japanese: 39 patients with primary APS, 69 with systemic lupus erythematosus (SLE) complicated with APS, 265 with SLE in the absence of APS, and 422 healthy subjects. All the APS patients fulfilled the Sydney-revised Sapporo criteria of APS, and all the SLE patients fulfilled the American College of Rheumatology classification criteria of SLE. Two following CD36 gene polymorphisms were investigated in this population using the TaqMan PCR genotyping method, the T for C allele substitution at nt478 for Pro90Ser (rs3765187), a common variation linked to CD36 deficiency, and the A for C substitution on the 5' untranslated region (rs1049654). Statistical analysis was performed by Fisher's exact test.

Results: The allele frequency of rs3765187 in each group is presented in the Table1; The T allele at nt478 was less frequent in APS patients than in healthy subjects. There was no significant difference in the allele frequency of rs1049654 among those groups.

Conclusion: The single nucleotide polymorphism linked to CD 36 deficiency was less frequent in APS patients, suggesting that impaired scavenger receptor function correlates with APS-resistant. This is a first report to show the link between CD36 gene and APS.

Table 1. The allele frequencies of CD36 SNP, nt478C/T for Pro90Ser rs3765187, in healthy subjects and patients with APS and SLE

	nt478 T frequency	p value	OR (95% CI)
Healthy subjects (n = 422)	10.2% (43/422)	-	-
All APS (n = 108)	2.8% (3/108)	0.024	0.25 (0.08 to 0.83)
All SLE (n = 334)	6.9% (23/334)	0.11	0.65 (0.38 to 1.11)
Primary APS (n = 39)	2.6% (1/39)	0.15	0.23 (0.03 to 1.73)
SLE+APS (n = 69)	2.9% (2/69)	0.085	0.26 (0.06 to 1.11)
SLE/non-APS (n = 265)	7.9% (21/265)	0.32	0.76 (0.44 to 1.31)

The p value and OR (95% CI) for each group were obtained by the comparison with healthy subjects.

APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; OR, odds ratio; SNP, single nucleotide polymorphism

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Oxidative Stress and Mitochondrial Membrane Potential in Circulating Leucocytes From Antiphospholipid Syndrome Patients: Key Intracellular Events in Thrombosis Development. Chary Lopez-Pedrera[1], Patricia Ruiz-Limon[1], MA. Aguirre[2], Nuria Barbarroja[1], Mj Luque[1], Antonio Rodriguez-Ariza[1], Eduardo Collantes-Estevez[3], José M. Villalba[4], F. Velasco[1], Munther A. Khamashta[5] and Mj. Cuadrado[5], [1]Reina Sofia Hospital, Cordoba, Spain, [2]Reina Sofia Hospital, Spain, [3]Universidad De Cordoba, Cordoba 14012, [4]Cell Biology Department, University of Cordoba, Spain, [5]The Rayne Institute, St Thomas' Hospital, London, United Kingdom

Purpose: Antiphospholipid antibodies (aPL) are involved in the induction of a procoagulant state; yet, precise intracellular mechanisms are poorly understood.There is evidence for oxidative damage in plasma from antiphospholipid syndrome (APS) patients but oxidative stress markers and mitochondrial integrity of circulating APS leucocytes have not been studied yet.

Objectives: To investigate prooxidant/antioxidant status and mitochondrial membrane potential (MMP) in peripheral leucocytes from APS patients, and their association with a procoagulant state.

Methods: The study was conducted in 20 APS patients and 20 healthy donors. Cell surface tissue factor (TF) expression was analyzed by flow cytometry in monocytes. Oxidative stress biomarkers were analysed in purified white blood cells (WBCs): lymphocytes, monocytes and neutrophils. Peroxides, superoxide, MMP and intracellular GSH were analysed by flow cytometry with 2',7'-dichlorodihydrofluorescein diacetate, dihydroetidium, Rhodamine-123, and 5-chloromethylfluorescein diacetate respectively. Monocytes from normal individuals were treated with APS or control IgG to assess the effect of aPL on the oxidative/antioxidant status. Plasma NO, Nitro tyrosine (N-Tyr) and Total Antioxidant Capacity (TAC) were also measured. Correlations between ROS, MMP and TF expression were tested for statistical significance.

Results: Peroxides and superoxide levels were increased in APS monocytes and neutrophils (P=0.032 and P=0.042, respectively) and intracellular glutathione was significantly decreased (P=0.021). More APS monocytes and neutrophils contained depolarised mitochondria (P=0.004). MMP and peroxide levels showed a significant positive correlation with monocyte TF expression (r=0.814, P=0.094 and r=0.988, P=0.0015, respectively, Pearson analysis). Plasma TAC tended to a more pro-oxidant status in APS patients. A drift towards a reduction in NO and N-Tyr plasma levels was also observed. A marked increase in peroxides and superoxide (P=0.03 and P=0.042, respectively) and a

decrease of MMP and GSH (P=0.04 and P=0.01, respectively) was observed after a 6-h stimulation of monocytes with patientxs but not with control IgG.

Conclusion: A redox-sensitive pathway might play a central role in the elicitation of thrombotic events in APS. Our results further suggest a role for mitochondrial alterations in thrombosis development in APS. Induction of a prooxidant state by APS IgG represents a new pathway potentially contributing to thrombotic complications, which would provide alternative targets for therapeutic interventions. Supported by JA0042/2007-P08CVI04234.

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Is It Possible to Differentiate " Natural " Antiphospholipid Antibodies From "Thrombophilic" Ones? - Analysis of the Fine Specificity against the Domains of Beta2glycoprotein I. Angela Tincani[1], Laura Andreoli[1], Cecilia Nalli[1], Mario Motta[1], Gary L. Norman[2], Zakera Shums[2], Walter L. Binder[2], Monica Nuzzo[1], Micol Frassi[1], Andrea Lojacono[1], Tadej Avcin[3] and Pier Luigi Meroni[4], [1]University and Spedali Civili of Brescia, Brescia, Italy, [2]INOVA Diagnostics, Inc., San Diego, CA, [3]University Medical Center Ljubljana, Ljubljana, Slovenia, [4]University of Milan, Milan, Italy

Purpose: Anti-$\beta_2$glycoprotein I antibodies (a-β_2GPI) were demonstrated to be directly involved in the pathogenesis of the Antiphospholipid Syndrome (APS). However, they can be detected in asymptomatic patients, especially those affected by systemic autoimmune diseases (SAD). Healthy children may also display a-β_2GPI as a consequence of infections and nutritional exposure to β_2GPI, but they do not usually develop any thrombotic event. It has been suggested that a-β2GPI against domain 1 (D1) associate with thrombosis, while those recognizing domain 4/5 (D4/5) have been identified in non-thrombotic conditions. Aim of this study was to evaluate the fine specificity of a-β_2GPI in different groups of adults and infants. .

Method: The study included 39 one-year-old healthy children born to mothers with SAD (11 Primary APS, 9 SLE, 9 UCTD, 6 Sjögren, 3 MCTD, 1 RA; 33% out of these mothers were a-β_2GPI positive) and 33 children with Atopic Dermatitis (AD). The children of both groups were found positive at Routine a-β_2GPI. No thrombotic events were recorded in both one-year old and AD children.

As controls, 54 adult patients with APS (47 PAPS, 7 associated with SLE) and 5 children with paediatric APS were considered. All subjects were IgG a-β_2GPI pos at our routinely performed home-made ELISA assay. Sera were studied for IgG a-β_2GPI D1 and D4/5 using research ELISAs containing recombinant β_2GPI domain antigens. Cut-off values were calculated as the 95th percentile on 50 NHD.

Results: One-year-old children and AD children displayed a preferential reactivity for D4/5, whereas patients with APS, both adults and infants, were positive mainly for D1. Percentages are shown in the table.

	D1 + D4/5 -	D1 - D4/5 +	D1+ D4/5+
1-year-old children (n=39)	2.5%	33%	8%
AD (n=33)	15%	30%	3%
Adult APS (n=54)	61%	7.4%	3.7%
Paediatric APS (n=5)	50%	17%	0%

A good correlation was present between a-β_2GPI and anti-D4/5 in one-year-old children and DA ($r=0.85$, $r=0.88$; $p<0.01$), and anti-D1 in adult APS ($r=0.66$; $p<0.01$). This suggests that reactivity against a particular domain truly reflects the main specificity of the whole autoantibody population.

Conclusion: A-β_2GPI detected in healthy infants displayed preferential recognition for D4/5, in contrast to the prevalent specificity for D1 in subjects with APS. This could account for the "innocent" profile of natural antibodies against β_2GPI that may develop during infancy. Our study supports the hypothesis that different subpopulations of a-β_2GPI carry a different pathogenic potential.

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Do Clinically Relevant IgA-Anti-B2glycoprotein I (anti-B2GPI) Antibodies Bind to Domain IV/V of β2GPI? Laura Aline Martinez-Martinez[1], Renan Aguilar-Valenzuela[1], Alan M. Seif[1], Elizabeth Papalardo[1], Luis M. Vilá[2], Sabeen Najam[1], Terry A. McNearney[1], Emilio B. Gonzalez[1], Prashanth R. Sunkureddi[1], Walter L. Binder[3], John D. Reveille[4], Gary L. Norman[3], Zakera Shums[3], Graciela S. Alarcon[5] and Silvia S. Pierangeli[1], [1]University of Texas Medical Branch, Galveston, TX, [2]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [3]Inova Diagnostics, Inc., San Diego, CA, [4]University of Texas Medical School at Houston, Houston, TX, [5]University of Alabama, Birmingham, AL

Purpose: In vitro and in vivo studies have shown that "pathogenic" IgG anti-β_2GPI mainly recognize epitopes in domain I of the protein. Recently, it has been suggested that IgA anti-β_2GPI antibodies may recognize epitopes in domains IV/V of β_2GPI and these antibodies appear to be associated with certain manifestations of Antiphospholipid Syndrome (APS).

Objectives: a) To determine in patients previously found to be positive for IgA anti-β_2GPI whether: a) these antibodies bind to β_2GPI domain IV/V, and b) whether those antibodies are associated with clinical manifestations of APS.

Method: 80 IgA-anti-β_2GPI positive sera were selected from 588 SLE patients in a multi-ethnic, multi-center cohort (LUMINA); Similarly, 35 IgA anti-β_2GPI positive sera were obtained from 2188 patients that were referred to our reference laboratory (APLS) for APS work-up between Jan-2008 and May-2009 (Table 1). IgA anti-β_2GPI binding of the sera to domain IV/V of β_2GPI were examined by ELISA using prototype kits (INOVA Diagnostics, Inc.) A test was considered positive when values were above kit recommended cut-off points. Table 1.

Patients Characteristics	LUMINA cohort (%) (n=80)	APLS lab cohort (%) (n=35)
Females/Males	89/11	25/10
Mean age	35.3	42.6
SLE diagnosis	100	40
African American	46	29
Caucasian	14	34
Other ethnic groups	40	37

Results:

Group	# of samples positive for DIV/V IgA anti-β_2GPI/ (%)	# of samples positive for DIV/V IgA anti-β_2GPI with APS clinical manifestations/(%)
LUMINA (exclusively IgA	30(64%)	27(90%)

anti-β_2GPI positive) n=47		
LUMINA (IgA anti-β_2GPI and other aPL positive) n= 33	18(55%)	16(89%)
APLS (exclusively IgA anti-β_2GPI positive) n=21	5(24%)	2(40%)
APLS (IgA anti-β2GPI and other aPL positive) n=14	9(64%)	3(40%)
Total N=115	62(54%)	48(77%)

A total of 62 out of 115 IgA (54%) anti-β_2GPI positive samples were positive in domain IV/V assay and 77 % of those had clinical manifestations of APS that included: arterial and venous thromboses, pregnancy losses, other APS-related pregnancy complications, seizures, thrombocytopenia, skin ulcers, pulmonary hypertension, livedo reticularis, cardiac valvular disease, and migraines. Correlation of IgA anti-β_2GPI titers between the two kits was 0.69

Conclusion: IgA anti-β_2GPI antibodies that bind to domain IV/V of β_2GPI may represent an important subgroup of clinically-relevant aPL antibodies.

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Isolated Elevated Levels of IgA-Anti-Beta2glycoprotein I Antibodies Are Associated with Clinical Manifestations of the Antiphospholipid Syndrome. Renan Aguilar-Valenzuela[1], Alan M. Seif[1], Graciela S. Alarcon[2], Laura Aline Martinez-Martinez[1], Neha Dang[1], Elizabeth Papalardo[1], Jigna Liu[3], Luis M. Vila[4], Sabeen Najam[5], Terry A. McNearney[6], Emilio B. Gonzalez[7], Walter L. Binder[8], Marius C. Teodorescu[9], John D. Reveille[10] and Silvia S. Pierangeli[1], [1]University of Texas Medical Branch, Galveston, TX, [2]University of Alabama, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Univ of PuertoRico Schl of Med, San Juan, PR, [5]League City, TX, [6]Univ of Texas Med Branch, Galveston, TX, [7]Univ of Texas Medical Branch, Galveston, TX, [8]Inova Diagnostics Inc, San Diego, CA, [9]TheraTest Laboratories Inc, Lombard, IL, [10]University of Texas Health Science Center Houston, Houston, TX

Purpose: Although IgA anticardiolipoin (aCL) antibodies are more frequently found in Afro-Caribbean populations - usually in association with other IgG and/or IgM aCL antibodies – and have been shown to be pathogenic in animal models, their clinical significance has remained elusive. We recently reported five isolated cases of exclusive IgA anti-β2GPI antibody sero-positivity with concomitant APS clinical manifestations. Objectives: a) to examine the prevalence of exclusive IgA-anti-β_2GPI antibody positivity in a large cohort of patients with SLE and in patients suspected of having APS; b) to correlate IgA anti-β_2GPI positivity with APS-associated clinical manifestations

Method: aPL seropositivity was examined in sera of 588 SLE patients from a multi-ethnic, multi-center cohort (LUMINA) and in 2108 sera from patients that were referred to our laboratory (APLS) for APS work-up between Jan-2008 and May-2009. aCL (IgG, IgM, IgA), aPL IgG and IgM, and IgG, IgM anti-β_2GPI antibodies were evaluated by ELISA [in-house method], and by commercial kits (Louisville APL Diagnostics, and INOVA Diagnostics, respectively). IgA anti-β_2GPI titers were determined in two commercial ELISA [INOVA, kit 1) and [Theratest (kit 2)].

Results:

Ethnic group	Prevalence IgA-anti-β_2GPI LUMINA cohort (%)	Prevalence IgA-anti-β_2GPI APLS cohort (%)
African American	47	36.4
Caucasian	17	27.3
Other	46	36.3

Thirty-six patients' samples from the LUMINA cohort and 23 from the APLS laboratory were positive exclusively for IgA-anti-β_2GPI. All the samples were positive for IgA-anti-β_2GPI antibodies in at least one kit. Correlation of IgA anti-β2 GPI titers between the two kits was 0.93. Sixty-nine % of the LUMINA subjects and 78% in the APLS group had at least one APS-related clinical manifestation that included: arterial and venous thromboses, pregnancy losses, other APS-related pregnancy complications, seizures, thrombocytopenia, skin ulcers, pulmonary hypertension, livedo reticularis, cardiac valvular disease, and migraines. One patient in each group was LAC positive.

Conclusion: This study supports the notion that elevated IgA anti-β_2GPI antibody titers may identify additional patients who have clinical features of APS but who do not meet current diagnostic criteria. It may be therefore recommended to test for IgA anti-β_2GPI antibodies when other aPL tests are negative and APS is suspected.

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B2-Glycoprotein-I IgA Antibodies (a-b2GPI IgA Ab) but Not the IgG a-b2 and IgG a-Cardiolipin Listed in Sydney Criteria, Predispose to Vascular Events in Hispanics with SLE. George A. Karpouzas[1], Rosalinda C. Moran[1], Chasity Harris[1] and Bevra H. Hahn[2], [1]Harbor-UCLA Medical Center, Torrance, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: Antiphospholipid antibodies (APLs) have been commonly reported in Hispanic patients (pts) with SLE. Lupus anticoagulant (LA), IgM and IgG anticardiolipin (ACL) >40 MPL and GPL U/ml respectively, and a-b2GPI Ab>99th percentile, testing positive twice 12 weeks apart, have been proposed as laboratory diagnostic criteria of the antiphospholipid syndrome (APLS, Sydney-2006). IgA ACL and b2GPI Ab are not included in this classification, and their pathogenic role is less well defined. We examined the prevalence of different classes of APLs including a-b2GPI IgA in Hispanics with SLE, their association with thrombotic events, and the enrichment of individual APL subclasses in pts with thrombus compared to those without.

Methods: We reviewed the charts of 178 Hispanics with SLE from Mexico and Central America between 1/1997 and 6/2008. All fulfilled ≥4 1996 ACR criteria for SLE and had follow-up in a single center. All pts were tested at least twice 12 weeks apart. LA was tested with both aPTT and DRVVT. ACL and b2GPI Ab IgG, IgM, and IgA were tested using commercial ELISA kits (QUEST). ACL IgA>15 APL U/ml and a-b2GPI-IgA>10 U/ml were considered positive. Associations with clots were assessed using Fisher's exact test.

Results: Pts were predominantly female (87%) with mean age of 41±12 years, and largely indigent (84%). Only 5 pts (2.8%) had two positive APL confirmed twice 12 weeks apart, and 42 (23.6%) had at least one positive APL test (table 1). Clots occurred in 28 pts (15.7%): 17 were venous, 9 arterial and 2 glomerular. The presence of any APL more than once significantly increased the risk of thrombosis. LA was the most prevalent APL class (14%) and was significantly associated with thrombotic events (OR=14.8, CI=5.5-39.2, p<0.0001). Interestingly, anti-b2GPI IgA emerged as the 2nd most prevalent Ab (13.6%), also with significant contribution to clotting (OR=4.5, CI=1.6-12.5, p=0.006). Presence of other APL subclasses were overall low (<3%), with insignificant contribution to thrombus formation, except for ACL-IgM (table 1).

Conclusion: In this cohort of Mexican/Central American Hispanics with SLE in Los Angeles, LA was the most prevalent APL Ab and was significantly associated with thrombotic events. Unexpectedly, anti-b2GPI IgA emerged as a prevalent and significant contributor to thrombotic events. Other subclasses of a-b2 and a-CL were uncommon with overall trivial input. B2-GPI IgA Ab should therefore be routinely tested in Hispanic pts with SLE and the diagnosis of APLS entertained in positive pts with events.

Table 1: Patient Demographics

	Prevalence-%	**Event(+)%**	**Event(-)%**	**OR**	**CI**	**p-Fisher's**
pan-APL(-)	44.4	3.8	96.2	referent		
≥ any 1 APL(+)	23.6	42.9	57.1	***19***	5.1-70.1	***<0.0001***
≥ any 2 APL(+)	2.8	80	20	***101***	8.5-1207	***<0.0001***
LA (+)	14	52	6.8	***14.8***	5.5-39.2	***<0.0001***
ACL-IgG(+)	0.6	3.6	0	15.5	0.6-392	0.16
ACL-IgM(+)	1.2	7.1	0	***26.9***	1.3-576	***0.03***
ACL-IgA(+)	0	0	0	NA	NA	NA
b2GPI-IgG(+)	1.9	0	2.3	0.7	0.04-14.9	1
b2GPI-IgM(+)	2.6	8.3	1.1	5.8	0.8-43.5	0.1
b2GPI-IgA(+)	13.6	33	10	***4.5***	1.6-12.5	***0.006***

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Detection of IgG/IgM Antibodies That Recognize Epitope Gly40-Arg43 in Domain I of Beta2GPI with An ELISA Assay: A New Perspective in Prediction of Thrombotic Manifestations in Antiphospholipid Syndrome? Valentina De Angelis[1], Gwendolyn Van Os[2], Francesca Pregnolato[3], Claudia Grossi[3], Cecilia B. Chighizola[1], Martina Biggioggero[1], Philip G. de Groot[2], Ron H.W.M. Derksen[2], Pier Luigi Meroni[1] and Rolf T. Urbanus[2], [1]University of Milan, Milano, Italy, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Istituto Auxologico Italiano, Milan, Italy

Purpose: Antiphospholipid antibodies (aPL), serological markers of the antiphospholipid syndrome (APS), are mainly directed against β2-glycoprotein I (b2GPI), a plasma protein with phospholipid binding properties. b2GPI consists of five complement control protein or 'sushi'

domains (designated I to V), that are arranged in an elongated, fish-hook shape. Although the location of epitopes recognized by aPL remains the subject of controversy, several studies suggest pathological aPL are directed against the Gly40-Arg43 epitope in domain I of β2GPI.

With this study we want to determine the specificity of assays that detect antibodies against domain I or domain IV of b2GPI for the diagnosis of APS, as well as their predictive value in the clinical outcome of the disease.

Method: We tested plasma or serum samples of 39 primary APS patients, who fulfilled the Sapporo criteria, 9 patients with APS secondary to autoimmune connective tissue disease, 6 asymptomatic aPL positive patients and 8 asymptomatic patients with autoimmune connective tissue disease. We determined the presence of aPL (lupus anticoagulants, anticardiolipin and anti-b2GPI antibodies), as well as serological markers for autoimmune connective tissue disease. Patients with paraproteinaemia (n=10), hypergammaglobulinaemia (n=10), infectious disease (n=22) such as HIV (n=4) or hepatitis B (n=3) and –C (n=15), and autoimmune diseases without aPL (n=35) were used as controls. IgG- and IgM anti-domain I and domain IV antibodies were detected with a home-made assay. Cut-off values were set at the 99th percentile of 50 healthy subjects.

Results: 52 patients with aPL were positive for IgG - and 31 for IgM- anti-b2GPI antibodies , of which 21 (40%) were positive for anti-DI IgG and 10 (32%) for IgM. Only 9 (17%) were positive for anti-DIV IgG with 10 (32%) positive for anti-DIV IgM. 70 % of the patients with anti-DI antibodies had thrombotic events in their clinical history. Anti-domain I and domain IV antibodies were only detected in patients with anti-β2GPI antibodies. None of the controls had anti-domain I or IV antibodies, but 5 samples were positive for IgM anti-domain IV.

Conclusion: APS samples display reactivity against epitopes in both domain I and domain IV of β2GPI. Anti-DI antibodies correlated with a clinical history of thrombotic manifestations

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Moderate Versus High Titer Persistently Anticardiolipin Antibody Positive Patients: Are They Clinically Different? Medha Barbhaiya[1], Doruk Erkan[2], Diane George[3], Lisa R. Sammaritano[2] and Michael D. Lockshin[2], [1]Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Yale School of Medicine, CT

Background: The association between antiphospholipid antibodies (aPL) and clinical events is stronger with higher anticardiolipin antibody (aCL) titers.

Purpose: To determine the clinical characteristics of persistently moderate-titer (40-79U) aCL-positive patients compared to those with persistently high (≥80U) aCL titers.

Method: In this cross sectional study, we compared the demographic, clinical, and aPL characteristics of 58 patients with at least two moderate-titer aCL-positive results to another 85 patients with at least two high-titer aCL results. The highest aCL was used in the analyses; in cases with multiple isotypes with the same titer, IgG isotype was chosen over IgM/A, and IgM was chosen over IgA. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate.

Results: Table demonstrates the demographic and clinical characteristics. High-titer aCL positive patients were more likely to have primary aPL/APS (relative risk [RR] 1.82, confidence interval [CI] 1.25-2.65, $p<0.01$) and positive LA test (RR 2.06, CI 1.38-3.08, $p<0.01$). Although aPL-related criteria (vascular and pregnancy) events were similar between the two aCL groups, the number of patients with at least one non-criteria aPL event was significantly higher in the high-titer aCL group (RR 1.66, CI 1.20-2.30, p: 0.0005). Magnetic resonance imaging (MRI) white matter changes were statistically more common in the high-titer aCL group (RR 2.03, CI 1.04-3.94, p: 0.02), and there was a trend towards increased prevalence of livedo reticularis, cardiac valve disease, and cognitive dysfunction occurring in the high-titer aCL group.

Conclusion: Our results suggest that patients with high aCL titers, compared to those with moderate titers, are more likely to have a positive LA test and a similar risk of aPL-related vascular and pregnancy events, but a higher prevalence of non-criteria aPL features.

aPL Features n^+/n^t (%)*	**Moderate-titer aCL 40-79 (n: 58)**	**High-titer aCL ≥ 80 (n: 85)**	**p**
Demographics			
Female	50/58 (86%)	76/85 (89%)	0.56
Primary aPL/APS	21/58 (36%)	56/85 (66%)	<0.01
.			
aPLProfile			
LA + patients (n^+/n^t)	18/53 (34%)	56/80 (36%)	<0.01
Criteria Events			
Vascular Events	24/58 (41%)	39/85 (46%)	0.65
Recurrent Vascular Events	10/58 (10%)	17/85 (20%)	0.70
Pregnancy Morbidity	18/52 (35%)	26/76 (34%)	0.96
.			
Non-Criteria Events			
Thrombocytopenia	10/58 (17%)	14/85 (16%)	0.90
Livedo Reticularis	8/58 (14%)	21/85 (25%)	0.11
Cardiac Valve Disease	5/34 (15%)	12/42 (29%)	0.15
Nephropathy	3/58 (5%)	1/85 (1%)	0.30
Chorea	0/58 (0%)	2/85 (2%)	0.51
MRI White Matter Changes	7/22 (32%)	20/31 (65%)	0.02
Cognitive Dysfunction	2/58 (3%)	10/85 (12%)	0.12
≥1 Non-Criteria Events	25/58 (43%)	61/85 (72%)	0.0005
.			
Criteria or Non-Criteria Events	39/58 (67%)	73/85 (86%)	0.008

* n^+/n^t = the number of patients with positive feature / the number of patients with available tests.

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Silent Ischemic Myocardial Disease in Antiphospholipid Syndrome. Karim Sacre, Benoit Brihaye, Fabien Hyafil, Jean-Pierre Laissy, Olivier Lidove and Thomas Papo, Bichat-Claude Bernard Hospital, University Paris-7, Paris, France

Purpose: To study prospectively the prevalence of subclinical ischemic myocardial disease in antiphospholipid syndrome (APS)

Method: Fifty four patients of our APS cohort satisfied the APS criteria proposed by the International Consensus Statement in 2006. Eight patients declined to participate to the study. Seven patients were excluded because of severe renal disease (5/7) or claustrophobia (2/7). On the 39 patients included, 24 have completed the study at the present time. Twenty-one had primary APS and 3 had APS associated with systemic lupus erythematosus. Following data were recorded: gender, ethnicity, hypertension, triglycerides, cholesterol, smoking, diabetes mellitus, body mass index, homocysteine, hormone replacement therapy/oral contraceptives and familial cardiovascular events. Electrocardiogram (EKG), transthoracic echocardiography and cardiac magnetic resonance imaging (MRI) using late gadolinium enhancement imaging were systematically performed the same day in all patients.

Results: Fifteen female and 9 male patients participated. The mean age was 44 years (range 19-78) and the mean duration of APS was 9 years (range 1-34). Cardiac MRI showed localised area of late gadolinium contrast enhancement (LGE) in 9 patients (LGE+). Of the 9 patients, 6/9 had LGE extending from the subendocardial region outward in the defined territory of a coronary artery and 3/9 had patchy LGE in a non-coronary artery distribution pattern. The remaining 15 patients had normal cardiac MRI (LGE-). Trans-thoracic echocardiography and EKG did not show myocardial changes in all cases. LGE+ patients (mean age: 61, range: 34-77) were older than LGE- (mean age: 33, range: 19-78) ($p=0.029$) and men seemed to be at significant risk for LGE (male: 6/9 LGL+ versus 3/15 LGL-, $p=0.029$). Other usual risk factors for atherosclerosis were not associated with LGE. Of the 24 patients, 2/9 LGE+ and 2/15 LGE- had a history of stroke, and 2/9 LGE+ and 1/15 LGE- had suffered peripheral arterial disease. Of the 9 LGE+ patients, 6 had no previous cardiac symptom and 3 had had acute myocardial infarction (AMI) documented on troponin rise and abnormalities on EKG. Interestingly, coronarography was normal in the 3 cases of AMI.

Conclusion: Cardiac MRI may detect silent infarcts in APS patients with normal electrocardiogram and trans-thoracic echocardiography.

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The Role of Antiphospholipid Syndrome-Related Features in the Development of Cardiovascular Events in Patients with Sjogren Syndrome. Marta Perez-de-Lis[1], Rafael Belenguer[2], Manuel Ramos-Casals[1], Pilar Brito-Zeron[1], Albert Bove[1], Candido Diaz-Lagares[1], Myriam Gandia[1], Antoni Siso[3] and Antonio Coca[4], [1]IDIBAPS, Hospital Clinic, Barcelona, Spain, [2]Hospital 9 d'Octubre, Valencia, Spain, [3]CAP Les Corts, Barcelona, Spain, [4]ICMiD, Hospital Clinic, Barcelona, Spain

Purpose: To investigate the association of the clinical, analytical and immunological features related to antiphospholipid syndrome (APS) with the development of cardiovascular events (CVE) in a large cohort of patients with primary Sjögren's syndrome (SS).

Method: Five hundred and five consecutive patients diagnosed with primary SS between 1980 and 2008 were evaluated (470 females and 35 males, mean age at diagnosis of 57 years). Outcomes measured were CVE (ischemic heart disease, cerebrovascular disease and peripheral arterial ischemia) and death.

Results: Sixty five (13%) patients developed a total of 78 CVE after a mean time of follow-up of 7.75 years. There were 57 (88%) females and 8 (12%) males, with a mean event age of 66.4 years (range 42-91) and a mean time of 4.7 years after primary SS diagnosis. Forty-five patients had ischemic heart disease, 29 had cerebrovascular disease and 4 peripheral arterial disease. Antiphospholipid antibodies (aPL) were detected in 9/26 (41%) patients with CDVE: lupus anticoagulant –LA- was found in 7 patients and anticardiolipin antibodies –aCL- in 4 patients (IgG in 4 and IgM in one). Three SS-CVE-aPL+ patients fulfilled the current classification criteria for APS and 4 had a probable APS (with thrombosis but with only one positive aPL determination in serial measurements). All patients but two had concomitant traditional cardiovascular risk factors. Six (86%) out of the 7 SS-CVE-LA+ patients had stroke and 4 (57%) myocardial infarction.

Conclusion: Nearly half the patients with primary SS and cardiovascular events tested for aPL had positive results, with a close association between LA and stroke/myocardial infarction. We recommend testing for antiphospholipid antibodies in patients with primary SS and cardiovascular events even if patients have concomitant traditional cardiovascular risk factors.

Disclosure: M. Perez-de-Lis, None; **R. Belenguer**, None; **M. Ramos-Casals**, None; **P. Brito-Zeron**, None; **A. Bove**, None; **C. Diaz-Lagares**, None; **M. Gandia**, None; **A. Siso**, None; **A. Coca**, None.

1281

Cardiovascular and Stroke Risk in Patients with Antiphospholipid Syndrome and Renal Artery Stenosis. Marina Zakalka[1], Shirish.R Sangle[2] and David P. D'Cruz[1], [1]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [2]The Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom

Purpose: We have demonstrated increased arterial stiffness by carotid-femoral pulse wave velocity (PWV_{CF}), digital volume pulse contour analysis stiffness index (SI_{DVP}) and by ankle brachial pressure index (ABPI) in patients with APS and renal artery stenosis (RAS) (APS+RAS) compared with 3 control groups. Aim of this is to determine 10-yr predicted coronary heart disease (CHD) and stroke risks in patients with APS+RAS and 3 control groups.

Method: We recruited 17 Caucasian patients with APS+RAS, with positive antiphospholipid antibodies on more than two occasions and uni- or bilateral RAS on imaging. All had treated hypertension (defined as BP>140/90). The control groups were: 18 women with PAPS thrombosis; 18 women with SLE, negative for aPL (SLE, aPL-ve) and 15 matched healthy women (HC). After informed consent, cardiovascular risk factors, physical activity, disease-related variables and fasting blood specimens were collected. 10-yr predicted coronary heart disease (CHD) and stroke risk scores were calculated with The Joint Societies' Cardiac Risk Assessor program. Physical activity scores were estimated for all study subjects; in SLE patients, SLEDAI disease activity and SLICC damage index were recorded.

Results: Framingham cardiovascular risk profiles did not differ between groups. 10-yr predicted CHD and stroke risk scores were significantly higher in the APS+RAS group versus PAPS patients ($p<0.001$ and $p=0.004$), versus SLE, aPL-ve patients ($p=0.006$ and $p=0.030$) and HC ($p<0.001$ and $p=0.002$) respectively. In the APS+RAS group $\ln PWV_{CF}$ was significantly increased (10.95±5.7m/s) compared to HC (7.61±1.5m/s) ($p=0.006$) and mean ABPI was significantly lower (1.15±0.18mmHg) compared to HC (1.245±0.13mmHg) ($p=0.031$).

Mean SLEDAI of the 10 SLE, APS+RAS patients was 4.6 (2.8) compared to 2.7 (3.2) in the 18 SLE, aPL-ve patients. Median SLICC damage index of the former group was 2.5(IQR: 1-4) and 0.5(IQR: 0-2) in the latter.

In the disease subjects as a group, 10-yr predicted CHD risk score correlated with PWV_{CF} ($r=0.51$, $p<0.01$) and SI_{DVP} ($r=0.53$, $p<0.01$). 10-yr predicted stroke risk score correlated with PWV_{CF} ($r=0.6$, $p<0.01$) and SI_{DVP} ($r=0.53$, $p<0.01$). PWV_{CF} correlated with SI_{DVP} ($r=0.3$, $p=0.031$). ABPI inversely correlated with SI_{DVP} ($r=-0.3$, $p=0.047$). ABPI and physical activity index score were correlated in APS+RAS patients ($r=0.589$, $p=0.016$), in PAPS patients ($r=0.620$, $p=0.008$) and in SLE, aPL-ve patients ($r=0.495$, $p=0.043$).

PWV_{CF} correlated with the SLICC damage index in the 10 SLE, APS+RAS patients ($r=0.640$, $p=0.046$), ABPI correlated with disease duration in the APS+RAS group ($r=0.0519$, $p=0.033$). ABPI correlated inversely with disease duration in PAPS patients ($r=-0.490$, $p=0.046$).

Conclusion: APS+RAS patients had a worse cardiovascular and stroke risk profile than PAPS and SLE patients implying a role for a vasculopathy. Arterial stiffness may be a valuable tool with traditional cardiovascular risk factors in the assessment of APS patients.

Disclosure: M. Zakalka, None; **S. R. Sangle**, None; **D. P. D'Cruz**, Aspreva, 5 .

1282

Hematologic Manifestations Among Patients Who Fulfill the Sidney Laboratory Criteria for Antiphospholipid Syndrome: a 6 Year Follow-up. Lucía Comellas-Kirkerup[1], Antonio R. Cabral[1] and Gabriela Hernandez-Molina[2], [1]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico

Purpose: To study patients with thrombocytopenia (TP), hemolytic anemia (HA) or both who meet the antiphospholipid syndrome (APS) Sidney laboratory criteria but do or not fulfill the clinical criteria.

Methods: We reviewed the medical charts of 187 patients with primary APS from our patient's Registry (Jan 1986- Dec 2008) and selected those who met the following criteria: a) 2 or more positive determinations of anti-phospholipid antibodies (aPL) according to the Sidney criteria and b) thrombocytopenia (PLTs <100,000 µl) or HA (Coombs+, corrected reticulocyte count >2%, elevated indirect billirrubin and

LDH) or Evans´ syndrome (ES). Patients with SLE and/or positive anti-dsDNA (ELISA) were excluded. Age at onset, follow-up until last medical appointment (LMA), treatment and clinical APS status were assessed. We defined response to treatment (RT) as PLTs ≥100,000 µl at LMA if basal PLTs were >50,000 µl, or PLTs >50,000 µl at LMA if basal PLTs were ≤50,000 µl; and for HA hemoglobin >10 mg/dl in the absence of hemolysis. Relapse was considered when the RT (any point at follow-up) could not be maintained. We used X^2, Student *t* test or U-Mann Whitney test (SPSS).

Results: Fifty-five patients (44 women) met the inclusion criteria, mean age at disease onset 40 ± 12 years with a median follow-up of 5.8 years (0.12-23). Thirty-five had TP, 14 HA and 6 ES. Twenty-five patients (45%) also met one Sidney clinical criteria: 13 thrombosis and 12 pregnancy morbidity. In 4 patients (16%) the hemocytopenia and the clinical criteria started simultaneously, in 6 (24%) the hemocytopenia preceded the obstetric or thrombotic manifestation (3 years (0.5-12)) whereas in 15 patients (60%) the hematological event presented 4.4 years later (0-34). Thirty patients did not develop thrombosis or pregnancy morbidity during follow-up (16 TP, 8 HA, 1 ES). No significant difference was found in the prevalence of aCL and anti-β-$_2$GPI in patients with or without the clinical criteria for APS. A higher prevalence of lupus anticoagulant (LA) (56% vs. 30%, p=0.02) as well as the combination of aCL+LA was found in patients with the clinical criteria for APS (73% vs. 33%, p=0.01; OR=5.6, 95% CI 1.5- 20.4). There were no differences in age, type of hemocytopenia, use of prednisone (83% vs. 76%), immunosuppressive drugs (56 vs. 66%), aspirin (80%), splenectomy (32% vs. 26%), RT at LMA (96% vs. 86%), relapses (52% vs. 46%), basal PLTs and hemoglobin in patients with and without clinical APS.

Conclusion: Hemocytopenia may antedate or follow the accepted clinical criteria for APS. There seems to be no difference at its presentation and RT regardless of the clinical APS status. LA alone or in combination with aCL associates with clinical APS. We are tempted to suggest that aPL associated with hemocytopenia are pathogenically different from those associated with thrombosis.

Disclosure: L. Comellas-Kirkerup, None; **A. R. Cabral**, None; **G. Hernandez-Molina**, None.

1283

Longterm Follow-up of ASA/P Trial Participants: No Evidence of Thrombotic Sequelae 20 Years After Anti-Phospholipid-Associated Recurrent Pregnancy Loss. Christine A. Clark[1], Karen A. Spitzer[1] and Carl A. Laskin[2], [1]University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, [2]Mt. Sinai Hosp, Toronto, ON

Purpose: ASA/P (1988-94) was a double-blind, controlled, randomized therapeutic trial of 202 women with a history of recurrent pregnancy loss (RPL) with or without antiphospholipid antibodies (aPL). The study found no difference in live birth rates between treatment with either aspirin and prednisone (ASA/P) or placebo, between a history of early vs late losses, or between aPL positive or negative patients. Others have reported increased rates of thrombotic events (TE) and development of the antiphospholipid syndrome (APS) in this patient population in longterm followup studies 1-12 years after pregnancy loss accompanied by aPL. We wanted to determine the incidence of subsequent TE and APS in our longterm followup cohort.

Method: All participants in the ASA/P trial were sent questionnaires in 2008-09 that included a series of self-report yes/no questions based upon the clinical classification criteria for SLE/APS. We also requested information regarding subsequent pregnancies, medications currently being taken, and medical specialists currently being seen.

Results: Forty (19.8%) patients were considered lost to followup after their questionnaires were “returned-to-sender” and further attempts to update contact information failed. Fifty-five completed questionnaires were received (34.0% response rate). Median age of respondents: 51 (range 42-57); median years since trial participation: 17 (range 14-20). When comparing respondents to the original trial participants, 52% of respondents had received ASA/P, 67% had a live birth in the trial, and 51% were aPL-positive, not significantly different from the group as a whole. Twenty-three women had 34 subsequent pregnancies resulting in 22 live births, 10 early losses, 1 stillbirth, and 1 ectopic pregnancy (18/23 women had at least 1 live birth in the interval since trial participation). There have been no TE and no one has been diagnosed with APS.

Conclusion: The group of 55 women who responded to our followup questionnaire 14-20 years after participating in the ASA/P trial was representative of the original study cohort. In contrast to other longterm followups of patients with RPL and aPL, none of our respondents reported any TE and none has been diagnosed with APS. These results suggest that RPL, even in the context of aPL, is neither associated with nor predictive of the development of subsequent TE even as long as 20 years after initial presentation.

Disclosure: C. A. Clark, None; **K. A. Spitzer**, None; **C. A. Laskin**, None.

1284

Efficacy and Safety of Long Term Low Molecular Weight Heparin in Antiphospholipid Patients. Jose Vargas, Shirish.R Sangle, Oier A. Barrutia, David P. D'Cruz and Munther A. Khamashta, Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom

Purpose: Main objective of this study was to assess both the efficacy and safety of long term Loe molecular weight heparin (LMWH) in patients with antiphospholipid syndrome (APS) that had not previously responded to and/or tolerated Warfarin.

Method: We retrospectively recruited 23 APS patients (22 women) with confirmed (Sapporo Criteria) diagnosis of APS. Patients with primary and APS associated other autoimmune disorders were included in this study. All patients had one or more thrombotic events. All patients were switched to LMWH on account of bleeding, intolerance and /or no response to warfarin therapy. Cardiovascular risk factors and the reasons for switching to LMWH and duration of LMWH treatment was noted. The main outcome was thrombotic events on LMWH. Adverse events such as heparin induced thrombocytopenia (HITS), osteoporosis and bleeding were recorded.

Results: The median age of patients was 42 (26- 67). Eleven patients (47.8%), had Systemic Lupus Erythematosus (SLE), 1 (4.3%) Sjögren syndrome and 1 had (4.3%). Behçet's disease. Other patients had primary APS. Three patients (13%) had arterial thrombosis, 6 (26%) venous thrombosis, 4 (17.4%) had both. 4 were anticoagulated due to cognitive dysfunction and had high density (ischemic) lesions in the brain on Magnetic Resonance Imaging. Five patients had pregnancy morbidity and thrombotic events (2 arterial). Seventeen (73.9%) did not have any cardiovascular risk factors, 2 (8.7%), hypertension, 2 (8.7%) diabetes mellitus and 2 (8.7%). were active smokers. Four (17.4%) received calcium and vitamin D supplements, 6 (26%) on calcium, vitamin D and bisphosphonates and 13 (56.5%) were not on any bone-protective-drug.. atients were switched to LMWH from warfarin due to - 9 (39.1%) no improvement in neurological manifestations, 6 (26%) major bleeding, 4 (17.4%) skin lesions and 2 (8.7%) preference of the patients. The average duration of the LMWH treatment was 44 months (14 – 216). Sixteen (59%) patients received Enoxaparin, 5 (22%) Dalteparin and Tinzaparin 2 (8.7%). Twenty patients remained without any thrombtic events, 3 (13%). had re-thrombosis with no clinical improvement. Osteoporosis, (confirmed by DEXA scan), was reported in 5 (21.7%) who had received corticosteroid treatment previously.

Conclusion: Long term LMWH may be a safe and efficient alternative to warfarin who could not tolerate and/or reluctant to take warfarin.

Disclosure: J. Vargas, None; **S. R. Sangle**, None; **O. A. Barrutia**, None; **D. P. D'Cruz**, None; **M. A. Khamashta**, None.

1285

Primary Prevention of Thrombosis in Antiphospholipid Antibodies Positive Patients: A Prospective, Multicenter, Randomised, Open Trial Comparing Low Dose Aspirin with Low Dose Aspirin Plus Low Intensity Oral Anticoagulation. Mj. Cuadrado[1], ML. Bertolaccini[1], P. Seed[1], M. Tektonidou[2], A. Aguirre[3], L. Mico[4], C. Gordon[5], G. Ruiz-Irastorza[6], A. Gil[7], G. Espinosa[8], F. Houssiau[9], A. Rahman[10], H. Martin[11], M. Galindo[12], MC Amigo[13] and MA Khamashta[1], [1]St Thomas Hospital, London, United Kingdom, [2]University of Athens, Athens, Greece, [3]Hospital Reina Sofia, Spain, [4]Hospital La Fe, Spain, [5]University of Birmingham, United Kingdom, [6]Universidad del País Vasco, Bizkaia, Spain, [7]Hospital La Paz, Spain, [8]Hospital Clinic, Barcelona, Spain, [9]Universite Catholique Louvain, Brussels, Belgium, [10]University College London, England, [11]Hospital de Alcorcon, Spain, [12]Hospital 12 de Octubre, Madrid, Spain, [13]ABC Medical Center, Mexico City,

Purpose: Antiphospholipid antibodies (aPL) has been closely associated with the development of thrombosis. The optimal treatment to prevent the first thrombosis in these patients is controversial. Our aims were**:** 1) To compare the efficacy and safety of low dose aspirin (75mg) with low-dose aspirin plus low-intensity oral anticoagulation (INR-1.5) in the primary prevention of thrombosis. 2) To investigate the contribution of traditional risk factors to the development of thrombosis.

Methods: It is a multicentre, randomised, open controlled trial. One hundred sixty six patients with aPL were assigned to one of the 2 groups of treatment: low dose aspirin (75mg daily) [LDA] or low dose aspirin + warfarin (INR-1.5) [LDA+W]. Allocation to treatment groups was performed randomly, using a minimisation protocol. The sample size required was 1,000 patients. Inclusion criteria were a) the presence of

aPL (medium/ high titres of aCL and/or LA on at least two occasions) b) Four or more ACR classification criteria for SLE and/or obstetric criteria for the classification of APS. Patients meeting the inclusion criteria who declined randomisation were followed-up in an observational arm. Clinical events, conventional risk factors for thrombosis, serological changes in aPL and medication side effects were collected. Duration of treatment was between 1-5 years. The primary outcome measure was time to thrombosis.

Results: Eighty-two patients were randomised to LDA and 84 to LDA+W. Sixty six patients were included in the observational arm. There were no differences in the number of thrombotic events between patients treated with LDA (4/82) or LDA+W (4/84). The incidence of thrombotic events in the randomised patients was 1.76 events/100 person-years at risk and in the observational arm was 4.9 events/.100 person-years at risk (7/66). There were no demographic, clinical or serological differences between both groups.

None of the clinical or biological markers analysed appeared to predict thrombosis in our study.

Side effects for both drugs were: gastrointestinal symptoms in LDA group (n=4). In the LDA+W group, 11 patients suffered minor episodes of bleeding (1 nasal and 10 menorrhagia).

Conclusion: The sample size required to find statistical differences between the two groups was not achieved. With the number of patients included, there were no differences in the number of thrombotic events between patients treated with LDA vs patients treated with LDA+W. We could not identify predictive markers of thrombosis in this population

Disclosure: M. Cuadrado, None; **M. Bertolaccini**, None; **P. Seed**, None; **M. Tektonidou**, None; **A. Aguirre**, None; **L. Mico**, None; **C. Gordon**, None; **G. Ruiz-Irastorza**, None; **A. Gil**, None; **G. Espinosa**, None; **F. Houssiau**, None; **A. Rahman**, None; **H. Martin**, None; **M. Galindo**, None; **M. Amigo**, None; **M. Khamashta**, None.

1286

Autoimmune Diseases Pregnancy Clinic: A Three Year Experience. Cristina Martinez-Dubois[1], Marcos Lopez-Hoyos Sr.[1], Rafael del Barrio Sr.[1], Lorena Alvarez-Rodriguez[2], Mario Agudo Sr.[2], Javier Rueda Sr.[1], Ricardo Blanco Sr.[1], Vicente Rodriguez-Valverde[1] and Victor M. Martinez-Taboada Sr.[2], [1]Hospital Universitario Marques de Valdecilla-IFIMAV, Santander, Spain, [2]Hospital Universitario Marques de Valdecilla, Santander, Spain

Purpose: Women with systemic autoimmune diseases face significant risks during the pregnancy, but the control of these patients in a multidisciplinary setting can improve outcome for women and their babies. The aim of the present study is to describe the 3 year experience of a multidisciplinary clinic at a university hospital

Method: We collected data from patients referred to our autoimmune diseases pregnancy clinic (ADPC) because of suspicion of an autoimmune disease and pregnancy.

Results: The mean age of the patients was 31.8±5.6 years. Patients were mainly referred from the Obstetrics (49%) and Rheumatology departments (16%). After evaluation, patients were divided in several groups: a) Antiphospholipid syndrome (APS): 43 patients (32%); b) serological positive anti-phospholipid antibodies (APL) without fulfilling APS criteria: 30 patients (22%); c) suggestive clinical picture without APL confirmation in 17 (13%); d) patients with other autoimmune conditions different from APS (including 10% of SLE); e) coagulopathies (6%), and f) no evidence of disease in 42 (32%). Isolated obstetric pathology was observed in 71.2% of the patients, whereas 8.3% had associated thrombotic episodes and 2.3% thrombopenia. The most frequent reason for referral were early pregnancy loss (< 10 weeks) in 52.7% and late pregnancy loss (>10 weeks) in 28%, although in one third of the patients there were more than one manifestation. With regard to APL, isolated anti-cardiolipin antibodies were found in 26.1% of patients, isolated anti-beta 2 glycoprotein I in 13.6%, and isolated lupus anticoagulant in 4%. The combination of the three types of APL at the same time was only found in 7.2% of patients. Overall, 92% of the patients were treated with aspirin, and in 38.1% it was combined with low-weight molecular heparin. Only a minority of the patients received other treatments: antimalarials (9.3%), corticosteroids (5%) or azathioprine (2.8%). During the 3-year period a total of 139 pregnancies (133 patients) were followed and treated in our unit. 85. 6% of these pregnancies ended in a successful delivery. Previously, these patients had a total of 257 pregnancies with a 25.7% of successful deliveries.

Conclusion: The experience of our ADPC supports the utility of dedicated clinics in the management of autoimmune diseases during pregnancy. APS is the most frequent disease attended in this type of unit. In this setting, the frequency of seronegative and serological but not clinical APS is rather high and these subtypes of patients not fulfilling the Sidney criteria must be taken into account.

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Disclosure: C. Martinez-Dubois, None; **M. Lopez-Hoyos**, None; **R. del Barrio**, None; **L. Alvarez-Rodriguez**, None; **M. Agudo**, None; **J. Rueda**, None; **R. Blanco**, None; **V. Rodriguez-Valverde**, None; **V. M. Martinez-Taboada**, Roche , 2 .

ACR/ARHP Poster Session C

Biology and pathology of bone and joint

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Activation of the EphB4 Receptor by Its Specific Ligand Ephrin B2 Positively Impacts Human Osteoarthritic Chondrocytes. Steeve Kwan Tat[1], Jean-Pierre Pelletier[1], Nathalie Amiable[1], Christelle Boileau[1], Martin Lavigne[2] and Johanne Martel-Pelletier[1], [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]Department of Orthopaedic Surgery, Maisonneuve-Rosemont Hospital, Montreal, Quebec, Canada

Purpose: We recently showed that treatment of human osteoarthritic (OA) subchondral bone osteoblasts by a member of the ephrin system, ephrin B2, inhibits the abnormal resorptive properties of these cells. Hence, we further investigated the possible implication of this ephrin and activation of its specific receptor EphB4 on the catabolic/anabolic activities of human OA chondrocytes.

Method: Ephrin B2 and EphB4 receptor levels were determined by quantitative PCR and immunohistochemistry, and the effects of ephrin B2 by the expression/production of factors involved in the OA process. siRNA was used to investigate the ephrin B2 activation of EphB4 receptors.

Results: Ephrin B2 and EphB4 receptors are expressed and produced by human normal and OA chondrocytes. Ephrin B2 protein levels were similar in both cartilage types, whereas EphB4 receptor expression ($p<0.0001$) and production ($p<0.01$) levels were significantly increased in OA chondrocytes/cartilage. Ephrin B2 treatment significantly inhibited the IL-1β, IL-6, MMP-1, MMP-9, MMP-13, and PAR-2 expression levels, whereas MMP-2 was unaffected, and significantly increased collagen type II. It also markedly inhibited the IL-1β stimulated protein production of IL-6, MMP-1 and MMP-13. Moreover, data revealed that silencing the EphB4 receptor gene abolished the effects of ephrin B2, confirming that these effects are mediated by EphB4 receptors.

Conclusion: Our study is the first to provide data on the presence and role of ephrin B2/EphB4 receptors in human chondrocytes/cartilage. Activation of the EphB4 receptor by ephrin B2 positively impacts the abnormal metabolism of OA cartilage by inhibiting important catabolic factors involved in this disease while increasing anabolic activity.

Disclosure: S. Kwan Tat, None; **J. P. Pelletier**, None; **N. Amiable**, None; **C. Boileau**, None; **M. Lavigne**, None; **J. Martel-Pelletier**, None.

1288

Quantification of Cells Expressing Mesenchymal Stem Cell Markers in Synovial Membranes and Osteoarthritic Cartilage Repair. Tamara Hermida-Gomez[1], Isaac Fuentes[2], Silvia Diaz-Prado[2], Mª Carmen Arufe[2], Maria Jose Sanchez-Dopico[1], Francisco Javier de Toro[1] and Francisco Javier Blanco[1], [1]INIBIC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [2]INIBIC - University of A Coruña, A Coruña, Spain

Purpose: Mesenchymal stem cells (MSCs) have been identified in human synovial membrane and articular cartilage from patients with osteoarthritis (OA). However, detailed quantification studies of MSCs in synovial membranes were not performed. The purpose of this study was to quantitatively measure the expression of stem cells markers in synovial membranes from human health and OA joints and in OA cartilage repair.

Methods: The co-expression of CD44, CD90, CD105 and CD271 was determined by immunofluorescence in health and OA synovial membranes and spontaneous cartilage repair. Synovial membrane-derived cells were isolated from health and OA joints and characterized by flow cytometry for hematopoietic (CD34 and CD45) and mesenchymal (CD44, CD29, CD73, CD90, CD105, CD117 and CD271) markers,

and for differentiation experiments (chondrogenesis, adipogenesis and osteogenesis). Chondrogenesis was assessed by staining for proteoglycans and type II collagen, adipogenesis by using a stain for lipid drops and osteogenesis by detecting calcium deposits.

Results: The number of cells expressing MSCs markers was higher in OA synovial membranes than in synovia from health joints, corresponding the highest percentage of cellular expression to the co-expression of CD90/CD271 (9.8% vs. 2.6%) (Fig 1). Spontaneous repair tissue contained cells positive for CD44 (12.3%), CD90 (10.4%) and CD271 (9.9%) antigens, but the CD105 antigen was absent (Fig 2). Cells positive for MSC markers were diffusely distributed in OA synovial membranes. In health synovia, these cells were localized in the subintimal zone. More than 90% of OA synovial membrane-derived cells were positive for CD44, CD73, and CD90 and negative for CD34 and CD45. OA synovial membrane-derived cells were also positive for CD29 (85.23%), CD117 (72.35%) and CD105 (45.5%). Micropellet analyses showed that culture of the cells with TGF-beta3 stimulated proteoglycan and type II collagen synthesis. Synovial membrane-derived cells culture developed lipid droplets in adipogenic medium and calcification in osteogenic medium.

Conclusion: These results suggest that during the OA process an increment of cells expressing MSCs markers percentage occur in synovial membrane. Absent expression of the CD105 antigen in the OA cartilage repair indicates that cells expressing this marker may be necessary for effective repair processes in OA cartilage.

This study was supported by grants from Secretaría Xeral de I+D, Xunta de Galicia, FISCP03/00127 and FIS05/2495; Fundación Española de Reumatología.

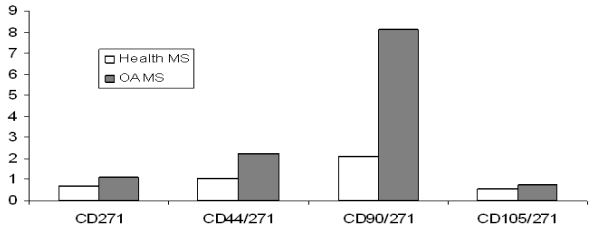

Figure 1. Expression of stem cells markers in synovial membranes from human health and OA joints.

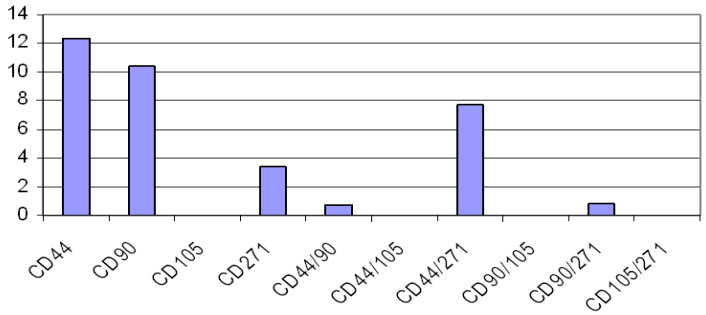

Figure 2. Expression of stem cells markers in OA cartilage repair.

Disclosure: T. Hermida-Gomez, None; **I. Fuentes**, None; **S. Diaz-Prado**, None; **M. C. Arufe**, None; **M. J. Sanchez-Dopico**, None; **F. J. de Toro**, None; **F. J. Blanco**, None.

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Molecular and Cellular Characterization of Different Populations of Mesenchymal Stem Cells During Chondrogenesis. Claudia Cicione[1], Silvia Diaz-Prado[2], Emma Muiños[1], Isaac Fuentes[2], Francisco Javier de Toro[1] and Francisco Javier Blanco[1], [1]INIBIC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [2]INIBIC - University of A Coruña, A Coruña, Spain

Purpose: Mesenchymal stem cells (MSCs) are considered as a promising candidate for cell-based therapy of damaged or degenerated cartilage. Bone marrow represents the most commonly used tissue source of adult MSCs. Bone marrow MSCs are multipotent cells, which can differentiate into different cell types (osteoblasts, adipocytes and chondrocytes). Understanding the potential of the cells and the molecular mechanisms underlying their differentiation should lead to innovative protocols for clinical applications. The aim of this study was to determine if there was an improvement of the chondrogenic potential, in hypoxic conditions, given by the separation of different populations of bone marrow MSCs.

Method: MSCs were isolated from BM stroma and were expanded in monolayer cultures. The subpopulation CD105+ was separated using a magnetic separator (MACS separation columns, Miltenyi Biotec). The three populations of MSCs (CD105+, CD105- and total BM) were differentiated towards chondrocytes using pellet-culture in hypoxic conditions. Chondrogenesis was studied at different intervals of time (0, 2, 4, 7, 14, 21, and 28 days) and differentiation was confirmed by histochemistry (Hematoxylin-Eosin, Massonxs Thrichome, Alcian Blue, Safranin O), immunohistochemistry (types II and I Collagens, and Aggrecan) and Real Time PCR (Sox2, Nanog, Oct3/4, CDH2, TNC, Sox9, Agg, Col I, Col II, Col X and RunX2).

Results: The gene expression analysis of the three populations highlighted some differences. As shown in the table, at the starting point, the stem cell phenotype markers (Sox2, Nanog and Oct3/4) showed higher expression levels in the CD105+ population. These markers remained expressed until day 28th, both in CD105+ and in CD105- populations, indicating that not all the stem cells were differentiated towards chondrocytes but some of them remained undifferentiated. After 21 days of differentiation, the expression levels of the cartilage specific marker Col II was higher in the total BM than CD105- and CD105+ populations. However, the expression level of Sox9 was higher in the CD105- population followed by the total BM.

Conclusion: In our experimental conditions, isolation of CD105+ and CD105- populations showed no improvement of chondrogenic potential regarding to the total BM population.

	0 day			21 day		
	Total BM	CD105+	CD105-	Total BM	CD105+	CD105-
SOX2	1	6.64	4.89	1	7.86	1.1
NANOG	3.21	14.93	1	1	455.1	41.35
OCT3/4	1	6.33	1.22	1	12.21	1.19
SOX9	10.97	7.44	1	23.02	1	41.78
COL2A1	1	10.04	18.47	639.14	1.6	1

For each gene in each time of assay, the reference value 1 is given to the lower expression level

Disclosure: C. Cicione, None; **S. Diaz-Prado**, None; **E. Muiños**, None; **I. Fuentes**, None; **F. J. de Toro**, None; **F. J. Blanco**, None.

1290

Oral Treatment with a Brachystemma Calycinum D. Don Plant Extract Reduces Disease Symptoms and the Development of Cartilage Lesions in Experimental Dog Osteoarthritis: Inhibition of Protease Activated Receptor-2 (PAR-2). Christelle Boileau[1], Johanne Martel-Pelletier[1], Judith Caron[1], Frédéric Paré[1], Eric Troncy[2], Maxim Moreau[3] and Jean-Pierre Pelletier[1], [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]GREPAQ – Department of Veterinary Biomedicine, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, [3]The Companion Animal Research Group, Department of Clinical Science, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC

Purpose: The aims of this study were to evaluate the effect of oral treatment with a whole plant extract of Brachystemma calycinum D. don (BCD) on the development of osteoarthritic (OA) lesions and symptoms in the experimental dog anterior cruciate ligament (ACL) transection model and to document its mechanism of action.

Method: OA was induced by sectioning the ACL of the right knee in crossbred dogs. There were two experimental groups (n = 6-7 dogs/group): placebo and BCD extract (200 mg/kg/day) given orally for 8 weeks. Macroscopic and histopathological evaluation of cartilage lesions and immunohistochemical analysis of cartilage to assess levels of iNOS, MMP-13, and protease activated receptor (PAR)-2 were done. A gait analysis of dogs was performed.

Results: Treatment with BCD reduced the severity (depth) ($p=0.04$) and histopathological score ($p<0.02$) of OA cartilage lesions. BCD treatment also significantly reduced the OA chondrocyte level of key inflammatory and catabolic factors (iNOS, $p=0.009$ and MMP-13, $p=0.003$) as well as the level of PAR-2 ($p=0.03$). Dogs treated with BCD showed significant improvement in peak vertical force measured at 8 weeks ($p<0.05$).

Conclusion: Treatment with BCD extract can exert a positive effect on the prevention of cartilage lesions induced by joint instability and improve joint function. This effect was associated with the inhibition of major catabolic and inflammatory mediators. This study is the first to demonstrate that a therapeutic intervention that can inhibit PAR-2 is associated with a disease-modifying OA effect.

Disclosure: C. Boileau, None; **J. Martel-Pelletier**, Vita Green, 2, Vita Green, 5 ; **J. Caron**, None; **F. Paré**, None; **E. Troncy**, None; **M. Moreau**, None; **J. P. Pelletier**, Vita Green, 2, Vita Green, 5 .

1291

Normal Intramembranous Bone Repair of Cortical Bone Defects in Mice with Osteoblast-Targeted Disruption of Glucocorticoid Signalling in Mice. Agnes Weber[1], Gang Li[1], Colin Dunstan[1], Frank Buttgereit[2], Markus Seibel[1] and Hong Zhou[1], [1]Bone Research Program, ANZAC Research Institute, The University of Sydney, Sydney, Australia, [2]Charite University Med-Berlin, Berlin, Germany

Purpose: Mechanisms by which glucocorticoids (GC) exert their effects on bone cells, particularly in the fracture healing process, are poorly understood. While GC at pharmacological doses have been shown to interfere with fracture repair the role of endogenous GC in bone healing has not been fully investigated.

Here we examined whether disruption of endogenous GC signalling in osteoblasts affects intramembranous fracture healing in an *in vivo* model of cortical defect repair.

Method: We employed a transgenic (tg) mouse model in which intracellular GC signalling was disrupted exclusively in mature osteoblasts and osteocytes through tg overexpression of 11ß-hydroxysteroid-dehydrogenase type 2 (11ßHSD2) under the control of a collagen type I promoter (Col2.3-11ßHSD2). Unicortical bone defects (Ø 0.8mm) were created in these tg mice (n= 36) and their wild-type (WT) littermates (n=34) using a drill on the anteromedial aspect of the left tibia. Fracture repair was assessed by microcomputed tomography (micro-CT) and histomorphometry at 1, 2, and 3 weeks post-fracture.

Results: Micro-CT images demonstrated the progression of defect repair. One week post-surgery, mineralized bone was present which increased in volume and density throughout week two. At week three, healing of the defect was nearly complete with the fracture site no longer indistinguishable from the surrounding cortical bone. Micro-CT analyses comparing WT and tg animals revealed similar amounts of newly formed bone (BV/TV) for the analyzable time-points at week one and two post-fracture ($p>0.05$). Moreover, histomorphometric analyses performed for all time-points demonstrated similar newly formed bone volume (BV/TV) in WT and tg animals ($p>0.05$). Accordingly, no statistical differences where found between the two groups of mice for the proportion of bone surface covered by osteoblasts (Ob.S/BS), osteoclast surfaces (Oc.S/BS) and osteoclast numbers (N.Oc./BS) at any post-surgical time point.

Conclusion: Our results suggest that osteoblast-targeted disruption of endogenous glucocorticoid signalling does not affect intramembranous fracture healing in a tibia defect repair model. However, it remains to be shown whether GC play a role in endochondral fracture healing.

Disclosure: A. Weber, None; **G. Li**, None; **C. Dunstan**, None; **F. Buttgereit**, None; **M. Seibel**, None; **H. Zhou**, None.

1292

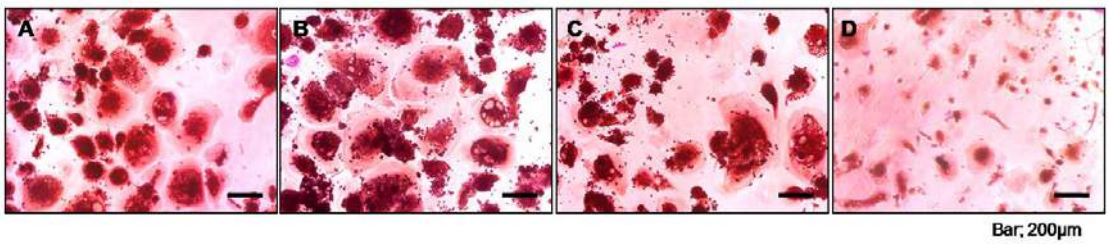
Microrna-146 Inhibit Human Osteoclast Differentiation in Vitro. Tomoyuki Nakasa, Hayatoshi Shibuya, Takuya Niimoto, Masakazu Ishikawa and Mitsuo Ochi, Hiroshima University, Hiroshima City, Japan

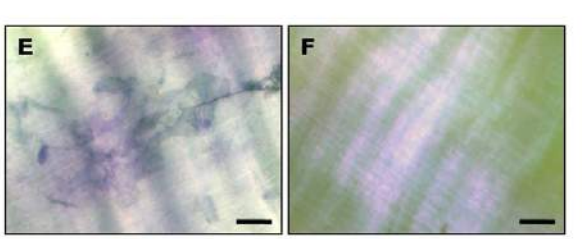
Purpose: MicroRNAs (miRNAs) are a class of non-coding RNAs that regulate gene expression by translational inhibition and messenger RNAs degradation. Several microRNAs exhibit a tissue-specific or developmental stage–specific expression pattern and have been reported to be associated with human diseases. miRNA (miR)-146 was reported to highly express in rheumatoid arthritis (RA) synovium and peripheral blood mononuclear cells (PBMC), and inhibit the expression of IRAK 1 and TRAF6 by binding to the 3' UTR of their mRNAs. TRAF6 is the one of the important mediator in osteoclstogenesis, therefore, the aim of this study was to confirm whether over expression of miR-146 inhibit osteoclastogenesis in vitro.

Method: Human blood was collected from healthy volunteers, and PBMCs were isolated, and seeded in 96-well culture plates. The following day, double strand (ds) miR-146a was transfected into the cells in various concentrations and cultured for 3 weeks in the presence of macrophage colony stimulating factor (M-CSF) and TNFα. After 3 weeks, TRAP positive and multinuclear cells were counted, and pit formation assay was performed. At 3 days after transfection, the expression of PU-1, c-Jun, NFATc1 and TRAP were evaluated by real time PCR.

Results: The number of TRAP positive large multinucleated cell was significantly decreased by over expression of miR-146 in a dose dependent manner. Bone resorption on dentin slice could not be observed with ds miR-146 of concentration of 50nM (Figure 1). The expression of PU-1, c-Jun, NFATc1 and TRAP was significantly down regulated at 3 days after the transfection of miR-146a (Figure 2).

Conclusion: Our result indicated that miR-146 could inhibit TNFα mediated osteoclastogenesis from human PBMC in vitro, and miR-146 might be a novel therapeutic target for bone destruction of RA.





(A)(B)(C)(D); TRAP staining. (A) scrambled siRNA, (B) ds miR-146a 0.5nM (C) Ds miR-146a 5nM, (D) ds miR-146a 50nM.
(E)(F); pit formation assay. (E) Scrambled siRNA, (F) ds miR-146a 50nM. Bar; 200μm.
(G) TRAP positive multinuclear cell number per well in each group.

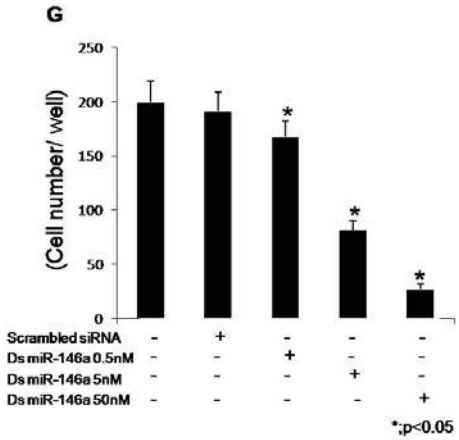


Figure 1

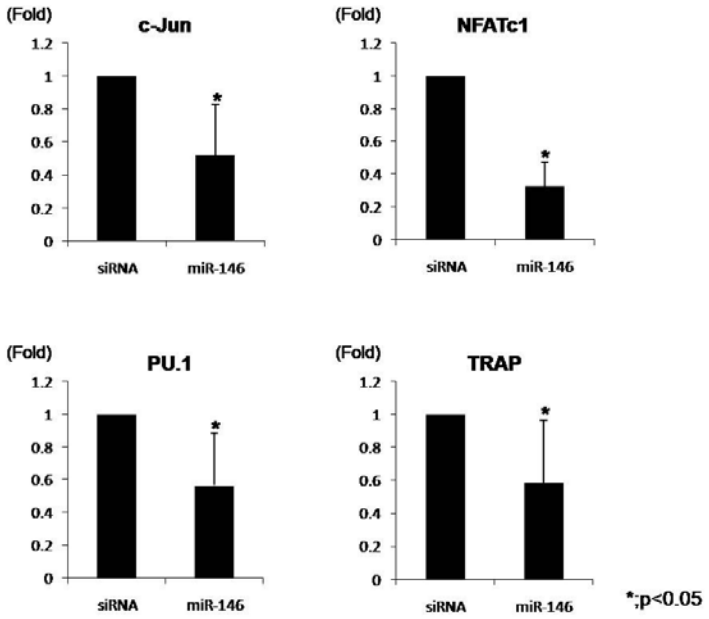


Figure 2

Disclosure: T. Nakasa, None; **H. Shibuya**, None; **T. Niimoto**, None; **M. Ishikawa**, None; **M. Ochi**, None.

1293

IL-1 Stimulated Production of Chemokines, Aggrecanases and Tissue Inhibitors of Metalloproteinases Are Modulated by IL-4 in OA Chondrocytes. Elisa Assirelli[1], Paolo Dolzani[1], Eleonora Olivotto[1], Stefania Pagani[1], Lia Pulsatelli[1], Rosa M. Borzì[1], Marco Di Carlo[2], Andrea Facchini[3] and Riccardo Meliconi[3], [1]Istituto Ortopedico Rizzoli, Bologna, Italy, [2]Università di Bologna, Bologna, Italy, [3]Istituto Ortopedico Rizzoli and Università di Bologna, Bologna, Italy

Purpose: In osteoarthritis (OA), the final result of chondrocyte metabolic modification is the enhancement of cartilage matrix catabolism, not adequately counterbalanced by anabolic events. Interleukin-4 (IL-4)/interleukin-4 receptor (IL-4R) system has a pivotal role in chondrocyte anabolic response to mechanical stimulation which in turn is an essential condition to maintain cartilage homeostasis. Previous studies reported a modification of mechanotrasduction response in OA chondrocytes suggesting an impaired efficacy of the IL-4/IL-4R system protective effect and underline the importance of disordered mechanical signalling in cartilage breakdown pathways.

We aim to investigate chondrocyte response induced by IL-4/IL-4R system**,** focusing on modulation of peculiar pathways involved in cartilage breakdown.

Method: Articular cartilage specimens were obtained from OA patients undergoing joint replacement surgery. Chondrocytes were isolated from articular cartilage by sequential enzymatic digestion. Chondrocyte micromass and hyperconfluent cultures were set up with IL-4 alone or with pro-inflammatory (IL-1). RNA were extracted from chondrocytes cultured in described conditions and real time PCR analysis were performed. mRNA expression of chemokines (IL-8/CXCL8, GROalpha/CXCL1, IP-10/CXCL10, RANTES/CCL5, MIP-1alpha/CCL3, MIP-1beta/CCL4), matrix degrading enzymes (metalloprotease-13/MMP-13, aggrecanases ADAMTS-4 and ADAMTS-5) and tissue inhibitors of metalloproteinases (TIMP-1, -3, -4) were investigated. Culture supernatants were analysed for chemokine production, IL-8, GROalpha, RANTES, by enzyme-linked immuno-sorbent assay (ELISA).

Results: Data obtained from mRNA modulation analysis of chemokine production by OA chondrocyte cultures showed that IL-4 presence significantly inhibits RANTES, MIP-1alpha, MIP-1beta and IP-10 mRNA expression induced by IL-1. On the other hand, IL-4 did not affect GROalpha and IL-8 mRNA expression induced by IL-1. ELISA quantification of IL-8, GROalpha and RANTES production showed an overlapping pattern to corresponding mRNA expression. mRNA modulation analysis of matrix degrading enzymes and their inhibitors shows that IL-4 down modulated also MMP-13 (confirmed by ELISA measurement of the protein), ADAMTS-4, -5 and TIMP-3, -4 mRNA expression induced by IL-1. On the contrary, TIMP-1 mRNA expression does not appear to be modulated either by IL-1 or by IL-4.

Conclusion: These data underline the complexity of IL-4/IL-4R activity and suggest the involvement of multiple signal transduction pathways of cellular response.

Disclosure: E. Assirelli, None; **P. Dolzani**, None; **E. Olivotto**, None; **S. Pagani**, None; **L. Pulsatelli**, None; **R. M. Borzì**, None; **M. Di Carlo**, None; **A. Facchini**, None; **R. Meliconi**, None.

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Inhibition of Osteoclastogenesis by Mesenchymal Stem Cells (MSCs): Potential Role of MSCs for the Treatment of Rheumatoid Arthritis. Koichi Oshita, Kunihiro Yamaoka, Keisuke Maeshima, Shigeru Iwata, Sonosuke Yukawa, Shunsuke Fukuyo, Koshiro Sonomoto and Yoshiya Tanaka, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background: Mesenchymal stem cells (MSCs) are multipotent cells that are able to differentiate into various cell lineages including osteoblasts, chondrocytes, and adipocytes. Recently, MSCs were shown to possess immunosuppressive effects on activated T cells and dendritic cells *in vitro*. In relation with this immunosuppressive capacity, MSCs have been reported to prevent the development of arthritis and the progression of bone destruction in collagen-induced arthritis mice. Based on these notions, we considered the possibility of utilizing MSCs as a new choice of therapy against rheumatoid arthritis (RA).

Purpose: Aim of this study was to elucidate the effects of human MSCs on differentiation and function of osteoclasts.

Method: Human MSCs was purchased from Lonza Walkersville, Inc. Peripheral blood mononuclear cells (PBMCs) from healthy donors were cultured in osteoclast-induction medium (OIM) (M-CSF 50 ng/mL, soluble RANKL 50 ng/mL and $1,25(OH)_2D3$ 100 nmol/L) to obtain osteoclast-like cells. In co-culture experiments, cells were cultured under contact-free condition using Transwell® plate. Multi-nuclear cells positive for TRAP-staining were counted under the microscope as osteoclast-like cells.

Results: When PBMCs were co-cultured with either MSCs or condition medium derived from MSCs for 16 days, number of osteoclast-like cells markedly decreased. Osteoprotegerin (OPG), a decoy receptor for RANKL, was produced by MSCs in a time-dependent manner by co-culture with PBMCs. Accordingly, addition of anti-OPG antibody to co-culture system inhibited osteoclastogenesis. Expression of cathepsin K, a protease necessary for bone resorption, was found to be decreased in co-culture of PBMCs and MSCs. Conditioned medium obtained from MSCs also reduced production of cathepsin K from PBMCs.

Conclusion: We have shown here that OPG can be produced by MSCs and its production can be dramatically enhanced by co-culture with PBMCs in a cell-cell contact free condition, which resulted in a decreased osteoclastogenesis and cathepsin K expression in osteoclast-like cells. Previously, it has been suggested that MSCs can be immunosuppressive. Therefore, we propose here that MSCs has a possibility to open a new category of an anti-rheumatic therapy not only by its immunosuppressive effect but also inhibiting osteoclastogenesis, leading suppression of bone resorption and osteoporosis due to disease activity.

Disclosure: K. Oshita, None; **K. Yamaoka**, None; **K. Maeshima**, None; **S. Iwata**, None; **S. Yukawa**, None; **S. Fukuyo**, None; **K. Sonomoto**, None; **Y. Tanaka**, None.

1295

Mitochondrial Respiratory Dysfunction Regulates the Metalloproteinases Expression in Human Normal Chondrocytes in Culture. Berta Cillero-Pastor, Ignacio Rego, Beatriz Lema, María J. López-Armada and Francisco J. Blanco, Osteoarticular and Aging Research Laboratory. INIBIC-Hospital Universitario A Coruña, Coruña, Spain

Purpose: Alteration of the mitochondrial respiratory complexes III and V contribute to the chondrocyte inflammation. In this study, we investigated the relationship between the dysfunction of MRC and the modulation of MMPs in human normal chondrocytes in culture.

Method: Human normal chondrocytes were isolated from cartilage obtained from autopsies without history of joint disease. Rotenone, NPA, antimycin A (AA), azide and oligomycin were employed to inhibit the mitochondrial complexes I, II, III, IV and V, respectively. MMPs -1, -3 and -13 mRNA expression was studied by real time PCR. Intracellular protein expression was evaluated by western blot as well as by inmunohystochemistry. Levels of MMPs and Proteoglican (PGs) in supernatant were analyzed by ELISA and alcian blue studies respectively.

Results: From all tested MRC inhibitors only AA and oligomycin modulated the MMPs expression: Oligomycin 5 µg/ml at 24 hours induced the expression of MMP-1 (68.10±39.9 vs. basal =1) and MMP-3 (60.13±29.7 vs. basal =1). In contrast, mRNA expression of MMP-13 decreased after treatment with AA 20 µg/ml (0.34±0.2) and oligomycin (0.67±0.3) vs. basal=1. Oligomycin 25 µg/ml for 36 h increased in the supernatants the levels of MMP-1 (18.06±10.35) and MMP-3 (8.49±4.32) vs basal=1 (n=5; $p<0.05$). However, MMP-13 levels in the supernatants decreased after treatment of chondrocytes with AA 40 µg/ml (0.63±0.13 vs. basal=1) and oligomycin 25 µg/ml (0.41±0.14 vs. basal=1); (n=5; $p<0.05$). These results were reproduced after the stimulation of tissue explants with oligomycin and AA. Alcian blue stain, showed a loose of PGs in tissues that were incubated with oligomycin.

Conclusion: These results show that the dysfunction of MRC modulates the MMPs expression in human normal chondrocytes.

Disclosure: B. Cillero-Pastor, None; **I. Rego**, None; **B. Lema**, None; **M. J. López-Armada**, None; **F. J. Blanco**, None.

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Adenosine Inhibits RANKL-Induced Osteoclastogenesis in Vitro. Elise Soltner[1], Benoit Le Goff[1], Laurence Duplomb[1], Jean-Marie Berthelot[2] and Dominique Heymann[1], [1]INSERM U957, Nantes, France, [2]University Hospital, Nantes, France

Purpose: Adenosine is an endogenous purine nucleoside that modulates many physiological processes. Cellular signaling occurs through four known adenosine receptor subtypes (A1, A2a, A2b, and A3). Adenosine is believed to be an anti-inflammatory agent, implicated in many pathologies such as asthma or inflammatory joint disease. However, there is very few information in the literature on the role and expression of adenosine receptors in bone cells. We investigated therefore whether osteoclasts express adenosine receptors and how adenosine could regulate osteoclastogenesis.

Method: Human peripheral blood mononuclear cells (PBMCs) were isolated by centrifugation over Ficoll gradient. CD14+ cells were magnetically labelled with CD14+ microbeads and positively selected by MACS technology. CD14+ cells were cultured with human M-CSF (25 ng/ml) and, after 3 days of culture, with or without hRANK-L (100 ng/ml). The formation of TRAP positive cells occurred around the 12th day of culture and was observed by TRAP staining. Expression of adenosine receptors was determined by RT-PCR and micro-array analysis of CD14+ cells and osteoclasts. Activity of the PI3K pathway, a key signaling protein downstream of adenosine receptors, was analysed by western blotting. TRAP staining was used to evaluate the effects of adenosine and 4 specific agonists of the adenosine receptors [CCPA (A1), CGS21680 (A2a), NECA (A2b), IB-MECA (A3)] on osteoclast differentiation.

Results: The mRNA for all four adenosine receptors (A1, A2a, A2b, and A3), was detectable by RT-PCR in both CD14+ cells and osteoclasts. Microarray analysis showed a 2-fold increase in expression of the A3 receptor subtype in osteoclasts compared to CD14+ cells, whereas expression of the 3 other subtypes remained stable during differentiation. Western blot analysis showed a decreased phosphorylation of PI3K in CD14+ cells and osteoclasts stimulated with adenosine. TRAP staining demonstrated that adenosine inhibited RANKL-induced osteoclastogenesis. All four specific agonists of individual receptor subtypes inhibited osteoclastogenesis with comparable efficacies.

Conclusion: Our work shows that osteoclasts and CD14+ cells express all four subtypes of adenosine receptor. Furthermore, phosphorylation of PI3K was decreased following stimulation with adenosine, confirming that these receptors are functional. We also demonstrated that adenosine has a potent inhibitory effect on RANKL-induced osteoclastogenesis *in vitro,* through its 4 receptor subtypes. We hypothesise that adenosine may be a regulator of osteoclastogenesis and contribute to the balance between bone formation and resorption in inflammatory conditions.

Disclosure: E. Soltner, None; **B. Le Goff**, None; **L. Duplomb**, None; **J. M. Berthelot**, None; **D. Heymann**, None.

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Inflammatory Response Is Modulated by Mitochondrial Dysfunction in Cultured Normal Human Chondrocytes. C. Vaamonde-García[1], MN Valcarcel-Ares[1], RR Riveiro-Naveira[1], B. Lema[2], Fj Blanco[2] and Mj López-Armada[1], [1]INIBIC-CHU A Coruña. Inflammation and Aging Unit, A Coruña, Spain, [2]INIBIC-CHU A Coruña. Osteoarticular and Aging Research Laboratory, A Coruña, Spain

Purpose: The molecular inflammation hypothesis of aging implicate the notion that the molecular activation of proinflammatory genes by altered redox-sensitive cellular signal pathway would serve as a bridge between normal aging and age-related diseases, such as Osteoarthritis (OA). In this work, we studied the effect that dysfunction of mitochondrial respiratory chain (MRC), main cellular source of Reactive Oxygen Species (ROS), could induce on inflammatory response in cultured normal human chondrocytes, specifically in IL-8 and COX-2 expression.

Method: Antimycin A (AA; 10 µg/ml) and Oligomycin (Oli; 10 µg/ml) were employed as inhibitors of complex III and V of MRC, respectively. IL-1β or TNF-α were employed as inductors of inflammatory response. Protein and mRNA IL-8 and COX-2 expression were analyzed by cytometry and real time PCR, and PGE_2 levels were assayed by ELISA. To identify underlying mechanisms responsible for inflammatory response, catalase, an antioxidative enzyme, and a chemical and a natural ROS scavenger, N-Acetyl-L-Cysteine (NAC; 40mM), and Resveratrol (RESV; 250uM) respectively, were employed. Finally, the implication of nuclear factor-κB (NF-κB) was studied by the inhibitor BAY-117085 (5µM).

Results: Firstly, we tested if mitochondrial dysfunction induced by AA or Oli could modulate the response induced by IL-1β (5, 1.5 and 0.5 ng/ml) on IL-8 expression. The results showed that the pre-treatment of chondrocytes with AA or Oli for 1h increased significantly the expression of IL-8 induced by IL-1β (table 1). Similar effects were observed with 10 ng/ml TNFα. In addiction, the intensification of inflammatory effects of cytokines by mitochondrial dysfunction was counteracted by the addiction of a chemical and a natural ROS scavenger (10.75±2.97% NAC+AA+IL-1ß or 18.10±5.04% RESV+AA+IL-1ß vs. 100% AA+IL-1ß, n= 3, $p<0.01$) and by catalase. When the role of NF-κB was investigated, the results showed that the pre-incubation of cells for 1h with BAY significantly reduced to 26.53±16.80% the production of IL-8 protein induced by AA + IL-1β (100%). Finally, we studied if mitochondrial dysfunction could modulate COX-2 expression induced by IL-1ß; and we found that both COX-2 mRNA and protein levels (399.96±79.93% Oli+IL-1ß vs. 100% IL-1ß and 90.66±7.97% Oli, n=3, $p< 0.001$) and its product, PGE_2 (13522 ±6845 Oli+IL-1ß vs. 1844±1419 IL-1ß and 6825±3813 pg/250000cells Oli, n=3, $p<0.01$) increased significantly in Oli pretreated chondrocytes induced by IL-1ß.

IL-8	IL-1ß (1.5ng/ml)	AA	Oli	AA+ IL-1ß	Oli+IL-1ß
mRNA (%)	100	0.08±0.01	0.19±0.03	256.33±77.03	342.90±59.28
Protein (%)	100	48.26±7.70	50.47±6.49	214.06±35.22	292.06±49.02

Conclusion: These findings suggest that mitochondrial dysfunction may be one of the factors that sensitize chondrocytes to increase cytokines-mediated inflammatory response in OA and aging.

Disclosure: C. Vaamonde-García, None; **M. Valcarcel-Ares**, None; **R. Riveiro-Naveira**, None; **B. Lema**, None; **F. Blanco**, None; **M. López-Armada**, None.

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Autophagy Is a Protective Mechanism in Normal Cartilage and Its Aging-Related Loss Is Linked with Cell Death and Osteoarthritis. Beatriz Caramés[1], Noboru Taniguchi[1], Shuhei Otsuki[1], Francisco J. Blanco[2] and Martin K. Lotz[1], [1]The Scripps Research Institute, La Jolla, CA, [2]INIBIC–Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

Purpose: Autophagy is a process for turnover of intracellular organelles and molecules that protects cells during stress responses. This study evaluated the potential role of ULK1, an inducer of autophagy, Beclin1, a regulator of autophagy and LC3, which executes autophagy, in the development of osteoarthritis (OA) and in cartilage cell death.

Method: DNA array studies were performed to analyze differences in the expression of ULK1 in normal and OA human knee cartilage. Protein expression of ULK1, Beclin1 and LC3 was analyzed in human normal and OA chondrocytes and cartilage by western blot and immunohistochemistry (IHC). Autophagy markers were also studied in mouse models of aging-associated and surgically-induced OA. The apoptosis marker poly-ADP(ribose) polymerase (Parp p85) was used to determine the relationship between cell death and autophagy.

Results: In normal human articular cartilage ULK1, Beclin1 and LC3 were constitutively expressed. ULK1 gene expression and ULK1, Beclin1 and LC3 protein expression were reduced in OA chondrocytes and cartilage but these three proteins were expressed in the cell clusters in OA cartilage. In mouse knee joints loss of glycosaminoglycans (GAGs) was observed at 9 months of age and in the surgical OA model 8 weeks after knee destabilization. Expression of ULK1, Beclin1 and LC3 decreased together with loss of GAGs, suggesting decreased autophagy correlates with extracellular matrix changes in OA. The decrease in autophagy in the same human and mouse OA cartilage was associated with an increase in Parp p85.

Conclusion: Autophagy may be a protective or homeostatic mechanism in normal cartilage. By contrast, human OA, spontaneous and surgically-induced OA in mice are associated with a reduction and loss of ULK1, Beclin1 and LC3 expression and a related increase in apoptosis. These results suggest that compromised autophagy represents a novel mechanism in the development of OA.

Disclosure: B. Caramés, None; **N. Taniguchi**, None; **S. Otsuki**, None; **F. J. Blanco**, None; **M. K. Lotz**, None.

1299

Soluble Syndecan-3 (ssyn3): An Anionic Serum Protein in Ovariectomised Rats Controlling Osteoblastic (OB) Function. Tassos P. Anastassiades[1] and Karen Rees-Milton[2], [1]Etherington Hall Rm 2050, Kingston, ON, [2]Queen's University, Kingston, ON

Purpose: Studies in bone homeostasis in post-menopausal OP have emphasized primarily osteoclastic rather than osteoblastic (OB) regulation. We have been using a model of post-menopausal OP, the ovariectomised (Ovx) rat, for pre-clinical studies of N-butyryl glucosamine (GlcNBu), as an agent for preventing OP in this model. We found that soluble syndecan-3 (ssyn3) was significantly up-regulated in the livers of the Ovx, untreated rats. Here we report on the inhibitory effect of sera from Ovx rats on OB proliferation and the possible role of ssyn3 as accounting for this effect.

Method: The groups of mature female rats were: (1) Glucose (Glc)-fed, non-OVX (control); (2)GlcNBu-fed, non-OVX; (3) Glc-fed, OVX; (4) GlcNbu-fed, OVX. At 6 months, animals were euthanized and the bones evaluated for bio-mechanical properties and bone mineral densities (BMD). RNA was extracted from the livers and subjected to microarray analysis. The serum from Ovx and control rats was used in cell culture experiments with primary neonatal rat calvarial OB and UMR-106 OB. The levels ssyn3 in the sera were quantitated using immunoassays, utilizing chitosan coated plates, which permit a preliminary isolation of the anionic ssyn3.

Results: Ovariectomy (Ovy) resulted in lower femoral and spinal BMDs. GlcNBu-fed OVX rats (Group 4) demonstrated maintenance of femoral head, total femur and spine BMDs. Orally administered GlcNbu, preserved bone biomechanical properties in the OVX rat. Microarray sub-group analysis revealed a small number of genes with relatively low expression that very significantly regulated ($p<0.001$), which included ssyn3. The proliferation of rat OB *in-vitro* was significantly less ($p<0.01$) in sera from Ovx, untreated compared to non-Ovx or GlcNBu rats. There was a neutralization of serum anti-proliferative activity in OVX sera on calvarial OB and UMR-106 proliferation by different antibodies to ssyn3. The addition of syn-3 antibody to OB had no effect on proliferation. The antiproliferative activity fractionated in the region expected for ssyn3. Further, there was a strong correlation ($r=-0.962$) between increasing antibody dilutions and OB proliferation, suggestive of a role of ssyn-3 in inhibiting OB proliferation. The immunoassays on chitosan coated plates are also applicable human sera and are suitable for immunoassays for other bone-related serum anionic proteins, such as soluble phosphoprotein 24.

Conclusion: 1. Orally administered GlcNBu, preserves BMD and bone biomechanical properties in the OVX rat, an animal model for post-menopausal OP. 2. ssyn3 may be a novel modulator of OB proliferation in this model. 3. The effect of GlcNBu in preventing bone loss may be mediated, in part, by regulation of ssyn-3, acting on OB function.

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Disclosure: T. P. Anastassiades, Anacoti Ltd, 4 ; **K. Rees-Milton**, None.

1300

Constitutive Expression of NOX4 in Human Articular Chondrocytes and Its Regulation by Cytokines and Transforming Growth Factor-ß. Sonsoles Piera-Velazquez, Alma Makul and Sergio A. Jimenez, Jefferson Institute of Molecular Medicine, Thomas Jefferson Univ, Philadelphia, PA

Purpose: Reactive oxygen species (ROS) are normal by-products of cellular metabolism but alterations in the type and amount of ROS release can cause pathologic effects. ROS are a major factor in the regulation of the metabolism of articular chondrocytes. ROS production is increased in osteoarthritis (OA) and rheumatoid arthritis (RA). ROS overproduction results in oxidative stress mediated cell damage, therefore oxidative stress may be involved in cartilage degradation. NADPH oxidases play a major role in the production of ROS. NOX4 is a member of the NADPH oxidase family and is expressed by SV40 immortalized human articular chondrocyte cell lines. NOX4 expression is increased by hypoxia and TGF-β in vascular endothelial cells and is reduced by interleukin-1 (IL-1) in vascular smooth muscle cells. However, the NOX4 role in articular cartilage pathology and the regulation of its expression by relevant cytokines and growth factors have not been examined. The objective of this study was to examine the expression of NOX4 and the regulation of its expression by cytokines (IL-1 and TNF-α) and TGF-β in normal and OA chondrocytes.

Method: Normal human articular chondrocytes (hAC) were obtained from the knee joint cartilage from normal organ donors through the Cooperative Human Tissue Network. OA chondrocytes were obtained from knee cartilage from patients undergoing knee joint replacement. Chondrocytes were isolated by enzymatic digestion and frozen until used. Primary human chondrocytes were cultured in monolayer and treated with 10 ng/ml of human recombinant TGF-β1 in complete media for 24 h with or without 2.5 and 5 μM of Rottlerin, an inhibitor of protein kinase Cδ (PKCδ), or with 10 ng/ml of IL-1β or 10 ng/ml of TNF-α or both. RNA and proteins were isolated and PCR for NOX4 and GAPDH performed. Cell extracts were prepared from freshly isolated chondrocytes and from the cultured chondrocytes following cytokine/growth factor treatment and Western blots performed using NOX4 antibody.

Results: Normal and OA human articular chondrocytes constitutively express NOX4 protein. NOX4 protein and mRNA are downregulated by either IL-1β or TNF-α *in vitro* and the combination of both cytokines showed synergistic inhibition. NOX4 protein and mRNA were upregulated by TGF-β *in vitro*. The specific PKCδ inhibitor, rottlerin, decreases NOX4 mRNA expression by primary human articular chondrocytes *in vitro* and abolishes the TGF-β-induced stimulation of its expression.

Conclusion: NOX4 is constitutively expressed by freshly isolated normal and OA human articular chondrocytes and its expression is regulated by IL-1β, TNF-α, and TGF-β *in vitro*. IL-1β and TNF-α cause NOX4 downregulation, whereas TGF-β upregulates NOX4 in primary hAC *in vitro.* The upregulation of NOX4 by TGF-β is mediated by PKCδ. The results suggest an important role of this constitutively expressed NADPH oxidase in OA and in articular cartilage function and pathology.

Disclosure: S. Piera-Velazquez, None; **A. Makul**, None; **S. A. Jimenez**, None.

1301

Biomechanical Stretch Is a Key Initiating Event in the Development of Enthesitis in Murine Spondyloarthritis. Peggy Jacques[1], Stijn Lambrecht[1], Rik J. Lories[2], George Kollias[3], Gust Verbruggen[1] and Dirk Elewaut[1], [1]Laboratory for Molecular Immunology and Inflammation, Ghent, Belgium, [2]Laboratory for Skeletal Development and Joint Disorders - KU Leuven, Leuven, Belgium, [3]Biomedical Sciences Research Center Alexander Fleming, Vari, Greece

Purpose: One of the hallmarks of spondyloarthritis (SpA), is the development of enthesitis, most typically of the Achilles tendon and plantar fascia. However, the precise sites where inflammation originates within joints have been a matter of controversy, as enthesitis, synovitis and even bone marrow inflammation may occur during the course of SpA. In this study, we aimed to investigate the initiating events leading towards enthesitis development. We postulated that biomechanical stress is a principal feature of the early events leading to the inflammatory pathway resulting in enthesitis. To evaluate this, we used $TNF^{\Delta ARE}$ mice, which are characterized by an enhanced TNF mRNA stability, which in turn leads to the development of several features of SpA, including peripheral and axial arthritis (sacroiliitis, spondylitis), and Crohn´s like ileitis. One of the striking features of this model is the early appearance of tendinitis/enthesitis of the Achilles tendon, and the small ligaments of the interphalangeal joints. Inflammation of tendons and ligaments is in fact one of the first signs of disease in this model.

Methods: To study enthesitis development, we subjected $TNF^{\Delta ARE}$ mice which had not yet developed signs of inflammation to a biomechanical unloading procedure. Thus, a tail suspension procedure was conducted for 7-14 days, thereby prohibiting weight loading on hind paws. Western blotting was performed for phosphorylated Erk, one of the mitogen-activated protein kinases (MAPK) on cell lysates from Achilles tendon samples of tail suspended $TNF^{\Delta ARE}$ mice, versus mice that were allowed to walk for 15 minutes after a 7 days period of tail suspension. The effect of small molecular inhibitors of Erk and p38 on enthesitis development was evaluated.

Results: Biomechanical unloading studies indicated that virtually no inflammation of the Achilles tendon occurred in unloaded animals compared to weight bearing controls. By contrast, weight bearing front paws exhibited severe inflammation. As early as 15 minutes after

initiation of weight bearing, phosphorylated Erk, one of the mitogen-activated protein kinases (MAPK), was strongly upregulated compared to continuously unloaded conditions. Furthermore treatment of $TNF^{\Delta ARE}$ mice with small molecular inhibitors of Erk and p38 markedly prevented the onset of Achilles tendon enthesitis.

Conclusion: These findings provide a novel proof that biomechanical stretch and the resulting activation of the MAPK pathway through Erk phosphorylation and downstream transactivation, is required for the induction of pathologic loads of TNF sufficient to develop enthesitis in SpA.

Disclosure: P. Jacques, None; **S. Lambrecht**, None; **R. J. Lories**, None; **G. Kollias**, None; **G. Verbruggen**, None; **D. Elewaut**, None.

1302

Decreased Levels of Sirt1 in OA Articular Cartilage Are Associated with An Increase in MMP-3, -13 and Apoptosis. Odile H. Gabay, Viktoria Gagarina, Eun Jin Lee, Mona Dvir-Ginzberg, Jun Onodera and David Hall Sr., NIH, Bethesda, MD

Purpose: Osteoarthritis is a multi-factorial disease that results from an imbalance between cartilage anabolism and catabolism, which results from the over-expression of pro-inflammatory mediators. Elevation in chondrocyte apoptosis is also evident in OA cartilage, contributing to a lack of cartilage repair. Since OA is a disease associated with aging, the role of the longevity factor SirT1, a protein deacetylase that can prolong lifespan in a variety of organisms, was examined in a number of critical features of OA. :

Method: Human articular cartilage was obtained from OA patients undergoing total knee arthroplasty while normal samples were obtained from cadeavers. Cartilage was embedded sectioned and processed for immunohistochemistry using antibodies for SirT1, DBC1, PTP1B, MMP-3 and -13. Additionally, chondrocytes isolated from cartilage samples were cultured in vitro and used for analysis of gene expression and for immunoblotting. Human chondrocytes were Amaxa transfected with a SirT1 expression plasmid.

Results: In human chondrocyte cell culture we find that overexpression of SirT1 enhances expression of cartilage specific matrix genes (collagen 2, aggrecan) while it represses the expression of matrix degrading metalloproteinases (MMP3, 8, 13, Lee et al., 2009 submitted). Further, Sirt1 was found to be a potent inhibitor of apoptosis in human chondrocytes through repression of the protein tyrosine phosphatase 1B (PTP1B, Gagarina et al, 2009 submitted), an extremely potent pro-apoptotic protein in chondrocytes. Examination of tissue sections revealed that SirT1 levels were significantly downregulated in OA cartilage compared to normal cartilage, while PTP1B, MMP-3 and -13 levels were elevated in OA tissue. DBC1, a protein known to associate with Sirt1 and repress its enzymatic activity was also examined in chondrocytes and cartilage sections. DBC1 was upregulated in OA. These data are consistent with the finding that SirT1 enzyme activity is significantly decreased in OA chondrocytes.

Conclusion: These data indicate that the longevity protein SirT1 is a powerful regulator of cartilage matrix and MMP gene expression as well as chondrocyte apoptosis in human chondrocytes. The results suggest that SirT1 has features of an anti-osteoarthritic protein, consistent with its ability to reduce the severity of age-associated diseases.

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1303

Green Tea Polyphenol EGCG Inhibits Advanced Glycation End Products-Induced Endoplasmic Reticulum Stress Stimulated Expression of COX-2 in Human Chondrocytes. Zafar Rasheed, Nahid Akhtar, Arivarasu N. Anbazhagan, Frank R. Voss and Tariq M. Haqqi, School of Medicine, University of South Carolina, Columbia, SC

Purpose: During aging, an important risk factor for osteoarthritis (OA), nonenzymatic glycation of proteins and other molecules results in the accumulation of Advanced Glycation End Products (AGEs) in articular cartilage. AGEs have been shown to activate chondrocytes resulting in the production of proinflammatory molecules. Here we investigated whether AGEs induce endoplasmic reticulum (ER) stress in human chondrocytes and which of the ER stress-activated pathways induce COX-2 in human chondrocytes.

Method: Human chondrocytes derived from OA cartilage by enzymatic digestion were stimulated with AGE-modified BSA (AGE-BSA) and EGCG. Expression of COX-1, COX-2, and mPGES-1 mRNAs was determined by qRT-PCR and protein expression was determined by Western immunoblotting. PGE_2 released in the culture medium was quantified by EIA. Phosphorylation and activation of MAPKs was

detected by Western immunoblotting and activation of NF-KB was analyzed using Luciferase based reporter constructs. Pharmacological studies to elucidate the involved pathways were executed using specific inhibitors of MAPKs and NF-KB.

Results: Several pathways that maintain cellular homeostasis were activated in human chondrocytes in response to AGE-BSA treatment. AGE-BSA induced the expression of the ER chaperone protein BiD and increased the expression of COX-2 and mPGES-1 with concomitant increase in PGE_2 production. Nuclear translocation and activation of NF-kB and phosphorylation of MAPKs was observed in AGE-BSA-stimulated human chondrocytes. IkBα kinase inhibitor Bay-11-7082 or Parthenolide significantly inhibited the expression of COX-2 and mPGES-1. Treatment with EGCG inhibited the p38-MAPK and JNK phosphorylation and attenuated the NF-kB DNA binding activity and COX-2 and mPGES-1 expression. Similar results were obtained when chondrocytes were treated with p38-MAPK specific inhibitor SB-202190 and 2-aminopurine (an inhibitor of eIF2a). In contrast JNK inhibitor SP600125 had no effect on AGE-BSA-induced expression of COX-2 and mPGES-1 whereas MEK inhibitor PD98059 inhibited PGE_2 release in the culture medium but had no effect on the expression of COX-2 or mPGES-1 in AGE-BSA-stimulated human chondrocytes.

Conclusion: Our results demonstrate that AGE-BSA induce ER stress in human chondrocytes and stimulated the expression of COX-2 and mPGES-1 and production of PGE_2 through the activation of NF-kB and p38-MAPK pathways. EGCG is a potent suppressor of ER stress-induced expression of COX-2 but had no effect on COX-1 expression. Our results also demonstrate that ER stress-induced expression of COX-2 and mPGES-1 was independent of the JNK pathway while ERK plays a role in PGE_2 export from human chondrocytes. Thus, our results provide important insights into the mechanism of AGE-BSA-induced ER stress stimulated production of PGE_2 in human chondrocytes. These results also indicate that use of EGCG or compounds derived from it may be of value in AGEs-induced catabolic activation of human chondrocytes.

Disclosure: Z. Rasheed, None; **N. Akhtar**, None; **A. N. Anbazhagan**, None; **F. R. Voss**, None; **T. M. Haqqi**, None.

1304

Regulation of MMP-13 Expression in Human Chondrocytes by MicroRNA-27b. Nahid Akhtar, Zafar Rasheed, Arivarasu Anbazhagan, Frank R. Voss and Tariq M. Haqqi, School of Medicine, University of South Carolina, Columbia, SC

Purpose: Deregulated posttranscriptional regulation of MMPs by microRNAs (miRNAs) may be an important factor in chronic degenerative diseases such as osteoarthritis (OA). In this study we determined the posttranscriptional regulation of matrix metalloproteinase-13 (MMP-13) expression by microRNA-27b (miR-27b) in human OA and normal chondrocytes.

Method: Chondrocytes were derived from OA cartilage by enzymatic digestion and stimulated with interleukin-1β (IL-1b) *in vitro*. Total RNA was prepared using TRIZOL reagent and MicroRNAs (miRNAs) were purified using the mirVANA system. PCR-based arrays were used to determine the expression profile of 352 human miRNAs. Expression of miRNA of interest was quantified using TaqMan miRNA Expression Assay and miRNA targets were identified using bioinformatics. Transfection with 3'UTR reporter construct and miRNA mimic or inhibitor was employed to verify the suppression of luciferase activity. OA chondrocytes were transfected with miR-27b mimic or inhibitor and amount of MMP-13 protein released in the culture medium was determined by ELISA. Expression of MMP-13, argonuate and Dicer mRNAs was determined by RT-PCR and quantified by TaqMan assays and protein expression was determined by Western immunoblotting. Nuclear translocation of NF-kB, degradation of IkBa and phosphorylation of MAPKs was determined using Western immunoblotting and role of MAPKs and NF-kB in regulating the expression of miR-27b and MMP-13 was evaluated using specific inhibitors.

Results: In OA chondrocytes stimulated with IL-1β for 6 h, 42 miRNAs were downregulated, 2 miRNAs were upregulated and expression of 308 miRNAs remained unchanged. Both normal and OA chondrocytes showed approximately 23 fold down regulation of miR-27b expression after stimulation with IL-1β. *In silico* analysis of targets identified a sequence in the 3'UTR of MMP-13 mRNA complementary to the seed sequence of miR-27b. Expression of MMP-13 correlated with the down regulation of miR-27b in OA and normal chondrocytes. Overexpression of miR-27b suppressed the activity of a reporter construct containing the 3'UTR of human MMP-13 mRNA. Further, transfection with miR-27b mimic resulted in down regulation of MMP-13 production, but not mRNA expression, in IL-1b-stimulated OA or normal chondrocytes. In addition transfection with miR-27b inhibitor reversed the inhibitory effect of miR-27b on MMP-13 expression. Additional studies with BAY-11-7082, SB202190 and SP600125 revealed that expression of miR-27b was negatively regulated by the activation of NF-kB and p38-MAPK and JNK pathways respectively.

Conclusion: Thus, we have identified miR-27b as a post-transcriptional regulator of MMP-13 expression in human chondrocytes. Activation of p38-MAPK, JNK and NF-kB, pathways required for optimum expression of MMP-13, down-regulate the expression of miR-27b. These results indicate that miR-27b plays a role in maintaining cartilage integrity by suppressing posttranscriptionally the expression of MMP-13.

Disclosure: N. Akhtar, None; **Z. Rasheed**, None; **A. Anbazhagan**, None; **F. R. Voss**, None; **T. M. Haqqi**, None.

1305

Modulation of Mir-27b Expression and Regulation of MMP-13 Production by EGCG in IL-1b Stimulated Human Osteoarthritic Chondrocytes. Nahid Akhtar[1], Zafar Rasheed[2], Arivarasu N. Anbazhagan[2], Frank R. Voss[2] and Tariq M. Haqqi[2], [1]University of South Carolina, Columbia, SC, [2]School of Medicine, University of South Carolina, Columbia, SC

Purpose: MicroRNAs (miRNAs) are recently discovered 20-40 nucleotides long non-coding RNAs involved in key biological processes via suppression of gene expression at posttranscriptional level. We have previously shown that epigallocatechin-3-gallate (EGCG), a polyphenol abundant in green tea (*Camellia sinensis)* suppress the expression of MMP-13 in human chondrocytes. In this study we determined whether this effect was mediated through the modulation of miRNA-27b expression in human OA chondrocytes.

Method: Human chondrocytes were derived from OA cartilage by enzymatic digestion and at 80% confluence stimulated with IL-1β (5 ng/ml) *in vitro*. Total RNA was prepared using TRIZOL reagent. miRNAs were purified using the mirVANA system and expression of miR-27b and MMP-13 was quantified using TaqMan Assays. Western immunoblotting was used to analyze the MMP-13 production in the culture medium. OA chondrocytes were transfected with miR-27b mimic or inhibitor and amount of MMP-13 protein released in the culture medium was determined by ELISA. Nuclear translocation of NF-kB, degradation of IkBa and phosphorylation of MAPKs was determined using Western immunoblotting and role of MAPKs and NF-kB in regulating the expression of miR-27b and MMP-13 was evaluated using specific inhibitors.

Results: Human OA chondrocytes do not express high levels of MMP-13 and this correlated with the expression level of miR-27b in these cells. IL-1β stimulation of human OA chondrocytes for 24 h suppressed the expression of miR-27b, with concomitant increase in the production of of MMP-13. Pretreatment of human chondrocytes with different concentration of EGCG (10 to 150μM) for 2 h and then stimulation with IL-1β showed 2.8 to 14.8 fold up-regulation of miR-27b expression (Mean 9.375 ± 1.66) in the samples analyzed (n=8). In comparison, chondrocytes stimulated with IL-1β alone showed approximately 18 fold downregulation of miR-27b expression. Pretreatment with EGCG showed concentration dependent inhibition of IL-1β-induced expression of MMP-13 in OA chondrocytes and this correlated with the blockage of inhibitory effect of IL-1b on miR-27b expression. Further, transfection with miR-27b mimic resulted in down regulation of MMP-13 production, but not mRNA expression, in IL-1b-stimulated OA chondrocytes. In addition transfection with miR-27b inhibitor reversed the inhibitory effect of miR-27b on MMP-13 expression. Human OA chondrocytes pretreated with EGCG showed inhibition of NF-kB DNA binding activity and JNK activation with a significant downregulation of MMP-13 protein in the culture medium and this correlated with the enhanced expression of miR-27b in these cells.

Conclusion: EGCG inhibits the IL-1b induced downregulation of miR-27b and expression of MMP-13 protein in human OA chondrocytes. This correlated with the inhibition of NF-kB and MAPKs pathways that are essential for the MMP-13 expression. Thus, modulation of miR-27b by dietary constituents may present a novel therapeutic and preventive approach for OA.

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1306

Suppression of Osteoclastogenesis From Human Peripheral Blood Mononuclear Cells Co-Cultured with Rheumatoid Arthritis Synovial Fibroblasts by Over-Expression of MiR-223. Hayatoshi Shibuya, Tomoyuki Nakasa, Takuya Niimoto, Nobuo Adachi, Masataka Deie and Mitsuo Ochi, Hiroshima University, Hiroshima City, Japan

Purpose: MicroRNAs (miRNAs) are a class of non-coding RNAs that control gene expression by translational inhibition and messenger RNAs degradation in plants and animals. Although miRNAs have been implicated in developmental and homeostatic events of vertebrates and invertebrates, the role of miRNAs in bone metabolism has not been explored. In previous study, microRNA-223 (miR-223) is expressed

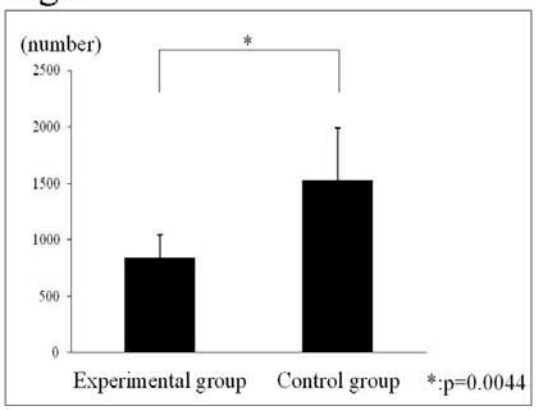
in RAW264.7 cells, mouse osteoclast precursor cell lines, and plays a critical role in osteoclast differentiation. The aim of this study was to confirm whether over expression of miR-223 inhibit osteoclastogenesis in rheumatoid arthritis (RA) in vitro.

Method: Human blood was collected from healthy volunteers, and peripheral blood mononuclear cells(PBMC) were isolated, and seeded in 96-well culture plates. The following day, co-cultured with fibroblast like synovial cell(FLS) of RA in the presence of macrophage colony stimulating factor (M-CSF) and $1,25(OH)_2D_3$. The day after next, for experimental group, double strand miR-223(ds-miR-223) transfected into the cells and co-cultured for 3 weeks. As controlled group, scramble siRNA was used. After 3 weeks, TRAP positive and multinuclear cells were counted. At 2 weeks after transfection, the expression of PU-1, RANKL, and OPG were evaluated by real time PCR. And we co-cultured PBMC and FLS with same method on dentin slice for 3weeks, we comfirmed co-cultured cells have bone resorption ability by toluidine blue stain. We cultured PBMCs in the presense of Tumor Necrosis factor-alpha (TNF-α) and M-CSF in 96 well culture plates. The following day, ds-miR-223 transfected into the cells and cultured for 3 weeks. And then, TRAP positive and multinuclear cells were counted.

Result s: The average number of TRAP positive multinuclear cell was 844±203 at experimental group. On the other hand, control group was 1531±458. There was significant difference between both groups. The expression of OPG in experimental group was higher than control group. Expression in experimental group of RANKL and PU-1 were lower than control group. On bone resorption assay, Pits on the dentin slices of experimental group was less than that of control group. There is a same trend in the PBMCs cultured with TNF-α at experimental group.

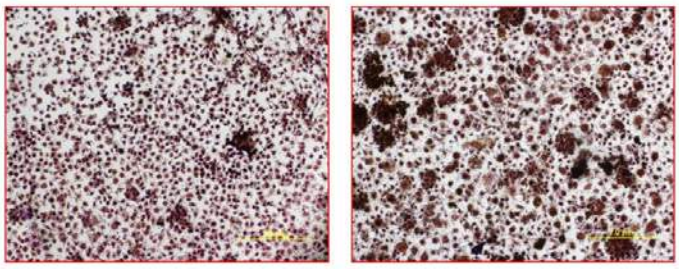
Conclusion: Our result indicated that miR-223 could inhibit osteoclastogenesis of RA in vitro, and miR-223 might be a viable therapeutic target for bone destruction of RA.

Fig.1



The average number of TRAP stain positive cells

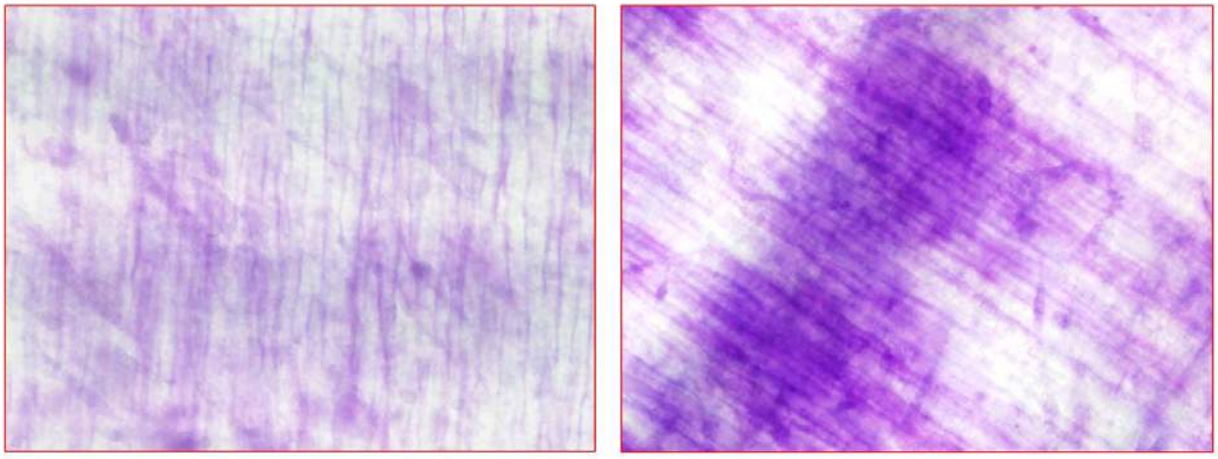
Fig.2



Experimental group **Control group**

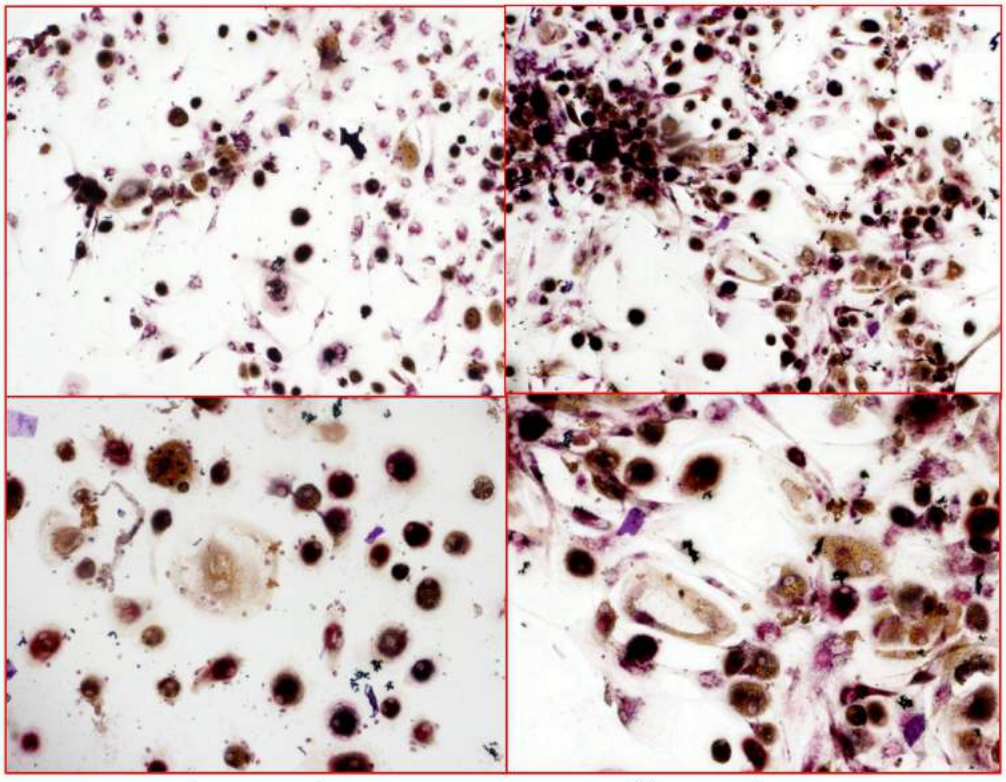
Trap staining

Fig.3 Dentin slice at Toluidine blue stain



Experimental group **Control group**

Fig.4 TRAP stain of PBMCs in the presence of TNF-α



× 40

× 100

Experimental group Control group

Disclosure: H. Shibuya, None; **T. Nakasa**, None; **T. Niimoto**, None; **N. Adachi**, None; **M. Deie**, None; **M. Ochi**, None.

1307

Immune Complex Mediated Inhibition of Osteoclastogenesis: Role for the Inhibitory Fcgamma Receptor IIb in Bone Erosion in Antigen Induced Arthritis? Lilyanne C. Grevers[1], Peter L.E.M. van Lent[1], Annet W. Sloetjes[1], Teun J. de Vries[2], Vincent Everts[2] and Wim B. van den Berg[1], [1]Radboud University Nijmegen, Medical Centre, Nijmegen, Netherlands, [2]Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University Amsterdam, Amsterdam, Amsterdam, Netherlands

Purpose: Rheumatoid arthritis is characterised by osteoclast mediated bone loss. In several studies it was shown that SHIP knockout mice are severely osteoporotic due to increased numbers of hyperreactive osteoclasts. Because SHIP is part of the signalling pathway of the inhibitory Fcg Receptor IIB (FcgRIIB) the aim of this study was to investigate the role of FcgRIIB in osteoclastogenesis and osteoclast function.

Method: Knee joints of arthritic FcgRIIB-/- mice and C57Bl/6 wild type controls were examined for bone erosion and cathepsin K expression. Bone marrow cells, isolated from FcgRIIB-/- mice and C57Bl/6 wild type controls, were cultured with M-CSF and RANKL to induce osteoclast differentiation. During differentiation cells were stimulated with or without heat-aggregated rabbit IgG to study the effect of immune complex (IC) mediated activation of FcgR. Osteoclastogenesis was examined by quantitation of TRACP+ cells containing at least three nuclei and by RT-PCR for osteoclast markers. Bone-resorbing capacity was analysed by pit formation after culturing osteoclasts on bovine cortical bone slices. FcgR expression was studied by FACS analysis.

Results: Bone erosion and cathepsin K staining are clearly enhanced during antigen induced arthritis in mice deficient for the inhibitory FcgRIIB, as compared to wild type mice. FACS analysis of in vitro differentiated osteoclasts showed that expression of FcgRIIB was somewhat lower in osteoclasts as compared to macrophages and negatively correlated with osteoclast size. Osteoclasts of FcgRIIB-/- mice and wild type controls showed no differences in the number of TRACP+ cells and mRNA expression of the osteoclast markers cathepsin K, CTR, DC-STAMP, and NFATc1. In line with this no differences were observed in the formation of resorption pits on bone. In the presence of IC differentiation of both FcgRIIB-/- and wild type osteoclasts resulted in significantly reduced numbers of large TRACP+ cells (containing more than 10 nuclei), but not of smaller sized osteoclasts (3 to 10 nuclei). Surprisingly, neither in FcgRIIB-/- nor in wild type mice did the IC-mediated reduction in osteoclast size result in decreased mRNA expression of osteoclast markers or formation of resorption pits on bone, showing that small osteoclasts resorb bone just as well as large osteoclasts.

Conclusion: This study shows that IC inhibit osteoclastogenesis resulting in smaller sized osteoclasts. However, this does not lead to decreased osteoclast function and, using FcgRIIB-/- mice, we demonstrated that the inhibitory effect of IC is not directly mediated by FcgRIIB.

Disclosure: L. C. Grevers, None; **P. L. E. M. van Lent**, None; **A. W. Sloetjes**, None; **T. J. de Vries**, None; **V. Everts**, None; **W. B. van den Berg**, None.

1308

Wnt16 Is a Cartilage-Specific Injury Response Gene Re-Expressed Following Acute and Chronic Cartilage Injury. Noha M. Eltawil, Costantino Pitzalis and Francesco Dell'Accio, EMR, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Purpose: The outcome of acute joint surface defects varies from healing to osteoarthritis development. The molecular signals regulating repair are largely unknown but their knowledge could be used to support joint surface repair. In an in vitro screening we have identified Wnt16 as a gene upregulated by injury to human articular cartilage. We now validate these finding in vivo, describe Wnt16 expression pattern and dynamics following cartilage injury and induction of osteoarthritis, and describe dynamics of the associated activation of the canonical Wnt signalling.

Method: Full thickness defects were generated in the patellar groove of adult C57BL/6 and DBA/1 mice by microsurgery (Eltawil et al. 2009). Osteoarthritis was induced by destabilization of the medial meniscus (DMM). Control knees were either not operated, or sham operated (arthrotomy and patellar dislocation, no cartilage injury or DMM). Gene expression was assessed by Q-PCR and immunohistochemistry.

Results: Following acute cartilage injury, DBA/1 mice healed consistently, whereas C57BL/6 did not repair. A transient synovial hyperplasia and inflammation was present for 1 week in both injured and sham operated knees. Wnt16 was not detectable in non operated or sham operated joints, but was upregulated at mRNA and protein level 24 hours following injury and DMM. Wnt16 upregulation was associated with downregulation of the secreted WNT inhibitor FRZB, nuclear translocation of β-catenin and up-regulation of the target gene axin2. At later time points, Wnt16 expression subsided, but β catenin accumulation persisted.

Conclusion: Wnt16 is a cartilage-specific early injury response gene (no upregulation took place in sham operated controls which underwent arthrotomy and developed transient synovitis to the same extent as injured knees).

Wnt16 transient expression was associated with the activation of the canonical wnt pathway, and was present in the early phases of osteoarthritis.

In vivo validation of Wnt16 re-activation upon injury and instability-induced osteoarthritis has allowed ongoing functional studies in vivo to investigate whether Wnt16 has a role in outcome determination of cartilage repair and OA in mice.

Disclosure: N. M. Eltawil, None; **C. Pitzalis**, None; **F. Dell'Accio**, None.

1309

PGE2 Differentially Regulates Expression of Chondrocyte Markers During Chondrogenesis of Human Bone Marrow Derived MSCs.

Glyn Palmer[1], Hayf Al-Mussawir[1], Mukundan Attur[1] and Steven B. Abramson[2], [1]NYU - Hospital for Joint Diseases, New York, NY, [2]NYU School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Purpose: A necessary step for the successful regeneration of cartilage lesions using stem cell-based therapies is the controlled differentiation of progenitor cells into a stable articular chondrocyte phenotype. Prostaglandin E2 (PGE2) has been shown to have an important role in both fracture healing and chondrocyte maturation during endochondral bone formation. This study investigates the effects of PGE2 on chondrocyte differentiation of adult, human mesenchymal stem cells (MSCs).

Methods: Bone marrow-derived MSCs were isolated from the discarded tissues of patients undergoing hip replacement surgery. Chondrogenesis was induced by seeding MSCs in serum-free aggregate cultures supplemented with dexamethasone (10^{-7} M) and TGF-b1 (10 ng/ml). At various time points, RNA was extracted for gene expression analysis by semi-quantitative RT-PCR. PGE2 levels were determined by RIA.

Results: Gene expression analysis of 4 patient samples revealed an order-of-magnitude increase in chondrogenic markers, col II, col X, MMP-13 and AP. In each case, expression was elevated by day 7 and persisted for the duration of the assay (21 d). To determine the effects of PGE2, aggregates were cocultured in the presence of exogenous PGE2 (10^{-6} M) and expression of chondrocyte markers determined after 14 d. PGE2 increased expression of col II (65%) and decreased expression of hypertrophic markers, col X (20%), MMP-13 (32 %) and AP (55%). Consistent with these observations, histological examination of treated aggregates after 21 d revealed fewer enlarged, hypertrophic chondrocytes following PGE2 treatment compared to control cultures. In aggregate cultures, PGE2 secretion was inhibited by the selective cox-2 inhibitor, celecoxib, approximately 50%, while cox-1 inhibition by treatment with SC-560 had no effect. Accordingly, celecoxib treatment of chondrogenic aggregates for 7 d decreased expression of sox-9 (80%) and col II (97%) compared non-treated controls. Cox-2 inhibition also increased expression of hypertrophic markers. Celecoxib treatment increased col X (95%) and AP (150%), but had no effect on MMP-13 levels. After 21 d, aggregates treated with celecoxib exhibited greater numbers of hypertrophic chondrocytes, and a modest decrease in proteoglycan staining. These findings suggest that cox-2 derived PGE2 has the capacity modulate chondrocyte differentiation of MSCs via differential regulation of chondrocyte marker genes.

Conclusion: PGE2, via upregulation of type II collagen, or inhibition of chondrocyte hypertrophy, has the capacity to regulate chondrocyte phenotype during *in vitro* chondrogenesis of hMSCs. Further characterization should uncover novel PGE2 pathways that can be exploited to modulate chondrocyte phenotype for tissue regeneration therapies.

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ACR/ARHP Poster Session C

Childhood Inflammatory Diseases: Pathogenesis and Genetics

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Novel *NOD2* Mutations Associated with Blau Syndrome and Related Phenotypes. Tammy M. Martin[1], Carine H. Wouters[2], Juan I. Aróstegui[3], Andrew D. Dick[4], C. Stephen Foster[5], Miroslav Harjaček[6], R. Russo[7], Maria D. Perez[8], Athimalaipet V. Ramanan[9], Srilakshmi M. Sharma[10] and Carlos D. Rosé[11], [1]Oregon Health & Science Univ, Portland, OR, [2]University Hospital Leuven, Leuven, [3]Hospital Clınic, Barcelona, Spain, [4]University of Bristol, Bristol, United Kingdom, [5]MERSI, Cambridge, MA, [6]Children's Hospital Zagreb, Zagreb, Croatia, [7]Hospital de Pediatria Juan P Garrahan, Buenos Aires, Argentina, [8]Texas Children's Hospital, Houston, TX, [9]Bristol Royal Hospital for Children, Bristol, United Kingdom, [10]University Hospitals Bristol NHS Foundation, Bristol, United Kingdom, [11]duPont Hospital for Children, Wilmington, DE

Purpose: Pediatric Granulomatous Arthritis (PGA) encompasses Blau Syndrome and Early Onset Sarcoidosis representing respectively familial and sporadic forms of a rare autosomal-dominant disease caused by coding mutations in *NOD2* exon 4, and classically presents as granulomatous arthritis, dermatitis and uveitis. The PGA International registry was created in 2005 to systematically examine rare *NOD2* genotypes and the clinical spectra of disease to better understand these relationships. In 2008 the registry and a national cohort of Spain were combined.

Method: PGA cases were entered into the Registry after review of de-identified clinical data. Presence of giant cell granuloma in tissue biopsy and arthritis were the inclusion criteria. *NOD2* exons were genotyped from genomic DNA by standard techniques. Study activities were approved by human subjects boards at the coordinating centers (duPont Hospital for Children and University Hospital Leuven) and the genetics center (Oregon Health & Science University).

Results: Of 180 subjects (from 58 families), 66 exhibit rare, non-synonymous mutations in *NOD2* exon 4. All with a mutation were affected, except 1 adult and 3 juveniles with incomplete penetrance in a family with classic PGA and 5 juveniles in a family with adult-onset disease involving only uveitis. The majority of affected subjects had substitutions R334Q or R334W. To date, 14 PGA substitutions have been reported. Herein, 5 previously unreported NOD2 substitutions are described: G481D, de novo mutation in 2 unrelated sporadic cases, 1 with expanded disease manifestations ; H520Y, de novo change in a sporadic case; E600K, 2 affected siblings with joint and skin involvement but no uveitis; E600A, large pedigree with inherited, adult-onset, severe uveitis without systemic disease nor joint nor skin involvement; and Q809K, de novo change in a sporadic case. The newly found *NOD2* mutations confirm the association with both complete and incomplete forms of PGA, as well as with expanding clinical manifestations as reported previously (2007 Arthritis Rheum 56:3805 and 2009 Arthritis Rheum 60:1797). E600A is the first example of a NOD2 substitution attributed to isolated severe uveitis without other PGA nor systemic manifestations. Q809K is the first PGA substitution located in the leucine rich repeat functional domain of NOD2 (all others are in/near the NACHT domain), which harbors Crohn's disease-associated NOD2 variants.

Conclusion: These findings significantly contribute both to the genetic (i.e., new mutations) and clinical (i.e., single organ/tissue involvement and new cases of expanded involvement) spectra of *NOD2* associated diseases.

Disclosure: T. M. Martin, None; **C. H. Wouters**, None; **J. I. Aróstegui**, None; **A. D. Dick**, None; **C. S. Foster**, None; **M. Harjaček**, None; **R. Russo**, None; **M. D. Perez**, None; **A. V. Ramanan**, None; **S. M. Sharma**, None; **C. D. Rosé**, None.

1311

Anti–Tnfα Therapy, but Not Methotrexate (MTX), Affects the Balance Between CD4+CD25+FOXP3+ Regulatory T Cells (Tregs) and Th17 Cells in Children with Juvenile Idiopathic Arthritis (JIA). Biagio Olivito, Gabriele Simonini, Gabriele Rossi, Letizia Betti, Maria Moriondo, Maurizio de Martino, Chiara Azzari and Rolando Cimaz, University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy

Purpose: Anti–TNFα therapy has become a valid and important treatment option for children with JIA although its role in modulating Tregs and Th17 cells has not fully elucidated, particularly in this disease. We therefore investigated the percentage and surface phenotype of Tregs

and Th17 cells from JIA children before and after treatment with two anti-TNFα inhibitors currently available (Adalimumab and Etanercept), comparing them with both healthy children and patients treated with MTX.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from 26 children (16 females and 10 males, median age: 6.2 years) with JIA before and after initiation of anti-TNFα or MTX therapy (median ± S.D.: 13.6 ± 6.6 months and 14.1 ± 4.5 months respectively, both groups n=13). Twenty demographically-matched controls were also included. Expression of FOXP3 was analyzed by flow cytometry and Real Time PCR. The relative expression of RORC2 was investigated on CD3+CD4+ sorted T cells. Surface expression of selectin L (CD62L) by gated CD4+FOXP3+ T cells was also evaluated. IL-17A on gated CD3+CD45RO+ memory T cells was assayed in PBMCs unstimulated and stimulated for 4 hrs with Phorbol Myristate Acetate (PMA) and Ionomycin. The expression of the activation marker CD69 on CD3+CD8+ and CD3+CD8- (representing CD4 T cells) was investigated to exclude the possibility that observed effects may be due to differences in T cell activation.

Results: At baseline, the percentage of Tregs as well as the amount of FOXP3 mRNA were significantly reduced in JIA patients when compared with controls, confirming our previous results. A significant increase in the percentage of CD3+CD45RO+ memory T cells secreting IL-17A was found, upon activation with PMA and Ionomycin, in JIA patients when compared with controls (median % ± S.D. 2.35 ± 0.8% vs 1.45 ± 0.77 %; P=0.0013). Interestingly, both these percentages changed, returning to that seen in controls, only in children who responded to anti-TNFα treatment. In contrast, the percentage of Tregs and Th17 cells remained unchanged in patients treated with MTX or unresponsive to anti-TNFα therapy and the same was true at transcriptional level. Furthermore, treatment with anti-TNFα and MTX did not produce significant changes in the percentage of CD3+CD69+ activated T cells. Of note, contrary to what has been observed in rheumatoid arthritis, no differences in the surface expression of CD62L by gated CD4+FOXP3+ T cells was noted after treatments with anti-TNFα and these levels were comparable to that detected in controls.

Conclusion: This study support an immunomodulatory effect of Etanercept and Adalimumab on Th17 and Treg cells, also suggesting a dominating Th17 responses in JIA children probably as a consequence of their peculiar immunological abnormalities.

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Immature Cell Populations and An Erythropoiesis Gene Expression Signature in Systemic Juvenile Idiopathic Arthritis: Implications for Pathogenesis. Claas H. Hinze[1], Ndate Fall[1], Sherry Thornton[1], Thomas A. Griffin[1], Susan D. Thompson[1], Robert A. Colbert[2], David N. Glass[1], Michael Barnes[1] and Alexei A. Grom[1], [1]Cincinnati Children's Hospital, Cincinnati, OH, [2]NIAMS/NIH, Bethesda, MD

Purpose: Previous observations suggest that active systemic juvenile idiopathic arthritis (sJIA) is associated with a prominent erythropoiesis gene expression signature. The aim of this study was to determine the association of this signature with peripheral blood mononuclear cell (PBMC) subpopulations and its specificity for active sJIA.

Methods: 199 patients with JIA (23 sJIA and 176 non-sJIA) and 88 controls were studied. PBMC were isolated and analyzed for multiple surface antigens by flow cytometry. PBMC RNA was isolated and gene expression profiling was performed using Affymetrix HG U133 Plus 2.0 GeneChips. The proportions of different PBMC subpopulations were compared among sJIA, non-sJIA patients and controls and subsequently correlated with the strength of the erythropoiesis signature. Additional gene expression data from patients with familial hemophagocytic lymphohistiocytosis (FHLH) and from a published sJIA cohort including controls with infectious diseases and other inflammatory conditions were analyzed to determine the presence and predictive strength of the erythropoiesis signature in these cohorts.

Results: Patients with sJIA had significantly increased proportions of immature cell populations, including CD34+ cells (sJIA vs. non-sJIA vs. controls = 0.16% vs. 0.08% vs. 0.09%; $p<0.001$, ANOVA). The proportions of CD34+ PBMC correlated highly with the strength of the erythropoiesis signature ($r=0.54$, $p<0.001$). This expansion was most prominently seen in patients with sJIA and anemia, even in the absence or reticulocytosis. Patients with non-sJIA and anemia did not exhibit the erythropoiesis signature. The erythropoiesis signature was found to be prominent in patients with FHLH and in a published cohort of patients with active sJIA but not in patients with inactive sJIA (receiver-operating characteristic curve area under the curve for active vs. inactive sJIA = 0.92). In addition, some patients with infection also exhibited a prominent erythropoiesis signature.

Conclusion: An erythropoiesis signature in active sJIA is associated with the expansion of CD34+ cells, and is also seen in some patients with FHLH and infection, suggesting a shared pathogenic mechanism among these conditions. The erythropoiesis signature may be an indicator of ineffective erythropoiesis and hemophagocytosis due to hypercytokinemia.

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Prevalence of Functionally Active, Senescent T Cells in Juvenile Idiopathic Arthritis. Jeffrey A. Dvergsten, Robert G. Mueller, Sameem Abedin, Bonnie H. Lemster, Allyson Pishko, Joshua Michel, Margalit E. Rosenkranz and Abbe N. Vallejo, Children's Hosp of Pittsburgh, Pittsburgh, PA

Purpose: All somatic cells have a finite proliferative lifespan. T cell activation through a lifetime exposure to antigens or in the setting of chronic immune-mediated disease could result in differentiated cells incapable of mitosis, a cell fate called replicative senescence. Indeed, we have reported that senescent T cells accumulate with normal chronologic aging. And adults with rheumatoid arthritis, disproportionate with age, have large populations of senescent T cells that colonize rheumatoid lesions. To further examine age-independent pathway(s) of T cell senescence, we examined the T cell repertoire of children diagnosed with Juvenile Idiopathic Arthritis (JIA). In JIA, pervasive T cell oligoclonality suggests underlying replicative stress. We hypothesize that T cells of JIA patients are prematurely senescent, abundance of these cells influences clinical disease manifestations.

Method: Children diagnosed with oligo- or poly-articular JIA, and age-matched controls were recruited. Blood and/or synovial fluid samples were collected. T cell phenotypes were examined by flow cytometry. T cell replicative potential was evaluated by telomere fluorescence in-situ hybridization (FISH), by population doubling assays, by rate of production of senescent cells in vitro, and by proliferation assays using CFSE (5- and 6-carboxyfluorescein diacetate succinimidyl ester). Where novel receptor expression on senescent T cells was indicated, receptor cross-linking bioassays were conducted to assess cellular function.

Results: Compared to controls, naïve T cells of children with JIA have significantly lower telomere-FISH fluorescence consistent with premature telomere erosion. In CSFE assays, up to 40% of T cells of JIA patients remained $CFSE^{hi}$ and expressed high levels of CD69 and low levels of CD25 indicating senescence but not quiescence. $CFSE^{hi}$ T cells were mostly $CD4^{+}CD28^{-}CD31^{low/-}$, and $CD8^{+}CD28^{-}CD31^{+}$. Flow cytometry showed over abundance of these cells in blood and synovial fluid. In JIA, $CD8^{+}CD28^{-}CD31^{+}$ T cells co-expressed senescence proteins γ-H2AX and/or pRB, consisting of up to 80% of the T cell repertoire of patients with oligo-JIA. In population doubling and senescence assays, pRB^{+}/γ-$H2AX^{+}$ T cells emerged within 15 days, maximum proliferation at 25 days, and mitotic arrest at 35 days. In receptor cross-linking assays, CD31 ligation, independent of CD3, induced extensive tyrosine phosphorylation and NFkB p65 activation. CD31-driven activation of $CD28^{-}$ T cells resulted in CD25 and CD45RO upregulation.

Conclusion: $CD8^{+}CD28^{-}CD31^{+}pRB^{+}$γ-$H2AX^{+}$ T cells are prematurely senescent T cells in JIA. They are functionally active despite their inability to undergo mitosis. Their prevalence in synovial fluid suggests a role in the pathophysiology of JIA, and are potential targets for therapy.

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DEK in the Synovium of JIA Patients: Characterization of DEK Antibodies and Posttranslational Modification of the DEK Autoantigen. Nirit Mor-Vaknin[1], Ferdinand Kappes[1], Amalie E. Dick[1], Maureen Legendre[1], Catalina Damoc[1], Roland Kwok[2], Elisa Ferrando-May[1], David M. Markovitz[1] and Barbara S. Adams[1], [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan

Purpose: DEK is a nuclear phosphoprotein that is an autoantigen in some children with juvenile idiopathic arthritis (JIA). The presence of autoantibodies to DEK in other autoimmune and granulomatous diseases suggests that DEK antibodies are present in a broad spectrum of disorders associated with abnormal immune activation. We have recently demonstrated that 1) activated macrophages secrete DEK, 2) apoptotic T cells release DEK, and 3) DEK is a leukocyte chemoattractant. Heavy post-translational modification of DEK suggests that these modifications may be important regulatory mechanisms that control DEK function. We have also identified DEK in synovial fluids (SF) from JIA patients, leading us to investigate how posttranslational modification of DEK may alter the affinity of DEK antibodies, thereby contributing to the pathogenesis of JIA.

Methods: DEK antibodies, immune complexes, and synovial macrophages were purified from SF from patients with active synovitis. Exosomes were purified from supernatants of cultured synovial macrophages by serial centrifugation and isolation by magnetic beads coated with anti-CD81 beads. Antibodies to DEK were purified from SF of 10 different JIA patients over a Sulfolink-coupled DEK column. Immune complexes were purified by staphylococcal-binding assay analyzed by 2-D gel and Western blot analysis. DEK antibody subclasses were determined by Western blot and ELISA. Recombinant His-DEK was used to study DEK posttranslational modification. DEK posttranslational modifications were analyzed by Western blot and by the Nano-LC-MS/MS sensitive method.

Results: DEK is secreted by synovial macrophages in a free form and also via exosomes; we have also shown for the first time that DEK antibodies and DEK protein are present in SF from JIA patients. Purified DEK antibodies from JIA SF primarily recognize the C-terminal half of the DEK protein. They are predominantly of the IgG_2 subclass, and are thus capable of activating the complement cascade. In addition to showing that DEK protein is present in immune complexes purified from JIA SF, we also demonstrate that DEK antibodies from JIA patients exhibit increased affinity for DEK protein that has been postranslationally modified by acetylation. This is consistent with our Nano-LC-MS/MS analysis of DEK posttranslational modification, which demonstrates that DEK undergoes acetylation on an unprecedented number of lysine residues.

Conclusion: Posttranslational modification of DEK protein by acetylation enhances the affinity of DEK antibodies. This finding suggests a mechanism by which DEK protein and DEK antibodies may contribute directly to joint inflammation by generating immune complexes in the joints of children with arthritis.

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Phosphorylated Mitogen-Activated Protein Kinases Are Colocalized with Membrane Attack Complex and Cyclin E in Juvenile Idiopathic Arthritis-Affected Synovial Tissue. Michael J. Ombrello[1], Anil Chauhan[2] and Terry L. Moore[1], [1]Saint Louis University School of Medicine, St Louis, MO, [2]Saint Louis University, St Louis, MO

Purpose: Juvenile idiopathic arthritis (JIA) describes a group of childhood-onset inflammatory arthritic disorders whose causes are unknown. In JIA, disease activity positively correlates with levels of synovial complement activation products and synovial deposition of immune complexes (IC), suggesting a role in JIA pathophysiology. Elevated levels of the complement membrane attack complex (MAC) are present in the synovial fluid of JIA patients, and deposits of MAC have been demonstrated in JIA synovial tissues. Yet, the specific roles of complement and ICs in the pathogenesis of JIA remain to be elucidated. In sublytic doses, MAC demonstrates pleiotropic effects on the cell cycle which are modulated through the mitogen-activated protein kinases (MAPKs). Our previous examination of JIA synovial tissue for cell cycle activation, as indicated by cyclin E (CyE) expression, found that it was almost exclusively confined to areas of MAC deposition. To further investigate the potential relationship between MAC deposition and cell cycle activation in JIA, we used immunohistochemistry (IHC) to examine JIA synovial tissue for MAC, CyE, and the phosphorylated MAPKs, pERK1/2 and pAkt.

Method: Synovial tissue was obtained from an 11-year-old female patient with ANA positive, oligoarticular JIA who underwent surgical synovectomy of the left knee for unremitting synovitis. Standard IHC methods were used to double stain specimens for MAC, CyE, pERK, and pAkt. Images of the specimens were obtained using fluorescent and confocal microscopy.

Results: The patterns of MAC deposition, CyE expression, and MAPK phosphorylation were identical, primarily in the synovial lining layer. CyE was colocalized with MAC deposits, pERK, and pAkt. MAC deposition was colocalized with CyE and pAkt. pAkt was colocalized with MAC deposits and CyE. Collectively, the phosphorylated MAPKs were universally and exclusively present at the sites of MAC deposition and CyE expression.

Conclusion: Cell cycle activation by sublytic MAC is a MAPK-dependent event. Phosphorylation of MAPKs activates the transcription factor, E2F, which in turn activates the G_1/S cell cycle checkpoint. The induction of CyE is a critical event of G_1/S checkpoint activation. Aside from periods of G1/S checkpoint activation, CyE expression is strongly repressed, CyE is rapidly degraded, and CyE protein is absent in most tissues. Based on this knowledge, we interpreted the colocalization of MAC and CyE as evidence of MAC-induced cell cycle activation in the JIA synovium. The current findings of MAPK phosphorylation, colocalized with MAC deposition and CyE expression, provides further support for a role for MAC-induced signaling in the synovial pathophysiology of JIA.

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Toll-Like Receptor-2 and -4 Independent Regulation of Cytokine Network in Juvenile Idiopathic Arthritis. Volker N. Umlauf, Martina Kirchner and Wilma Mannhardt-Laakmann, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

Background: In rheumatic diseases “damage associated molecular patterns” (DAMP) stimulate Toll-like receptors (TLR) to activate macrophages and secondly T cells as major cytokine producers. TLR-2/-4 expression is supposed to play a major role in juvenile idiopathic arthritis (JIA) pathogenesis. Although the cause of JIA, a heterogeneous group of childhood arthritides, remains unknown, it is well known that different cytokines are the main mediators of inflammation in several JIA subgroups.

Purpose: To investigate the pathogenetic association between TLR-2 and -4 expression and cytokine levels in JIA subgroups.

Method: 150 children (29 systemic JIA (SJIA), 38 persistent oligoarthritis (POA), 15 seronegative polyarthritis (SNP), 12 enthesitis related arthritis (ERA), and 32 healthy controls) were included in this study. Cellular expression of TLR-2 and -4 was determinated by staining blood derived monocytes with commercially available monoclonal antibodies for human TLR-2 and TLR-4 followed by flowcytometric analysis. A multiplex fluorescent bead immunoassay was first time used for quantititative detection by flow cytometry of pro- and anti-inflammatory cytokines in JIA blood plasma (proinflammatory cytokines mainly produced by macrophages: IL-1β, TNF-α; by Th1 cells: IL-2, -12p70, IFN-γ; by Th2 cells: IL-6, -8; antiinflammatory cytokines: IL-4, -5 and -10). Data were statistically analysed by Mann-Whitney-U- and Kruskal-Wallis-test and correlated by Spearman-Rho-test.

Results: While TLR-2 expression is decreased in all JIA subgroups, TLR-4 is elevated in certain groups. In SJIA we found a broad spectrum of proinflammatory cytokines (IL-6, IL-12p70, IFN-γ). IL-2 and IL-6 were found to characterize POA, whereas SNP is mainly described through IL-2. TNF-α levels seem to be highest in SNP. ERA is determined by IFN-γ and antiinflammatory IL-10. Interestingly, no correlations between TLR-2/-4 expression and cytokine levels were found. Nevertheless, pro- and antiinflammatory cytokines showed highly positive correlated ($r \geq 0.60$, $p \leq 0.01$) regulatory feedback patterns specific for JIA subgroups (SJIA: IL6 vs. IL-5; POA: IL-6/IL-2 vs. IL-5; SNP: TNF-α vs. IL-4; ERA: IL-6/IL-2 vs. IL-5).

Conclusion: TLR expression in JIA differs from known expression models in rheumatoid arthritis of the adult. The subgroups themselves can be characterized through specific combinations of pro- and antiinflammatory key cytokines which is a useful tool in differential diagnosis. TLR expression and cytokine production seem to be independent events in JIA. Pro- and antiinflammatory cytokines apparently regulate themselves within a disease specific cytokine network. However, the regulatory link between TLRs and inflammatory response in JIA is still under investigation.

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Replication of Genetic Associations in Juvenile Idiopathic Arthritis. H.M. Albers[1], T.H.C.M. Reinards[1], D.M.C. Brinkman[1], S.S.M. Kamphuis[2], L.W.A. van Suijlekom-Smit[2], M.A.J. van Rossum[3], E.P.A.H. Hoppenreijs[4], H.J. Girschick[5], C. Wouters[6], R.K. Saurenmann[7], Jeanine J. Houwing-Duistermaat[1], T.W.J. Huizinga[1], R.E.M. Toes[1], R. ten Cate[1] and M.W. Schilham[1], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]Academic Medical Center, Amsterdam, Netherlands, [4]Radboud University Medical Center, Nijmegen, Netherlands, [5]University of Wuerzburg, Wuerzburg, Germany, [6]University Hospital Gasthuisberg, Leuven, Belgium, [7]University Children's Hospital, Zürich, Switzerland

Purpose: Juvenile Idiopathic Arthritis (JIA) is an autoimmune disease in which both genetic and environmental components are involved. Different genetic variations have been reported as risk factors for JIA, but replication of results in an independent cohort with the same ethnic background remains a difficulty. In this study we have replicated several known genetic associations in a cohort of Caucasian JIA patients.

Method: A case-control association study has been performed in a cohort of 650 Caucasian JIA patients and 870 healthy controls. Patients with oligoarthritis (persistent and extended), polyarthritis (rheumafactor negative and positive) and systemic JIA have been included. Furthermore a transmission disequilibrium test (TDT) has been performed in 440 patient-parent trios. Several polymorphisms have been studied that have previously been described in literature as associated with JIA.

Results: We were able to replicate a genetic association in PTPN22 (in both case-control analysis and TDT), different associations in TNF-alpha and an association in IL6 and systemic JIA. A recent meta-analysis showed that CTLA4 is repeatedly not associated with JIA, as we observe in our data. Neither associations in IL10 and IL1A were observed.

Conclusion: These data show that some genetic associations in JIA are repeatedly found and thereby indicate that these genes might be important in the pathogenesis of (subtypes of) JIA. Moreover, this study underlines the importance of replication of associations in an independent cohort with a similar ethnic background.

Table 1: Association of single nucleotide polymorphisms (SNPs) with (subtypes of) JIA

Gene	SNP	Allelic OR (95%-CI)	p	p of TDT
PTPN22	rs2476601 - A	1.29 (1.03-1.61)	0.027	0.006
CTLA4	rs231775 - G	0.92 (0.79-1.07)	0.277	0.150
TNFA	rs1800629 - A	0.87 (0.71-1.05)	0.153	0.287
	rs361525 - A	0.61 (0.42-0.91)	0.014	0.080
	rs1799724 - T	1.41 (1.13-1.77)	0.003	0.049
	rs1800610 - A	1.39 (1.11-1.74)	0.004	0.054
	rs3093662 - G	0.82 (0.59-1.14)	0.232	0.149
	rs1800750 - A	0.36 (0.16-0.78)	0.010	0.132
IL6 (syst JIA pts)	rs1800795 - C	1.57 (1.10-2.24)	0.012	-
IL10	rs1800896 - C	0.90 (0.77-1.04)	0.144	0.236
IL1A	rs1800587 - A	0.92 (0.78-1.09)	0.328	0.222
	rs17561 - A	0.93 (0.79-1.10)	0.403	0.739

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Elevated Matrix Metalloproteinase-2 (MMP2) Levels in Cord Blood of Anti-Ro/La Exposed Neonates Associate with the Presence and Severity of Cardiac Manifestations of Neonatal Lupus. Tania L. Rivera, Jill P. Buyon and Robert M. Clancy, NYU School of Medicine, New York, NY

Purpose: Histologic evaluation of autopsies from hearts of neonates dying with cardiac manifestations of neonatal lupus (NL) support fibrosis (replacement of atrioventricular node and endocardial fibroelastosis) as the signature lesion. The role of the MMP2 in tissue remodeling and development of cardiac fibrosis has been studied in adults but never described in newborns. It has been reported that the transforming growth factor beta1 (TGFbeta1) induces secretion of MMP2 by fibroblasts during tissue regeneration. The aims of this study were to investigate the levels of MMP2 in cord bloods of children exposed to anti-Ro//La antibodies, and asses the value of these levels in predicting occurrence and severity of cardiac NL.

Method: One hundred and four cord bloods from children of families enrolled in the U.S. based Research Registry for Neonatal Lupus were evaluated. Criteria for inclusion were: 1) presence of maternal anti-Ro and/or La antibodies 2) substantial medical records regarding health status of the neonate. A neonate was considered to have cardiac NL based on the presence of heart block (1st, 2nd ,3rd, degree) documented by electrocardiogram (if 1st degree), echocardiogram, history of pacemaker, or statement in the medical record; and/or presence of cardiac injury which included autopsy evidence of a mononuclear infiltrate in the endocardium, myocardium and pericardium and/or endocardial fibroelastosis on echocardiogram always associated with cardiac dysfunction. Fifty-four neonates had cardiac NL diagnosed in utero or at birth. Levels of MMP2 were assessed by ELISA.

Results: Of the 104 children evaluated, 50% were females, 80% were Caucasians, and the average age of the mother at the time of birth was 33±0.5 years. Of the mothers, 42% had anti-Ro and anti-La, compared to 58% with anti-Ro alone. There were no differences in gender, race, diagnosis of the mothers, history of previous child with cardiac NL, or titers of maternal anti-Ro/La antibodies in the children with cardiac NL compared to those without cardiac NL. Significantly elevated levels of MMP2 were found in those with cardiac NL compared to those without (median MMP2 438ng/ml±18 vs 338ng/ml±20, p=0.0001).The levels of MMP2 did not predict the degree of advanced block (2^{nd} degree vs 3^{rd} degree 480±44 vs 439±20, p = 0.7). However, there was a trend toward higher levels in children who developed cardiomyopathy (n=6) compared to those who did not (520±42 vs 428±20, p=0.08). There were only 2 deaths in the cardiac NL group (likely underestimating true incidence of death because cord blood was unavailable on those with in uterine demise), and their MMP2 levels were extremely elevated at 574 and 570ng/ml. The heart rate of the children with 2^{nd} or 3^{rd} degree block at the time of diagnosis did not correlate with the levels of MMP2 at birth. There were no differences between MMP2 levels from cardiac NL children who underwent pacemaker implantation compared to those who did not (443±34 vs 434±21, p=0.6).

Conclusion: The increase of MMP2 levels may reflect tissue response to injury and more extensive disease, thus predicting a worse prognosis.

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Juvenile Systemic Lupus Erythematosus Frequently Develops in a "Background" of Primary Immunodeficiencies. Adriana A. Jesus[1], Bernadete Liphaus[1], Clovis A. Silva[1], Luis Eduardo C. Andrade[2], Antonio Coutinho[3] and Magda Carneiro-Sampaio[1], [1]Universidade de São Paulo, São Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil, [3]Instituto Gulbenkian de Ciência, Oeiras, Portugal

Purpose: To evaluate the frequency of complement and antibody primary immunodeficiencies (PIDs) in Juvenile Systemic Lupus Erythematosus (JSLE) patients and to compare lupus patients with and without PID regarding demographic data, clinical features, disease activity and damage, treatment and occurrence of severe sepsis.

Method: Seventy-two JSLE (ACR criteria) patients (1 to 16 yrs at diagnosis) were analyzed for early components of the classical complement pathway (C1q, C1r/C1s, C4, C2, C3) and immunoglobulin levels (IgG, IgA, IgM, IgE, and IgG2 subclass). Anti-C1q antibody was detected by ELISA (Inova Diagnostics - QUANTA Lite™ Anti-C1q, San Diego, USA). Statistical analysis was carried out according to Fisher´s exact test, Mann-Whitney test and Backward Stepwise multivariate analysis.

Results: Nineteen patients (26%) had underlying PIDs. Complement deficiencies were detected in 9 JSLE patients: C2 deficiency in 5 cases, C4 deficiency in 2 (all with persistently very low values in the presence of normal levels of other complement components, and SLEDAI < 4) and complete C1q deficiency in 2. All patients had normal C3 levels. Immunoglobulin deficiencies were found in 10 JSLE patients: IgG2 deficiency (<20mg%) in 4, IgA deficiency (<7mg%) in 3, IgM deficiency (<35mg%) in 3. All patients with immunoglobulin deficiencies were identified after 10-years of age and had normal or high total IgG levels. One IgA deficient patient also presented C4 and C2 deficiencies. The frequency of male gender was significantly higher in JSLE patients with PID compared to those without PID (37% vs. 11%, p=0.032). The 2 cases of infantile SLE (age at onset <2 years) were both males (one with C1q deficiency and other with IgM deficiency). A remarkably higher frequency of severe sepsis was observed in the PIDs group (31% vs. 7.5%; p=0.017). Lupus clinical features (cutaneous, mucosal, neuropsychiatric, cardiopulmonary, renal, hematological and articular manifestations and antiphospholipid syndrome) were comparable in patients with and without PID (p>0.05). SLEDAI score and anti-C1q antibody levels were also alike. On the other hand, the median of the cumulative damage (SLICC/ACR-DI) was significantly higher in PIDs group [1(0 - 5) vs 0 (0 - 3); p=0.0075]. Additionally, 44% of JSLE patients (30/68) had high IgE levels (>100UI/ml). Multivariate analysis revealed that male gender (Odds ratio=4.7; CI=1.2 – 19.2; p=0.034) and SLICC/ACR-DI (Odds ratio=2.5; IC=1.13 – 4.8; p=0.007) were the independent risk factors for PID.

Conclusion: An exceedingly high frequency of antibody and complement deficiency was observed amongst JSLE patients, suggesting that these immunologic defects may contribute to the disease development. Our results command that these two groups of PIDs should be systematically investigated particularly in males with disease damage.

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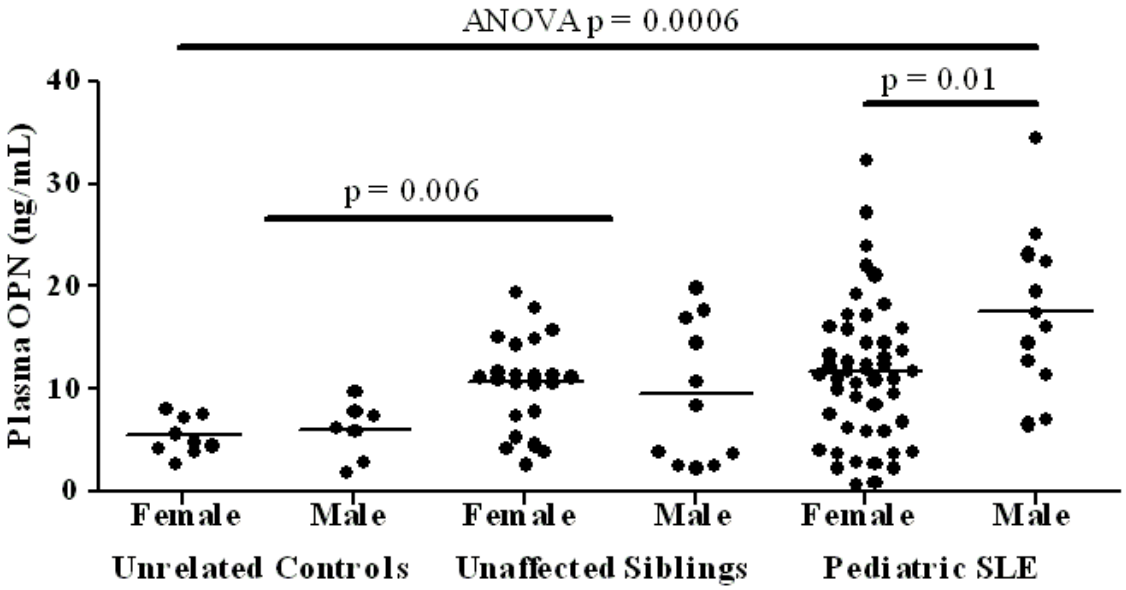
1320

Circulating Osteopontin Levels Are Elevated in Male Pediatric SLE and Their Unaffected Siblings. Ornella J. Rullo[1], J.M.P. Woo[2], Alice DC Hoftman[3], Deborah K. McCurdy[1] and Betty P. Tsao[2], [1]Mattel Children's Hospital UCLA, Los Angeles, CA, [2]Division of Rheumatology, UCLA, Los Angeles, CA, [3]CHOC, Orange, CA

Purpose: Osteopontin (OPN) plays a role in Interferon signaling, an important pathway in SLE pathogenesis. *OPN* gene variants have been associated with SLE, and gender- and age-specific variability in circulating OPN protein levels have also been described. We aim to study OPN in pediatric SLE patients and their unaffected siblings.

Method: Genomic DNA and plasma were collected from 60 (48 female; 12 male) pediatric-onset SLE patients (age of SLE onset <21 years), 35 unaffected healthy siblings (23 female; 12 male), and 16 healthy unrelated pediatric controls (9 female; 7 male). All subjects were < 24 years of age at time of study. Plasma OPN protein levels were measured using ELISA and *OPN* SNP genotyping was performed using Taqman assays. Statistical analysis was performed using Student's t test or nonparametric Mann Whitney U.

Results: Plasma OPN protein levels were higher in unaffected siblings of pediatric SLE patients than in unrelated pediatric controls ($p = 0.006$). Increasing levels of OPN were detected in unrelated controls, unaffected siblings and SLE cases (ANOVA $p = 0.0006$; see figure). OPN levels of the discordant sibling pairs correlated with a Pearson γ value of 0.58 ($p = 0.0009$). Of all the pediatric SLE patients, plasma OPN protein levels were higher in the 12 males compared with the 48 females ($p = 0.01$). No gender difference was observed in plasma OPN protein levels in unaffected siblings of pediatric SLE patients or in unrelated healthy controls ($p = 0.5$ and 0.6, respectively). Male pediatric SLE cases with the known *OPN* rs9138 SLE-risk allele had increased OPN levels compared with females ($p = 0.03$; $n = 9$ and 34, respectively). This increase in OPN levels was not seen based on genotype in the unrelated male controls and unaffected male siblings.



Conclusion: Significant increases in plasma OPN protein levels were seen when comparing pediatric unrelated controls, unaffected siblings, female SLE and male SLE patients, with pediatric male SLE patients having the highest OPN plasma protein concentration. The presence of the *OPN* SLE-risk allele may partially explain the OPN plasma protein gender difference seen in pediatric SLE, but not the difference seen between siblings and controls. The potential role for plasma OPN as a biomarker to help assess autoimmune risk in siblings of pediatric SLE patients needs further study.

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Novel Autoantigen for Anti-Endothelial Cell Antibodies (AECA) Identified by Proteomics in Kawasaki Disease. Rie Karasawa[1], Tomohiro Kato[2], Mikiya Fujieda[3] and Kazuo Yudoh[1], [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]St.Marianna University School of Medicine, Kawasaki, Japan, [3]Kochi Medical School, Nankoku, Japan

Purpose: Anti-endothelial cell antibodies (AECA) are thought to be involved in pathophysiology of vasculitis, including Kawasaki disease (KD). However, target molecules of AECA have been poorly identified, which hampers understanding of roles of AECA in detail. We tried to detect and identify target proteins of AECA comprehensively by proteomics. Further, we investigated clinical importance of the identified autoantigens and their related proteins.

Methods: To detect endothelial cell-specific autoantigens for AECA, we separated proteins extracted from human umbilical cord vein endothelial cell (HUVEC) and HeLa cells respectively by 2-dimensional electrophoresis (2DE) and then transferred them onto membranes. By western blotting (WB) using serum samples from patients with vasculitis, we detected autoantigens that were positive only in the HUVEC samples but not in the HeLa cell samples. We next identified the detected proteins by peptide mass finger-printing (PMF) and characterized antigenecity by preparing recombinant autoantigens and antibodies to them.

Results: We have identified 63 proteins out of the 150 HUVEC-specific autoantigens recognized by serum samples from patients with vasculitis by PMF so far. One of the identified proteins was found peroxiredoxin2 (Prx2), an anti-oxidative enzyme. The autoantibodies to Prx2 were detected in 60% of the patients with KD, but not in healthy controls. Interestingly, the autoantibodies to Prx2 were detected in all the tested KD patients with coronary artery lesions. The antigenecity of Prx2 was found different from its related enzymes of Prx1 and Prx4. Indirect immunofluorecence staining revealed existence of Prx2 on the cell surface of HUVEC and WB using cell lysate proved expression of Prx2 not only in HUVEC but also in other endothelial cells (ECs), including human aortic endothelial cells and human coronary artery

endothelial cells (HCAEC) . The anti-Prx2 antibodies also increased various inflammatory cytokine secretion significantly, in particular IL-6. IL-6 and sICAM-1 secretion of ECs stimulated with serum samples of patients with high anti-Prx2 titers was detected. Further, 1DE-WB analysis using HCAEC-extracted proteins as the antigen source detected three bands (53, 44 and 35 kDa) specific for serum samples from KD patients with coronary artery lesions.

Conclusion: The autoantibodies to Prx2, which we found for the first time, would be a useful marker for KD. The anti-Prx2 autoantibodies may have a pathogenic role in Kawasaki disease via inflammatory cytokine production and inhibition of anti-oxidative activity of Prx2 by binding Prx2 on ECs.

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Importance of Fcg Rl&lll and CD11b in Susceptibility and Immune Response to CAWS Induced Coronary Angiitis /Aortitis. Ingrid Tomanova-Soltys[1], Joy Whitbred[1], Beverly Dahms[1], Kazuo Suzuki[2], Noriko Miura[3], Naohito Ohno[3], Robert Whitbred[4] and Nora G. Singer[1], [1]University Hospitals/Case Medical Center/Rainbow Babies and Children's Hospital, Cleveland, OH, [2]Graduate School of Medicine, Chiba University, Chiba, Japan, [3]Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan, [4]Cleveland State University, Cleveland, OH

Purpose: To identify critical cell type(s) and receptors involved in the susceptibility and pathogenesis of coronary angiitis and aortitis in a mouse model of human Kawasaki Disease (KD) induced by immunization with *Candida albicans* Water Soluble fraction (CAWS).

Method: 6-12 week old C57Bl/6 (wt) and FcgRI&III knockout (k/o) mice were immunized with a total dose of 4 mg CAWS intraperitoneally (I.P.). Mice were sacrificed on 3-49 days post immunization. Splenocytes were analyzed by flow cytometry. Hearts were dissected and frozen for H&E staining or immunostaining and imaged by confocal microscopy. Statistical analysis was performed using SPSS.

Results: Greater than 75% of wt mice developed coronary angiitis/aortitis 21-28 days post-CAWS immunization. H&E staining demonstrated inflammation of the proximal aorta and/or coronary arteries and appeared to contain a mixed cellular infiltrate of neutrophils and macrophages. Affected mice exhibited splenomegaly consistent with immune activation and increased numbers of splenocytes that expressed CD11b on their surface. Immunoflorescence staining of heart sections analyzed by confocal microscopy demonstrated the presence of CD11b+, CD11c+, and Gr-1+cells within the inflammatory infiltrate along with occasional B220/CD45R+, CD3+ and F4/80+ cells. In contrast to wt mice, mice that lacked FcgRI&III receptors were resistant to CAWS-induced immune activation, as evidenced by absence of splenomegaly, aortitis/angitis, or increased CD11b expression on splenocytes following immunization.

Conclusion: CAWS immunization induces mouse coronary arteritis, aortitis, and splenomegaly and is accompanied by altered immune populations, especially CD11b+ cells, in the spleen. Mice lacking FcgRI and III are resistant to coronary angiitis and lack evidence of CAWS-related immune activation, suggesting that the presence of FcgRI and III are necessary for development of the vasculitis phenotype, and that CD11b+ neutrophils and/or macrophages play a prominent role in the inflammatory process.

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Juvenile Dermatomyositis (JDM): Responders and Non-Responders to Medical Therapy Have Differential Genetic Profiles. Nicholas Geraci[1], Lauren M. Pachman[1], Gabrielle Morgan[1] and Yi-wen Chen[2], [1]Children's Memorial Research Center, Chicago, IL, [2]Children's National Medical Center, Washington, DC

Purpose: 1) To identify changes in gene expression profiles of muscle before and after therapy in children with juvenile dermatomyositis (JDM) and, 2) to compare the profiles of those children who responded to medical therapy with those did not.

Method: 8 patients with JDM (mean age at diagnosis (Dx), 6.7 ± 5.5 yrs, 4 females, all with disease duration > 2 months, 5 non-responders) enrolled after informed consent. All patients had an MRI guided open muscle biopsy (Bx) at Dx and a needle Bx after medical therapy (mean 78 ± 1.6months post-Dx). Gene expression profiles of Bx RNA from 4 patient muscle pairs were generated using Affymetrix Human

Genome U133 Plus 2.0 Array with Affymetrix MAS (Version 5.0, Affymetrix, CA). Using Genespring, the JDM samples were normalized to the median of the samples of the responders collected post-treatment. Only probe sets with at least one MAS 5.0 "present calls" across all profiles were retained. Weltch t-test and the Benjamini and Hochberg false discovery rate (5%) were used. Hierarchical clustering was then performed and a branch of genes that differentially responded to treatment was manually selected. The array data was validated by quantitative real-time PCR (qRT-PCR) of 4 additional patient pairs with Qiagen Quantitect primers for 4 genes, and Qiagen Quantifast SYBR Green PCR kits (Valencia, CA). Samples were analyzed on an Applied Biosystems 7500 Fast Real-Time PCR thermal cycling system (Foster City, CA). Expression data were analyzed by Ingenuity Pathway Analysis (IPA, Version 7.5, Redwood City, CA).

Results: Four JDM pairs displayed 182 positively present genes with differential expression in Affymetrix expression arrays. None of the vascular remodeling genes identified in a previous study of JDM disease duration (Chen, *et al.* 2008) displayed differential expression based on treatment response. 20 genes of interest (differentially expressed $\geq$ 2 fold between responders and non-responders at time of diagnosis or at later needle biopsies) were selected for further study based on IPA display. Among those genes were PTPN22 (2.3 to 2.5 fold upregulation before, after treatment in non-responders compared to responders), CPA3 (3.1 to 2.5), LTB (2.6 to 1.7), and CAMK2N1 (1.5 to 3.8). Similar expression patterns were obtained by qRT-PCR, validating microarray results. PTPN22 remained markedly upregulated, 15.4 fold post-treatment in the JDM non-responders compared to responders.

Conclusion: This study of JDM, the responders to conventional JDM therapy display differential gene expression patterns compared to non-responders, both at Dx and at follow-up. Many of those genes are involved in innate immunity. These data suggest that analysis of diagnostic biopsies might identify gene candidates for use as predictors of responsiveness to treatment of JDM, and potentially more effective interventions. Support: R01-AR48289 & Cure-JM

Disclosure: N. Geraci, None; **L. M. Pachman**, None; **G. Morgan**, None; **Y. W. Chen**, None.

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Familial Aggregation of Autoimmune Disease in Families of Children with Juvenile Dermatomyositis: Family History of Lupus Is Associated with Increased IFN-α. Timothy B. Niewold[1], Stephanie C. Wu[2], Mariel Smith[2], Gabrielle A. Morgan[2] and Lauren M. Pachman[3], [1]University of Chicago, Chicago, IL, [2]Children's Memorial Research Center, Chicago, IL, [3]Childrens Memorial Research Center, Chicago, IL

Purpose: Familial aggregation of autoimmune diseases likely reflects shared pathogenic factors between different diseases. Familial aggregation of autoimmunity has not yet been examined in juvenile dermatomyositis (JDM). Interferon alpha (IFN-α) is thought to be a pathogenic factor in a number of autoimmune diseases, including systemic lupus erythematosus (SLE) and JDM, and we have previously demonstrated familial aggregation of serum IFN-α.

Methods: Family histories were obtained from 304 families of children with JDM via 3 generation structured interviews upon first visit to the clinic and every 36 months thereafter, by the same person (LMP, IRB #2008-13590). Adopted children were excluded due to lack of biological family history. Rates of autoimmune disease in JDM families as reported by family members are compared with population rates from published epidemiological studies. Serum IFN-α was measured using a functional reporter cell assay in a subset of samples from children with JDM.

Results: Among the 304 families of children with definite/probable JDM, 68.4% were reported to have at least one member affected by an autoimmune disease, and 29.3% of families had three or more individuals affected by autoimmune disease across the three generations ($p=0.0049$ for an increase over population rates). The most common autoimmune diseases found in JDM families included thyroid disease, type I diabetes, rheumatoid arthritis, and systemic lupus erythematosus (SLE). In particular, 11.5% of JDM families had a family member affected by SLE, which is over 5 times the rate which would be expected in the general population (OR=5.86, $p=5x10^{-6}$). Serum IFN-α was measured in a subset of these children with JDM, and untreated subjects with a family history of SLE had higher serum IFN-α than those who did not ($p=0.045$).

Conclusion: We find familial aggregation of autoimmune diseases in JDM families, and in particular SLE is over-represented. Serum IFN-α is higher in children with JDM who have a family history of SLE, suggesting that IFN-α could be a familial pathogenic factor which is common to these two diseases.

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Evaluation of Serum Neopterin Level as a Diagnostic Marker of Hemaphagocytic Lymphohistiocytosis Syndrome (HLH). Maria F. Ibarra[1], Marisa Klein-Gitelman[1], Elaine Morgan[1], Maria Proytcheva[1], Christine Sullivan[2], Gabrielle Morgan[2], Lauren M. Pachman[2] and Maurice O'Gorman[1], [1]Children's Memorial Hospital, Chicago, IL, [2]Children's Memorial Research Center, Chicago, IL

Purpose: The diagnosis of HLH is challenging.The presentation in primary and secondary HLH can be atypical and/or all of the clinical and laboratory criteria not present. Neopterin (tetrahydrobiopterin) is synthesized by macrophages and dendritic cells and is a marker of inflammation that has been associated with cell mediated immunity in various diseases. Our hypothesis is that high levels of serum neopterin provide a sensitive and specific diagnostic marker in patients suspected of HLH.

Methods: Demographic, clinical and laboratory characteristics were summarized by retrospective chart review of patients seen at CMH between January 2000 and May 2009 with a diagnosis of HLH (primary or secondary). Serum neopterin levels were measured using a competitive immunoassay with a normal range of <10 nmol/L. Receiver operating characteristic (ROC) analysis was used to examine the tradeoffs in sensitivity and specificity of neopterin as a diagnostic test. In the ROC analysis, we used neopterin levels from the HLH group and from a control group of 50 untreated active juvenile dermatomyositis (JDM) patients (who have neopterin levels measured routinely to assess disease activity) to assess various cutoffs in the tradeoff between sensitivity and specificity. The area under the curve (AUC) from the ROC analysis was also measured to assess the accuracy of neopterin levels as a diagnostic test of HLH. For HLH patients, the association between serum neopterin levels and biochemical data at diagnosis, three and six months was determined by repeated measures modeling.

Results: 17 patients with secondary and 2 patients with primary HLH were identified (mean age: 9.7 years, 53% male, 47% female) and compared with 50 JDM subjects (mean age: 7.5 years, 26% male, 74% female). A cutoff value of 46 nmol/L resulted in a sensitivity of 89% and a specificity of 81% for a diagnosis of HLH. Values above 46 gave lower sensitivity but higher specificity and values below 46 gave higher sensitivity but lower specificity. Area under the curve was 0.92 indicating high accuracy for neopterin as a diagnostic test of HLH. Neopterin levels were associated with ferritin (p=0.0007) and D-dimer levels (p=0.018), and inversely with platelet count (p= 0.034) and fibrinogen (p=0.035).

Cutoff for Neopterin (nmol/L)	**Sensitivity**	**Specificity**
59	61 %	100 %
56	67 %	95 %
51	72 %	86 %
46	89 %	81 %
43	94 %	76 %
37	100 %	64 %

Table 1: ROC results

Conclusion: All of the HLH patients had neopterin levels at least three times higher than the normal range. Compared to patients with active JDM, elevated serum neopterin levels were a very sensitive and specific marker for HLH. Future studies are aimed at confirming serum neopterin level as a new biomarker for the early diagnosis of HLH, and a marker of disease activity and response to therapy.

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Characterization of the Inflammatory Skin Lesions in NOMID Before and After Treatment with Anakinra. P. Aubert[1], H. Mitsui[2], M. Suárez-Fariñas[2], L. Johnson-Huang[2], K. Pierson[2], G. Dolan[1], J. Krueger[2], I. Novitskaya[2], I. Coats[2], J. Estes[1], E. Cowen[1], Nicole Plass[3], Raphaela Goldbach-Mansky[3] and MA Lowes[2], [1]NIAMS/NIH, Bethesda, MD, [2]Rockefeller U, New York, NY, [3]NIH | NIAMS, Bethesda, MD

Purpose: Neonatal-onset multisystem inflammatory disease (NOMID) is the most severe phenotype in the spectrum of "autoinflammatory" diseases caused by de novo mutations in the cold-induced autoinflammatory gene, *CIAS1 (also called NLRP2 or NALP3).* This mutation leads to increased assembly of the IL-1β processing NLRP3 or NALP3 inflammasome, which results in IL-1β activation and secretion. Patients with NOMID present with systemic and organ specific autoinflammation of the joints, skin and central nervous system and respond dramatically to treatment with IL-1 blocking agents. This work characterizes the immune pathways downstream of IL-1 in the skin in patients with NOMID treatment.

Method: Paired lesional and non-lesional pre-treatment skin biopsies and post treatment skin samples (n=14) were studied by immunohistochemisty and genomics, and compared to normal skin before and after treatment with anakinra (IL-1RA, Kineret®).

Results: Abundant neutrophils clearly distinguish lesional and nonlesional pretreatment skin, but other skin infiltrating leukocytes, $CD3^+$ T cells, HLA-DR^+ cells, $CD11c^+$ dermal dendritic cells (DCs) and $CD163^+$ macrophages were increased to similar levels in non-lesional and lesional skin compared to normal skin. $CD11c^+$ dermal DCs and $CD163^+$ macrophages expressed activated caspase-1, the enzyme that converts pro-IL-1b into its bioactive form. Gene expression profiling showed that only 64 probe sets were differentially expressed between lesional and non-lesional skin, compared to 2609 probe sets that were different comparing lesional and normal skin. There was marked IL-17 immunostaining in lesional dermis compared to normal skin. Neutrophil attracting chemokine mRNA for CXCL8/IL-8 and CXCL2, as well as CCL20, a chemokine for $CCR6^+$ DCs and T cells, were increased in lesional tissue, compared to non-lesional skin. With successful treatment with the IL-1 receptor antagonist (anakinra, Kineret®), neutrophils disappeared, and $CD11c^+$ DCs reduced, supporting their role as key pathogenic leukocytes.

Conclusion: Tissue macrophages and inflammatory myeloid dermal DCs which are increased in clinically normal looking and "urticarial" NOMID skin are capable of producing bioactive IL-1b likely amplifying the IL-1 response locally. Downstream pathways suggest increased IL-17 production in lesional dermis, which may induce the production of CXCL8/IL-8 and CXCL2, two chemokines known to recruit neutrophils, and CCL20, associated with the recruitment of $CCR6^+$ T cells and DCs. This study describes a stepwise recruitment of inflammatory pathways in NOMID skin and enhances our understanding of the histological and clinical phenotype of skin lesions in NOMID. The characterization of specific inflammatory pathways in the skin in NOMID, a disease with a genetically defined defect in IL-1 production, may help us to understand the organ specific immune responses in other inflammatory skin conditions that are genetically more complex.

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Long-Term Follow up of Children with the Low Penetrance R92Q Mutation of TNFRSF1A Gene. Maria Antonietta Pelagatti[1], Antonella Meini[2], Roberta Caorsi[1], Francesca Capra[2], Silvia Federici[1], F. Zulian[3], Alberto Tommasini[4], Alberto Martini[1] and Marco Gattorno[1], [1]UO Pediatria II, Istituto G. Gaslini, Genoa, Italy, [2]Unità di Immunologia e Reumatologia Pediatrica, Spedali Civili e University of Brescia, Brescia, Italy, [3]University of Padova School of Medicine, Padova, Italy, [4]IRCCS Burlo Garofalo, Trieste, Italy

Purpose: To analyze the actual impact of R92Q mutation on *TNFRSF1A* gene in children with periodic fever in comparison with TRAPS patients with structural mutations and periodic fever of unknown origin (PFAPA).

Methods: The extracellular region the *TNFRSF1A* gene was analyzed in 720 consecutive children with periodic fever by means of denaturing high-performance liquid chromatography (DHPLC) and DNA sequencing. The following patients were included in the study: children carrying TNFRSF1A molecularly diagnosed from 2002 to 2009 and routinely followed by centers of Pediatric Rheumatology. Pts were classified in 2 groups according to: 1) the presence of a structural mutations (cysteine or T50M) or 2) the presence of an R92Q substitution. 130 PFAPA patients (genetically negative for MVK, TNFRSF1A, MEFV) were used as disease-controls. Data on the follow-up were collected during routinely control visits or after a phone call to the family. The following variables were analyzed before and at follow-up: n. of episodes of fever/year, duration of the episodes, frequency and intensity of the clinical manifestations. Data from 78 unselected genetically-negative PFAPA patients were also analyzed as disease controls. The Child Health Questionaire (CHQ-PF 50) was used to access the health related quality of life; the results were compared with the ones obtained from an healthy patients control group of 315 healthy children (52.2% female), with a mean (SD) age of 11.2 (3.8) years.

Results: At baseline the TRAPS patients showed a poorer health-related quality of life than healthy children and R92Q patients , with a major impact on physical concepts ($p < 0.001$) in respect to psychosocial concepts. Data on 10 TRAPS patients with structural mutations of *TNFRSF1A* and 20 patients with the R92Q substitution are available. The mean follow-up is 8.7 rears (range 4.4-15.5), 5.6 years (range 2-13) for R92Q patients and 4.9 years (range 1-13 years) for PFAPA patients. At follow-up 32% of R92Q patients and 52% of PFAPA patients displayed a complete resolution of fever episodes. 22% of R92Q patients and 33% of PFAPA patients were improved. Persistence of fever episodes was observed in 20% of both R92Q and PFAPA patients. Conversely, all patients with structural mutations had a stable or worsening disease course and biological tretament (Etanercept or Anakinra) was needed in 5 patients. One R92Q patient developed a chronic disease course (persistent elevation of acute reactants, arthralgia and myalgia), requiring biologic treatment with Anakinra with a complete control of inflammation.

Conclusion: These preliminary data suggest that patients with R92Q mutation of *TNFRSF1A* present a disease course similar to that observed in PFAPA patients. However, a small subgroups of R92Q patients display the persistence of symptoms such as abdominal pain, arthralgia and myalgias, similar to what observed in TRAPS patients with structural mutations.

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1328

Genetic Regulation of Serum IFN-α in Juvenile Dermatomyositis. Timothy B. Niewold[1], Silvia N. Kariuki[1], Gabrielle A. Morgan[2], Sheela Shrestha[3] and Lauren M. Pachman[4], [1]University of Chicago, Chicago, IL, [2]Children's Memorial Research Center, Chicago, IL, [3]Children Memorial Research Center, Chicago, IL, [4]Childrens Memorial Research Center, Chicago, IL

Purpose: We have demonstrated that high serum IFN-α is common in children with juvenile dermatomyositis (JDM). In previous work in systemic lupus erythematosus (SLE), serum IFN-α is increased in the setting of particular genetic risk factors. We examined genetic polymorphisms linked to high IFN-α in SLE patients in a cohort of JDM patients to determine whether a similar phenomenon was present in JDM.

Methods: Genomic DNA from 24 children with JDM was genotyped at SNPs in the OPN, IRF5, and PTPN22 genes which have been linked to high serum IFN-α in SLE patients. The cohort consisted of 20 females and 4 males, with a mean age of 5 years old. Data regarding the TNF-α -308 promoter polymorphism were available for these subjects and included in the analysis (21% risk allele carriers). Serum IFN-α was measured using a sensitive reporter cell assay.

Results: The TNF-α -308 allele was independently associated with increased serum IFN-α in the JDM cohort ($p=0.04$). Surprisingly, a SNP in the promoter region of OPN showed evidence for statistical interaction with the TNF-α -308 allele ($p=0.014$), and subjects carrying both of these alleles formed the highest IFN-α subgroup. There was no evidence for association between serum IFN-α and the IRF5 SLE-risk haplotype or the autoimmune disease-associated allele of PTPN22 in our cohort.

Conclusion: In this preliminary study we find evidence for association of the TNF-α -308 allele and increased serum IFN-α in children with JDM. This is interesting as we find that serum IFN-α and TNF-α levels are correlated in simultaneous samples in JDM. The finding of an interaction between SNPs in the promoter regions of OPN and TNF requires further validation, but replicated would suggest a pathogenic synergy between these two loci.

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Lymphocyte Subset Analysis and Influenza Specific CD8 Responses in Children with Juvenile Idiopathic Arthritis On Immunosuppressive Medications. James W. Verbsky[1], Gwen Werra[2], Brandon Edwards[2], Jenny Grewal[2], Lance Relland[2], Jack Gorski[3] and Calvin B. Williams[2], [1]Medical College of WI, Milwaukee, WI, [2]Medical College of Wisconsin, Milwaukee, WI, [3]Blood Center of Wisconsin, Milwaukee, WI

Purpose: Infectious pathogens can adversely affect patients with Juvenile Idiopathic Arthritis due to their disease states as well as the immunosuppressive medications they are taking. We have analyzed the peripheral blood lymphocyte profiles of patients with JIA to determine if differences exist from healthy controls. We have also analyzed the ability of these patients to generate antigen specific T cells responses to influenza virus.

Methods: Peripheral blood from 48 HLA-A2 positive patients with JIA (pauciarticular, polyarticular, spondyloarthropathy, and systemic JIA) was longitudinally analyzed by flow cytometry to determine CD4, CD8, NK, T regulatory(Treg) and B cells profiles as well as the expression of the cytotoxic molecules granzyme A(GrzmA), granzyme B(Grzm B), and perforin. The ability to generate antigen specific CD8 cells specific for influenza A was determined by culture of PBMCs with the M1(58-66) peptide.

Results: No differences in CD4, NK, or Treg cells were detected between the different diseases. B cells and CD8 cell percentages were significantly decreased in patients with systemic JRA. There was no difference in the percentage of CD4, CD8, or NK cells expressing the cytotoxic molecules Grzm A, Grzm B, or perforin. When the effect of the immunosuppressant medications was considered, a significant increase in CD4 cells expressing Grzm B was detected in patients taking an anti-metabolite and TNF blockade. Pediatric patients were able to generate antigen specific CD8 cells specific for influenza that was unaffected by treatment with immunosuppressive medication.

Conclusion: Lymphocyte profiles are similar in JIA with the exception of systemic JIA where B and CD8 cells are decreased, likely reflecting the inflammatory state of these patients. Lymphocyte profiles and cytotoxic molecule expression was largely unaffected by immunosuppressive medications with the exception of patients taking combination anti-metabolite and anti-TNF therapies where elevated Grzm B expressing CD4 cells was detected. This could represent a potential biomarker for severe disease. Finally, immunosuppressant treatment of patients with JIA had no effect on the ability to generate influenza specific T cell responses *in vitro*, indicating that the ability to generate immune responses is relatively intact.

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ACR/ARHP Poster Session C

Cytokines, Mediators, and Gene Regulation II

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Autoantigen TRIM21/Ro52 Contributes to Suppression of NF-κB-Dependent Cytokine Expression in Fibroblasts. Ryusuke Yoshimi[1], Tsung-Hsien Chang[1], Hongsheng Wang[2], Toru Atsumi[1], Herbert C. Morse III[2] and Keiko Ozato[1], [1]National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD

Purpose: The tripartite motif (TRIM) family member, TRIM21, is an autoantigen known as Ro52/SS-A, which is recognized by antibodies in sera of patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Although it has been shown that TRIM21 is an E3 ubiquitin ligase for IRF3 and IRF8 that functions in both innate and acquired immunity, its physiological role *in vivo* has remained unclear. Here we investigated the *in vivo* function of TRIM21 using a gene disruption strategy.

Methods: We generated *Trim21*$^{-/-}$ mice with the *Trim21* gene replaced by an *EGFP* reporter. The populations of leukocyte subsets and detailed expression pattern of TRIM21 were investigated using *Trim21*$^{-/-}$ mice. We stimulated immune cells from *Trim21*$^{+/+}$ and *Trim21*$^{-/-}$ mice and tested cytokine induction, cell proliferation and antibody production. Mice were immunized by specific antigen for *in vivo* Ig production. We also performed promoter analyses using a NF-κB-driven luciferase reporter, ubiquitylation assays for IRF3 and IRF8 and quantitative RT-PCR for gene expression.

Results: *Trim21*$^{-/-}$ mice were born with the expected Mendelian ratio and young adult mice showed no gross abnormality. The populations of leukocyte subsets in thymus, spleen and lymph nodes were also normal in *Trim21*$^{-/-}$ mice. EGFP expression analyses revealed that *Trim21* was widely expressed in many tissues, with the highest levels in immune cells. Studies of *Trim21*$^{-/-}$ embryonic fibroblasts demonstrated that TLR-mediated induction of proinflammatory cytokines, including IL-1β, IL-6, TNFα and CXCL10, was consistently upregulated relative to wild-type cells. Reporter analyses revealed that TLR-mediated NF-κB activation was higher in *Trim21*$^{-/-}$ cells than in wild-type cells, accounting for their enhanced cytokine expression. However, functional analyses of immune cells from *Trim21*$^{-/-}$ mice demonstrated no abnormalities in their composition or function, even though ubiquitylation of IRF3 and IRF8 was impaired. Consistent with possible redundancies in TRIM21-mediated activities, we found that a number of TRIM family members were upregulated in *Trim21*$^{-/-}$ cells.

Conclusion: TRIM21 functions as a negative regulator in NF-κB-dependent proinflammatory cytokine responses in fibroblasts. It may contribute to regulation of inflammation in the pathogenesis of SLE and SS.

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Human S100 Proteins Differentially Regulate Pro-Inflammatory Cytokine Release and Cell Migration. Bo Chen[1], Jane Tian[1], Yan Chen[1], Chew-Shun Chang[1], Partha Chowdhury[1], Anthony J. Coyle[1], Ronald Herbst[2] and Gary Sims[1], [1]MedImmune, Gaithersburg, MD, [2]MedImmune, LLC, Gaithersburg, MD

Purpose: The S100 family of calcium-binding proteins regulates a variety of intracellular functions including signaling, trafficking, transcription and homeostasis. S100 proteins released from activated neutrophils and macrophages also play an important role in innate immunity by mediating local inflammation through the induction of pro-inflammatory cytokines and the recruitment of immune cells. S100A12 (EN-RAGE), S100A8, S100A9, and S100B have been implicated in a variety of human diseases including cancer, neurodegenerative disorders, cardiomyopathies, inflammation and autoimmunity. In this study, we have systematically examined S100 proteins for the signaling pathways responsible for pro-inflammatory cytokine induction and cell migration.

Method: Cells were stimulated with human S100 proteins for 16 hrs with or without anti-TLR4 or anti-RAGE Abs. Supernatants were collected and IFN-g, IL-6, IL-1b and TNFapro-inflammatory cytokine levels were measured using Meso Scale Discovery. Cell migration was assessed using a 96-well ChemoTX system. Migration of cells to S100 proteins was enumerated by flow cytometry.

Results: The potency of S100 proteins to induce cell migration and proinflammatory cytokines differed. Antibodies targeting RAGE and TLR4 signaling pathways differentially inhibited S100-mediated pro-inflammatory cytokine induction and cell migration. These data were confirmed using wild-type and knock-out mice.

Conclusion: These results suggest S100 proteins use distinct signaling pathways to induce cell migration and proinflammatory cytokine release. Antagonists targeting RAGE and TLR4 pathways can be used to dissect the relative functions of S100 proteins in models of inflammatory disorders to assess their potential therapeutic benefit.

Disclosure: B. Chen, MedImmune, 3 ; **J. Tian**, MedImmune, 3 ; **Y. Chen**, MedImmune, 3 ; **C. S. Chang**, MedImmune, 3 ; **P. Chowdhury**, MedImmune, 3 ; **A. J. Coyle**, MedImmune, 3 ; **R. Herbst**, MedImmune, 3 ; **G. Sims**, Medimmune, 3 .

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Urinary TWEAK as a Biomarker of Lupus Nephritis. Noa Schwartz[1], Tamar Rubinstein[1], Linda C. Burkly[2], Christopher E. Collins[3], Lihe Su[2], Bernard S. Hojaili[1], Meggan C. Mackay[4], C. Aranow[5], William Stohl[6], Brad H. Rovin[7], Jennifer S. Michaelson[2] and Chaim Putterman[1], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Biogen Idec, Cambridge, MA, [3]Washington Hospital Ctr, Washington, DC, [4]The Feinstein Institute for Medical Research, Manhassett, NY, [5]The Feinstein Institute, Manhasset, NY, [6]Univ Southern California, Los Angeles, CA, [7]Ohio State University Medical Center, Columbus, OH

Purpose: TNF-like weak inducer of apoptosis (TWEAK) has been implicated as a mediator of chronic inflammatory processes via prolonged activation of the NF-κB pathway in several tissues, including the kidney. We have recently demonstrated an important role for TWEAK signaling in the pathogenesis of nephritis in an animal model of SLE. Therefore, renal TWEAK production, as reflected by urinary TWEAK (uTWEAK) levels, may serve as an indicator for lupus nephritis (LN) status and activity – providing a tool to non-invasively monitor the progression of LN.

Method: Multicenter cohorts of LN patients and several disease (non-LN SLE, rheumatoid arthritis, osteoarthritis and non-SLE renal disease) and healthy control groups were recruited for cross-sectional and longitudinal analysis of uTWEAK as a potential biomarker of LN. Non-parametric studies were performed to compare uTWEAK levels in the different groups analyzed, as well as for correlating between disease activity and uTWEAK levels. Area-under-the-curve (AUC) calculations of non-parametric receiver operating characteristic (ROC) curves were used to evaluate biomarker capabilities in distinguishing between specific groups of patients. Logistic regression was performed on the cross-sectional data and odds ratio (OR) was derived. Longitudinal data were analyzed using repeated measures ANOVA, followed by Dunn's post-hoc testing for non-parametric data, as well as a linear mixed-effects model examining the relationship between uTWEAK levels and patients' disease activity over time.

Results: uTWEAK levels were significantly higher in LN patients than in non-LN SLE patients and other disease control groups (p=0.039), with neither renal disease nor SLE being lone predictors of high uTWEAK levels. uTWEAK was better at distinguishing between LN and non-LN SLE patients than anti-DNA antibodies and complement levels, with AUC of 0.724 (p<0.001). Furthermore, high uTWEAK levels predicted LN in SLE patients with OR of 7.36. Of note, uTWEAK levels peaked during LN flares, and were significantly higher during the flare than at 4 and 6 months prior and following the flare event. Furthermore, we found a significant association between uTWEAK levels in SLE patients and their renal disease activity over time (p=0.008).

Conclusion: High uTWEAK levels are indicative of LN, as opposed to non-LN SLE and other healthy and disease control populations, and reflect renal disease activity in longitudinal followup. Thus, our study further supports a role for TWEAK in the pathogenesis of LN, and provides strong evidence for uTWEAK as a candidate clinical biomarker for LN.

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Nerve Growth Factor Differential Effect On Toll-Like Receptor-Mediated Cytokine Production in Human Monocytes Is Due to Changes in p75-NTR/Trk A Receptor Ratio. Luisa Bracci-Laudiero[1], Giusy Prencipe[2], Raffaele Strippoli[2], Gaetana Minnone[2], Loredana De Pasquale[2], Stefania Petrini[2] and Fabrizio De Benedetti[2], [1]Bambino Gesú Children Hospital and INMM-CNR, Rome, Italy, [2]Bambino Gesú Children Hospital, Rome, Italy

Purpose: Neutralization of the neurotrophin Nerve Growth Factor (NGF) has recently emerged as a potential treatment of pain in humans. In normal condition NGF is ubiquitously present in the organism. However, NGF levels are markedly up-regulated in inflamed tissues, including joints of patients with chronic arthritis. Although immune cells are known to express NGF receptors, TrkA and p75-NTR, it is not clear how NGF levels affect immune cell activity during the inflammatory response. The aim of our study was to investigate NGF effects on cytokine production induced by pathogen-associated molecular patterns in human monocytes.

Method: Using peripheral blood monocytes, purified by Percoll gradient, we investigated the NGF effects on human monocytes after Toll-like receptor (TLR) activation. To mimic the physiological condition in which cells are constantly exposed to NGF, monocytes were pre-incubated overnight with NGF before adding TLR ligands. To mimic the inflammatory condition in which there is an increase in NGF

concentration, monocytes were stimulated with TLR ligands and NGF was added either at same or at later times. The expression of NGF receptors and TLRs, the activation of signalling pathways and the synthesis of IL-6 and IL-1b were evaluated using real-time PCR, western blot, flow cytometry and ELISA.

Results: Pre-incubation with NGF caused an enhanced response to TLR ligands (LPS, LTA, PAM) with a two-fold NGF dose-dependent increase in IL-6 production. NGF alone did not have any effect. The NGF pre-treated cells showed an up-regulation of TLR-2 expression after TLR2 ligand addition. The addition of NGF at the time of or after TLR stimulation induced a two-fold reduction in IL-6 and IL-1b synthesis and a down-regulation of TLR expression.

These dual, apparently opposite, effects of NGF on monocytes appear to be related to a modified ratio of p75-NTR/TrkA receptor expression. After overnight incubation with NGF a marked increase in p75-NTR/TrkA ratio is present. It is known that p75-NTR signals through the NF-kB pathway, and we found a marked increase in nuclear NF-kB translocation in monocytes preincubated with NGF and stimulated with TLR ligands. On the contrary a marked up-regulation of TrkA expression was found following TLR stimulation suggesting that the inhibitory effect of NGF on cytokine production may depend on TrkA signalling.

Conclusion: NGF is part of a physiological mechanism regulating inflammatory response. NGF can amplify or down-regulate monocyte activation via TLRs depending on the differential expression of NGF receptors with subsequent changes in the p75-NTR/TrkA ratio. A better knowledge of the NGF effects, via interaction with the two NGF receptors, on inflammatory response may help to identify proper targets of novel anti-inflammatory analgesic approaches.

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Reduced IL-7 Serum Titres in Relation with Symptom Duration Are Associated with Progression towards Rheumatoid Arthritis in Less Than 6 Months Inflammatory Arthritis. Vincent Goëb[1], Rich Cuthbert[1], Elizabeth Horner[1], Sarah Churchman[1], Laura C. Coates[2], Helena Marzo-Ortega[2], Jackie Nam[1], Edith Villeneuve[1], Ed Vital[1], Philip G. Conaghan[3], Patrice Fardellone[4], Xavier Le Loët[5], Paul Emery[6], Olivier Vittecoq[7] and Frédérique Ponchel[1], [1]Leeds University, Leeds, United Kingdom, [2]University of Leeds, Leeds, United Kingdom, [3]LIMM, Leeds, United Kingdom, [4]CHU d'Amiens, France, [5]CHU Rouen - INSERM U 905, France, [6]Leeds General Infirmary, Leeds, United Kingdom, [7]Rouen, France

Purpose: Early diagnosis of RA is crucial for initiation of therapy in order to obtain sustained remission. IL-7 is a pleiotropic cytokine that play a central role in the development and maintenance of T cells, and has recently been associated with RA. Injection of IL-7 in a collagen induced arthritis model aggravated the disease and the therapeutic value of IL-7 blocking antibodies has also been reported in two separate animal models. We showed that serum circulating levels of IL-7 are reduced in established RA patients. We hypothesised that this reduction may have predictive diagnostic value.

Our objectives are to determine whether IL-7 titres in serum will distinguish patients who will evolve into RA from early inflammatory arthritis (EIA), and whether they are correlated with clinical parameters of disease activity, structural radiographic damage, shared epitope or autoantibody status and titres.

Method: 359 patients with EIA (<6 months duration) were followed up for 2 years and diagnosed according to ACR criteria. 31 were lost to follow up and 77 diagnosed with other forms of musculoskeletal disease (reactive arthritis, osteoarthritis, lupus, connective tissue diseases etc…). 65 controls and 183 patients with established disease were also assessed. IL-7 levels in serum were determined by ELISA.

Results: Patients with EIA were diagnosed as having RA (n=162,), undifferentiated arthritis (UA, n=61), ankylosing spondylitis (AS n=12) or psoriatic arthritis (PsA n=16). IL-7 levels at recruitment were reduced coared to healthy controls (n=67, median 13.8 pg/ml) in RA (median 11.5 $P<0.001$), PsA ($P=0.012$ median 11.1) and UA (median 11.8$P=0.003$) but not in AS or osteoarthritis patients (n=19). We also confirmed reduction in IL-7 levels between healthy controls and established RA (n=106 median 7.9 $p<0.001$), AS (n=56 median 10.1 $p=0.001$) or PsA (n=21 median 7.8 $p=0.001$). There was no correlation between IL-7 titres and disease activity score (DAS), CRP, rheumatoid factor (RF), anti-CCP and *HLA*-SE status at recruitment . The presence of erosions at recruitment was also not associated with IL-7 in early RA. Importantly, IL-7 levels were inversely correlated with symptoms duration at presentation in less than 6 months RA ($R= -0.513$, $P<0.001$), but not in AS or PsA.

Conclusion: Our data demonstrate decrease levels of IL-7 across the inflammatory disease continuum. furthermore, no relationship between IL-7 titres and disease activity, blood inflammation, *HLA*-SE and auto-antibodies in early RA was observed. Further analysis is needed to establish the added value of IL-7 over other parameters in predicting evolution to RA, particularly in CCP negative patients.

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Role of the Th17 Phenotypic Differentiation in the Persistence of Early Arthritis. Elena Frati[1], Renato De Stefano[1], Fernando Nargi[1], Caterina Baldi[1], Luana Menza[1], Adriano Spreafico[2], Federico Chellini[2] and Mauro Galeazzi[2], [1]Azienda Ospedaliera Universitaria Senese, Siena, Italy, [2]U,O.C. Reumatologia, Siena, Italy

Purpose: The prevalent phenotypic differentiation toward Th17 instead of the phenotypic differentiation toward the cells Treg may be a possible pathogenetic mechanism for a chronic inflammatory process, otherwise destined to the auto-resolution.

Method: We conducted an investigation on a group of 57 patients with early arthritis to verify if the serum levels of cytokines, able to express a prevailing phenotypic differentiation of naive cells TCD4 + to the line Th17, may constitute potential biomarkers predictive of conversion of an early arthritis in early rheumatoid arthritis. All the patients, under basal conditions, were referred to a drawing of a blood sample stored immediately at -80°C to be subsequently used for determining, through a Bio-Plex Protein System, the serum level of IL-12, INFγ, TGF-ß, IL-17, IL-23, IL-6. After 6 months from the beginning of the arthritic symptoms, all the patients have been submitted to a new clinical, biohumoral and instrumental evaluation and they were inserted in 3 fundamental categories (auto-resolution, persistent idiopathic undifferentiated arthritis or rheumatoid arthritis, persistent differentiated arthritis not rheumatoid).

Results: Serum levels of the various cytokines appear independent from the age of the patients and from the level of the clinical-biohumoral parameters of inflammation, such as VES, number of tender and swollen joints, the DAS28. In the group of patients with a persistent idiopathic undifferentiated arthritis, there is a statistically significant increase of serum levels of the IL-17, IL-6 and IL-23. There is a statistically significant correlation among the serum levels of the IL-17 and the serum levels of the IL-23 ($r = 0.62$, $p = 0.0098$) and among the serum levels of the IL-17 and serum levels IL-6 ($r = 0.51$, $p = 0.039$). In the group of patients with idiopathic persistent undifferentiated arthritis emerge 2 well separate subgroups. One group characterized by serological markers of autoimmunity, rheumatoid factor and anti-CCP, that show a significant increase in the serum levels of the IL-6, but also of the IL-17 and of the IL-23. The second group, seronegative, shows contrarily an increase of the serum levels of the IL-6, an increase of the Il-17 in smaller measure, while the serum levels of IL-23 are similar to those found in the patients with autorisolution of the arthritis.

Conclusion: Results of our study would seem to point out that the prevailing phenotypic differentiation of the lymphocytes T-CD4 + toward the Th17 constitutes a pathogenetic line which is involved in the development of an idiopathic persistent undifferentiated arthritis, at least in those forms associated with the presence of biomarkers of autoimmunity such as rheumatoid factor and anti-CCP. In this group of patients, such phenotypic differentiation appears sustained by the IL-6 but especially by the IL-23.

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B and T Lymphocyte Attenuator Regulates TCR Associated Transcription Factors. Brian Greenberg[1], John Sedy[2] and Carl F. Ware[2], [1]UCSD Medical Ctr, La Jolla, CA, [2]La Jolla Institute for Allergy and Immunology, La Jolla, CA

Purpose: BTLA (B and T Lymphocyte Attenuator) is a member of the Ig superfamily that interacts with herpesvirus entry mediator (HVEM), a TNF receptor family member. Crosslinking of BTLA by HVEM results in phosphorylation of its cytoplasmic tyrosine residues and association with phosphatases SHP-1 and SHP-2. Cellular effects include attenuated TCR (T cell receptor) induced cell proliferation and cytokine production (Sedy, 2005). Additionally, a SNP (C800T) resulting in an amino acid change (P267L) in the cytoplasmic tail has been described and associated with rheumatoid arthritis (Lin, 2006). In B-cells, BTLA crosslinking attenuates Syk, BLNK and PLC-γ

phosphorylation upon BCR stimulation (Vendel, 2009). The targets of BTLA associated phosphatases in T cells are not known nor is it known whether the targets are proximal or distal in the TCR signaling cascade.

Methods: The T cell line (Jurkat) was used as a model to study BTLA function. BTLA is expressed on Jurkat cells. To enhance BTLA signaling Jurkat cells were transduced by retrovirus or electroporation to over express human BTLA. For IP and western blot experiments, cells were stimulated with anti-CD3-HVEM:Fc coated beads for 5 minutes before lysis. In other experiments, luciferase reporters specific for AP-1, NFκB, NFAT or IL-2 were co-transfected. These cells were stimulated with soluble α-CD3 (5 μg/ml), α-CD28 (5 μg/ml) and either α-BTLA (5 μg/ml) or HVEM:Fc (10 μg/ml) for 6 to 24 hours depending on the specific reporter construct.

Results: TCR activation with HVEM:Fc and α-CD3 coated beads down-regulated tyrosine phosphorylation as detected in whole cell lysates. Under the same stimulation conditions, immunoprecipitation with α-BTLA (clone 6F4) followed by western blot analysis demonstrated SHP-1 and SHP-2 co-precipitation. CD3 stimulation alone did not lead to SHP-1 or SHP-2 recruitment. Incubation with either HVEM:Fc or α-BTLA, in the setting of TCR activation, down-regulated the activity of multiple TCR-related transcription factors. AP-1 activity was reduced by 25% with HVEM:Fc, and NFκB activity was reduced by 53% with α-BTLA and by 66% with HVEM:FC. The IL-2 specific reporter was similarly inhibited showing a 65% reduction with HVEM:Fc and an 80% reduction with α-BTLA. Activity of NFAT was decreased by 30% with BTLA transfection alone. Treatment with HVEM:Fc or α-BTLA further decreased the signal by 30%. In contrast, transfection of BTLA lacking the cytoplasmic domain resulted in increased activation of NFAT by 50%. The function of BTLA with a leucine at residue 267 was also tested. There was no significant difference in IL-2 attenuation in cells transfected with wild-type BTLA compared to those with the SNP or equal quantities of both (heterozygous).

Conclusion: These results support the hypothesis that BTLA recruits phosphatases SHP-1 and SHP-2 when crosslinked and functions to decrease CD3 induced phosphorylation. The ability of BTLA to down-regulate the major TCR related transcription factors argues that its direct target is proximal in the TCR signaling cascade.

Disclosure: B. Greenberg, None; **J. Sedy**, None; **C. F. Ware**, None.

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Enriching for Sialylated IgG Increases the Inhibition of Interferon-Alpha Production by Human Plasmacytoid Dendritic Cells in Response to TLR7 and TLR9 Activation. Alice E. Wiedeman[1], Deanna M. Santer[1], Mary Bach[1], Fabian Käsermann[2], Sylvia Miescher[2] and Keith B. Elkon[1], [1]University of Washington, Seattle, WA, [2]CSL Behring, Bern, Switzerland

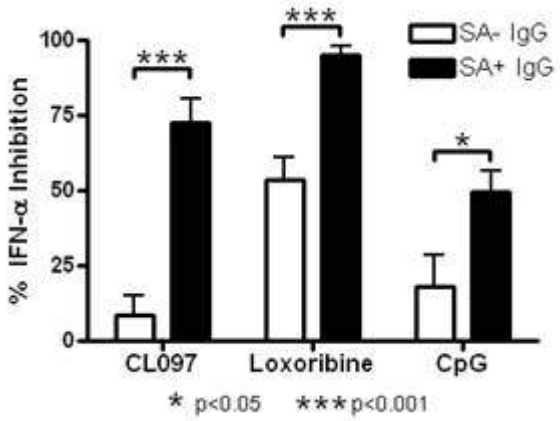
Purpose: IgG in the form of intravenous immunoglobulin (IVIg) has been used as an anti-inflammatory agent in multiple autoimmune diseases. Recent studies reported that it is the small fraction of sialylated IgG in human IVIg preparations that attenuates arthritis or immune thrombocytopenia. However, these studies were performed across species (human IgG injected into mouse models of disease). Our goal was to study the importance of the sialylated subset of IVIg in the inhibition of the inflammatory response by *human* cells stimulated with TLR agonists.

Method: Human IVIg preparations were enriched (SA+, 7- to 10-fold) or depleted (SA-, 2- to 5-fold) of the sialylated subset by lectin affinity chromatography. All preparations had < 0.1EU/mL endotoxin. For cell binding experiments, SA+ and SA- IgG were labeled with biotin. PBMC were isolated from whole blood of healthy individuals, cultured overnight in the presence of TLR7 (Loxoribine, CL097) or TLR9 (CpG) agonists with or without SA+ or SA- IgG at two doses (0.5 and 5 mg/mL). In certain experiments, monocytes were depleted from PBMC using CD14 magnetic beads. Supernatants were collected 20 hours post-treatment and analyzed by ELISA for IFN-α, TNF-α, IL-8, and IL-6. Percent of cytokine inhibition was determined by comparing IFN-α levels from IVIg-treated cultures to those that had not been treated with IVIg.

Results: Both SA+ and SA- IgG bound equally well to monocytes and to B cells as determined by flow cytometry. In response to all TLR7 and TLR9 agonists tested, SA+ IgG was significantly more inhibitory than SA- IgG for IFN-α production ($p<0.05$) **(Figure)** and inhibition by SA+ IgG increased with higher doses ($p<0.05$). Surprisingly, levels of IL-6, IL-8, and TNF-α in response to TLR agonists were not inhibited by SA+ or SA- IgG, and in fact, the production of TNF-α was significantly enhanced in cultures treated with SA+ compared to SA- IgG ($p<0.05$). Preliminary experiments suggest that inhibition of IFN-α by SA+ IgG was decreased in the absence of CD14+ monocytes.

Conclusion: SA+ IgG is more potent at inhibiting IFN-α production in response to TLR agonist stimulation compared to SA- IgG. CD14+ monocytes appear, in part, to mediate this inhibition, and the specific receptor for SA+ IgG is currently under investigation. The greater

potency of SA+ IgG has therapeutic implications because these results suggest that, in some circumstances, a lower dose of IVIg enriched for the active, sialylated subset may be efficacious. Also, identification of the receptor(s) and signaling pathways involved in the SA+ IgG anti-inflammatory effects could reveal targets for immune modulation.



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Increased Interferon-Alpha Activity Is Associated with Humoral Autoimmunity and Poor Antigen-Specific Immunity in Systemic Lupus Erythematosus. Lauren R. Cole[1], Sherry R. Crowe[2], Gillian M. Air[1], Linda F. Thompson[2], Timothy B. Niewold[3] and Judith A. James[2], [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]University of Chicago, Chicago, IL

Purpose: Interferon-α (IFNα) has been identified as a key mediator in systemic lupus erythematosus (SLE) pathogenesis. IFNα is a type I IFN that has the ability to disrupt self tolerance by activating antigen-presenting cells containing self-antigen. Elevated IFNα activity is detected in many SLE patient samples, and these elevations have been shown to correlate with disease activity as well as multiple organ involvement. Our goal is to further understand the pathogenic role of IFNα in SLE humoral autoimmunity, as well as to investigate the effect of an antigen-specific challenge in SLE and whether increased IFNα activity in SLE impairs antigen specific responses.

Method: This study enrolled 72 SLE patients who met ACR criteria and matched controls. Detailed clinical and therapeutic information, as well as disease activity measures were obtained at baseline and 2, 6, and 12 weeks after influenza vaccination. Influenza humoral immune responses (native/denatured ELISA responses, relative affinities and hemagglutination inhibition) were measured. Serial samples were tested for interferon activity through a reporter cell assay which measures serum's ability to upregulate three interferon inducible genes, MX1, PKR, and IFIT1. Lupus-associated autoantibodies (aAbs) (Ro, La, Sm, nRNP, ribosomal P, dsDNA, ANAs and phospholipid antibodies) were measured by ELISA and immunofluorescence.

Results: IFNα activity decreased in SLE patients 2 weeks after influenza vaccination compared to baseline levels (baseline mean = 6.4, 2 weeks post-vaccination mean = 3.9, p=0.0195, paired t-test). However, in the subset of patients whose disease activity scores increased after vaccination, this decrease in IFNα activity was not seen. A correlation was seen between elevated baseline IFNα activity and poor humoral immune response to the influenza vaccine (p=0.0126, r^2=0.22). Additionally, a significant association was seen between increased IFNα and total number of lupus-associated autoantibodies (IFNα < 1.0 [n=45], mean aAbs = 2.1, IFNα > 1.0 [n=27], mean aAbs = 3.4, p=0.0003, unpaired t-test). Consistent with previous reports, we also saw a significant association between increased IFNα and disease activity (IFNα < 1.0 [n=45], mean SLEDAI = 7.6, IFNα > 1.0 [n=27], mean SLEDAI = 10.2, p=0.0078, unpaired t-test).

Conclusion: A unique finding in this study was that IFNα decreases in SLE patients post-influenza vaccination. Increased baseline IFNα activity correlated with a poor humoral response to the influenza vaccine. Increased IFNα activity was also associated with an increased number of lupus-associated autoantibodies, as well as with increased disease activity.

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Orally Active TNF-Alpha Inhibitor Mediates Anti-Inflammatory Activity by Potentiating Adenosine A2a Receptor Signaling. Ajith A. Welihinda and Edward P. Amento, Theracos, Inc. and Molecular Medicine Research Institute, Sunnyvale, CA

Purpose: Orally active small molecule inhibitors of the pro-inflammatory cytokine TNF-alpha, exemplified by THR-090717 and its analogs, are currently being evaluated for treatment of rheumatoid arthritis and other TNF- alpha -driven inflammatory disorders. In rodent models of arthritis, THR-090717 significantly reduces joint swelling and improves clinical score. The present study examined its mechanism of TNF-alpha inhibition.

Method: Human monocytes were isolated from PBMCs by depleting other cell types. TNF- alpha levels in culture media and intracellular cAMP levels were quantitated by ELISA. Kinase inhibition was evaluated in a TR-FRET assay using recombinant enzymes and peptide substrates. COX and PDE4 assays were performed using commercially available assay kits. PPAR-gamma agonist activity was evaluated using a reporter plasmid. Binding affinity of adenosine A2a receptor was determined using [14C]NECA and cells over-expressing the receptor.

Results: A series of small molecules including THR-090717 and its analogs inhibited TNF- alpha release regulated by multiple distinct signaling pathways with similar efficacy. IC50 values for the inhibition of TNF- alpha by THR-090717 in PMA-stimulated human monocytes, LPS-stimulated human monocytes and IgG-stimulated THP-1 cells were 1.8 + 0.9 uM, 0.9 uM and 1.3 + 0.25 uM respectively. The compound failed to show significant inhibition towards a number of pharmacological targets of inflammation including COX-1, COX-2, p38, JNK1, JNK2, SYK, PDE4D3, PDE4D5 and PPAR-gamma. Of interest, in vivo anti-inflammatory activity was greater than that anticipated by in vitro IC50 values. One possible explanation is our finding that THR-090717 and its analogs enhanced adenosine-mediated cAMP production in PC-12 cells. Synergism between THR-090717 and adenosine was detected at 1 uM of compound ($p < 0.01$). Binding studies demonstrated that the compound increased the affinity of adenosine A2a receptor by 1.5-fold. Moreover, a highly selective adenosine A2a receptor antagonist, ZM241385, blocked THR-090717-mediated inhibition of TNF-alpha production by PMA-stimulated human monocytes.

Conclusion: Our results suggest that THR-090717 and its analogs may potentiate adenosine-mediated cAMP production at the adenosine A2a receptor to inhibit TNF- alpha production and reduce inflammation. These small molecule inhibitors of TNF- alpha production may act by increasing adenosine A2a receptor activity such that endogenously elevated adenosine levels at sites of inflammation effectively concentrate anti-inflammatory activity at disease sites.

Disclosure: A. A. Welihinda, Theracos, Inc., 3 ; **E. P. Amento**, Theracos, Inc, 1 .

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The Ang-1/Tie2 Angiogenic Axis Is Selectively Engaged in RA Synovial Tissue Even Before ACR Criteria of RA Are Met. Marleen G.H. van de Sande[1], Daphne deLaunay[1], Gijs P.M. van de Sande[1], Paul P. Tak[2] and Kris A. Reedquist[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Angiogenesis contributes to inflammation and joint destruction in rheumatoid arthritis (RA). Angiopoietins (Ang) -1 and -2, which mediate blood vessel remodeling, as well as their receptor Tie2, are expressed in inflamed synovial tissue. We have recently shown that Ang-1 expression relative to Ang-2, and associated Tie2 activation, was significantly higher in RA compared to psoriatic arthritis. It is unknown if these differences in activation of Ang-1 Tie2 axis are also present in the earliest phases of arthritis.

Therefore, we investigated the expression of Ang-1, Ang-2, total Tie2 and phosphorylated active Tie2 in disease-modifying antirheumatic drug (DMARD) naïve early arthritis patients.

Methods: We analyzed synovial tissue biopsies of 55 DMARD naïve early arthritis patients. Patients were prospectively followed and diagnosed after 2 years according to established classification criteria. Quantitative analysis of expression or activation of the angiogenic markers was examined by immunohistochemical analysis combined with computer-assisted digital imaging. Activation status and expression of all markers was compared between different diagnostic groups.

Results: 21 Patients had RA at baseline, 8 patients had undifferentiated arthritis (UA) at baseline and fulfilled ACR criteria for RA after 2 years of follow up, 19 patients had still UA after 2 years of follow up and 7 had spondyloarthritis (SpA) diagnosed at baseline. Expression of Ang-1, Tie2 and pTie2 was comparable between the patients with RA at baseline and the patients who fulfilled ACR criteria over time. Expression of Tie2, pTie and Ang-1 was significantly higher in RA patients compared to the SpA patients (P=0.001, P=0.001, P=0.02 respectively) and UA patients who developed RA compared to SpA patients (P=0.002, P=0.004, P=0.02 respectively). This shows that the Ang-1 Tie-2 axis is specifically activated in RA, even before patients fulfill ACR criteria for RA. On the other hand SpA patients showed a higher expression of Ang-2 compared to the RA patients (P=0.003). UA patients with RA after 2 years of follow up showed increased Tie2 (P=0.001, pTie2 (p=0.006) and Ang-1 (P=0.01) expression compared to patients that remained UA after 2 years of follow up.

Conclusion: Our study extends the results of our previous studies, showing that engagement of the Ang-1/Tie2 axis is specifically active in RA patients, even in the earliest phases of the disease, indicating that this pathway might play an important role in the pathogenesis of RA, whereas Ang-2 plays a more important role in spondyloarthritis .

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Regulation of IFN Response Gene Activity During Infliximab Treatment in Rheumatoid Arthritis Is Associated with Clinical Response to Treatment. Lisa G.M. Van Baarsen[1], Carla A. Wijbrandts[2], Francois Rustenburg[1], Tineke Cantaert[2], Tineke C.T.M. van der Pouw Kraan[1], Dominique L. Baeten[2], Ben A.C. Dijkmans[1], Paul P. Tak[3] and Cornelis L. Verweij[1], [1]VU University Medical Center, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Cross-regulation between TNF and type I IFN has been postulated to play an important role in autoimmune diseases. Therefore we determined the effect of TNF-blockade in rheumatoid arthritis (RA) on the type I IFN-response gene activity in relation to clinical response.

Method: Peripheral blood from 33 RA patients was collected in PAXgene tubes before and after the start of infliximab treatment. In a first group of 15 patients the baseline expression of type I IFN-regulated genes was determined using cDNA-microarrays and compared to levels one month after treatment. The remaining 18 patients were used as an independent group for validation using quantitative (q)PCR.

Results: Gene expression analysis revealed that anti-TNF antibody treatment induced a significant increase in type I IFN-response activity in a subset of RA patients, whereas expression levels remained similar or were slightly decreased in others. The findings appear clinically relevant since patients with an anti-TNF induced increased IFN-response gene activity had a poor clinical outcome. This association was confirmed and extended for an IFN-response gene set consisting of OAS1, LGALS3BP, Mx2, OAS2 and SERPING1 in five EULAR good and five EULAR poor responders, by qPCR.

Conclusion: Regulation of IFN-response gene activity upon TNF-blockade in RA is not as consistent as previously described, but varies between patients. The differential changes in IFN-response gene activity appear relevant to the clinical outcome of TNF-blockade in RA.

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Th1, Th2 and Th17- Derived Cytokines Levels in Synovial Fluid of RA: Relation with Synovial Lymphoid Neogenesis and Erosive Disease. Juan D. Canete[1], Raquel Celis[2], Miguel Angel Descalzo Sr.[3], Jose L. Pablos[4] and Raimon Sanmarti[5], [1]Hospital Clinic de Barcelona and IDIBAPS, Barcelona, Spain, [2]Arthritis Unit, Barcelona, Spain, [3]Fundacion Española de Reumatologia, Madrid, Spain, [4]Hospital 12 de Octubre, Madrid, Spain, [5]Arthritis Unit, Rheumatology Department, Barcelona, Spain

Background: Synovial lymphoid neogenesis (LN) in rheumatoid arthritis (RA) has been associated with refractory disease but not with the presence of autoantibodies. B cells in LN could also drive antibody-independent Synovial inflammation through the development of T cells responses or enhances cytokine production.

Purpose: To analyze 1) Th1, Th2 and Th17 cytokine levels in Synovial fluid of RA patients regarding the presence or not of Synovial tissue lymphoneogenesis; 2) To determine whether baseline levels of cytokines are associated to erosive disease

Method: Arthroscopic Synovial biopsy specimens from patients with RA were classified as LN+ or LN- by immunohistochemistry for CD3, CD20, T/B cell segregation and peripheral node addressin (PNAd)-positive HEV in relation to the size of lymphoid aggregates. Synovial fluid obtained at the time of the arthroscopy was analyzed by duplicate using the Procarta Cytokine Assay Kit (Panomics, Inc, Freemont, CA) for IFN-gamma, IL-4, IL-7, IL-10, IL12p40, IL-17, IL-23, IL-1beta, TNF-alpha and IL-6. Relevant clinical and biological data of patients were recorded at inclusion and at the end of follow-up. Patients were further classified as having erosive or non erosive RA, as defined by having more than 2 radiographic erosive lesions in at least 2 different joints.

Results: 65 RA patients (68% female, 71% RF+, 51% ACPA+) with matched Synovial tissue and Synovial fluid samples were included with a follow-up, median (p25-p75) of 107 months (83-176). 78% of them had erosive at end of follow-up, 33 (51%) RA patients were LN+ and 32 (49%) LN-, without significant differences in disease duration, RF, ACPA, CRP and DAS28. Also, no significant differences were found in the levels of all cytokines between LN+ and LN- patients.

Chi-square test showed a association between IL-1beta baseline levels and erosive RA (p=0.047). After Multivariable logistic regression adjusted for DAS28 at baseline, DAS28 increase, disease duration, CRP at baseline and anti-TNFa therapy, all of them with a significant association ($p<0.05$) with erosive disease, only IL-23 (p=0.02) and TNFalpha (p= 0.001) levels were associated with erosive RA.

Conclusion: There are no significant differences in the T-cell derived and proinflammatory cytokine levels in synovial fluid of RA with and without Synovial lymphoid neogenesis. This finding suggests that LN does not modifies the pattern of expression of theses cytokines, although analysis of cytokine expression in synovial tissue remains to be explored. On the other hand, Synovial fluid levels of TNFalpha and IL-23, but not IL-17 levels, are associated with erosive disease, highlighting the relevance of theses cyokines in the pathogenesis of RA.

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IL-17A Expression Is Upregulated in the Hypoxic Joint and Correlates with IL-6 Production, Inflammatory Cell Infiltrate and Oxidative Damage. Ellen Margaret Moran[1], Chin Teck Ng[1], Jennifer McCormick[1], Rene Heydrich[2], Heiner Appel[2], Ursula Fearon[1] and Douglas Veale[1], [1]Dublin Academic Medical Centre, St.Vincent's University Hospital, Dublin, Ireland, [2]Charite, Campus Benjamin-Franklin, Berlin, Germany

Purpose: IL-17A is overexpressed in the human RA joint and has been implicated in the pathogenesis of RA. The aim of this study was to examine localised expression of IL-17A in the joint and to examine its relationship to inflammatory markers and synovial tissue oxygen tension.

Method: 19 patients with inflammatory arthritis underwent needle arthroscopy. Paired serum/synovial fluid and synovial tissue were obtained. Oxygen levels in synovial tissue (tpO2) were assessed in vivo using a combined oxygen/temperature LICOX probe at the baseline prior to biologic therapy. IL-17A, CD3, CD68 and HNE (lipid peroxidation) expression was assessed by immunohistochemistry in synovial tissue sections. Dual immunofluorescence staining was carried out to co-localise IL-17A to mast cells using mast cell tryptase. IL-17A and

IL-6 levels were measured by ELISA/MSD assay in the paired serum/synovial fluids (SF).Dual immunofluorescence staining was carried out to co-localise IL-17A to mast cells using mast cell tryptase.

Results: Dual immunoflourescent staining demonstrated co-localisation of IL-17A expression to mononuclear cells and mast cells in the sublining. The number of IL-17A producing mononuclear cells correlated with IL-17 serum levels (r2=.545, p<0.05). The number of IL-17-secreting mast cells was found to correlate with sublining CD68 expression (r2=.618) and expression of lipid peroxidation (HNE) staining (r2=.570) (p<0.05). IL-17A SF levels correlated with serum and SF IL-6 expression (p<0.05). SF levels also correlated with CD3 expression in the sublining (r2=.430, p<0.05) and lining layer (r2=.545, p<0.05) of synovial tissue. The median tpO2 level in the synovial tissue was profoundly hypoxic 3.2% (range 0.45-7.7%) and inversely correlated with synovial tissue expression of CD68 and CD3 (r2=-.615, p<0.001 and r2-.611, p<0.01 respectively). When patents were categorized into tp02 <>20mmHg there was no significant difference in tissue or SF levels of IL-17A, however serum levels of both IL-17A and IL-6 were significantly higher in patients with a tp02 <20mmHg (p<0.05) suggesting a systemic effect on these cytokines by hypoxia.

Conclusion: In this study we demonstrate localisation of IL-17A expression to mononuclear cells and mast cells, levels of which correlated with markers of tissue inflammation and damage in the joint. We demonstrated low tpO2 levels in the joint are inversely related to tissue inflammatory markers. Serum IL-17A levels were inversely related to tpO2 levels, however had no association with tissue and SF IL-17A levels, suggesting a divergence in mechanisms regulating IL-17A systemically and locally in the joint.

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The Four and a Half LIM Domains Protein 2 (FHL2) Is a Key Regulator of Inflammatory Tissue Damage in Chronic Destructive Arthritis. C. Cromme[1], LH Meyer[1], K. Neugebauer[1], A. Korb[1], C. Wunrau[1], G. Kollias[2], K. Redlich[3], C. Will[1], EM Schnaeker[1], R. Bassel-Duby[4], D. Baeten[5], V. Wixler[1] and T. Pap[1], [1]Univ Hosp, Munster, Germany, [2]A. Fleming BSRC, Vari, Greece, [3]Med Univ, Vienna, Austria, [4]Univ of Texas, TX, [5]AMC, University of Amsterdam, Amsterdam, Netherlands

Purpose: FHL2 is a mediator of protein interactions and involved in cellular processes that are of relevance for the activation of mesenchymal cells. It is interacting with integrins, the focal adhesion- and mitogen-activated kinases, transcription factor AP-1 and is involved in TRAF-6 dependent signalling. Based on these data, we analysed the function of FHL2 in chronic inflammatory arthritis.

Methods: Expression of FHL2 in synovial tissues from RA and OA patients as well as in destructive arthritis of hTNFtg mice was analysed by immunohistochemistry. Fibroblast-like synoviocytes from RA patients (RA-FLS) and from hTNFtg mice and controls were isolated and FHL2 levels were determined by immunoblot after stimulation with cytokines. Knock down of FHL2 was performed by RNAi, and the expression of MMPs was determined by Western blot analysis and ELISA. The invasiveness of FLS was analysed using our established MATRIN-assay. FHL2-mediated signalling pathways (activation of MAP-kinases as well AP-1 and NFkappaB) were also studied. Finally, we crossed hTNFtg with $FHL2^{-/-}$ mice and analysed clinical parameters of arthritis as well as histomorphometric parameters of joint destruction and MMP expression in wt, hTNFtg, $FHL2^{-/-}$ and $FHL2^{+/-}$/hTNFtg animals.

Results: Although there was a significantly higher expression of FHL2 in RA than in OA, only TGFbeta but not TNFalpha induced the expression of FHL2 in RA-FLS. Analysis of FHL2 expression in hTNFtg mice together with further *in vitro* studies confirmed these findings by showing an early TGFbeta dependent induction of FHL2 that was followed by a TNFalpha-mediated suppression of FHL2. However, the TNFalpha mediated suppression of FHL2 in hTNFtg mice was incomplete, as the levels of FHL2 were still significantly higher in hTNFtg mice than in wt controls. *In vitro* analysis revealed a prolonged phosphorylation of p38 MAPK and MAPKAP kinase 2 in murine $FHL2^{-/-}$ cells as well as in siRNA-treated RA-FLS as compared to controls. This was accompanied by significantly elevated MMP levels. We also found an increased invasiveness of RA-FLS after FHL2 knock down. When analysing the offspring of hTNFtg and $FHL2^{-/-}$ mice, we found that the $FHL2^{-/-}$/hTNFtg genotype is lethal before birth and that $FHL2^{+/-}$/hTNFtg mice show increased paw swelling and reduced grip strength as compared to hTNFtg mice. $FHL2^{+/-}$/hTNFtg mice had increased joint destruction with markedly elevated levels of MMPs *in situ*.

Conclusion: Our results suggest that through modulating p38 MAPK activation, FHL2 is involved in the limitation of cytokine-induced MMP expression and as such constitutes an important regulator of inflammatory tissue damage in arthritis. While early tissue damage leads to an up-regulation of FHL2 in affected tissues in frame of a healing attempt, chronic exposure to TNFalpha suppresses FHL2, which ultimately leads to unbalanced and chronically progressing joint destruction.

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IL-22 in Inflammatory Arthritis. Bernadette M. Lynch, Jennifer McCormick, Chin Teck Ng, Oliver FitzGerald, Ursula Fearon and Douglas J. Veale, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Purpose: IL-22 is produced by Th17 T cells. It may have both pro- and anti-inflammatory activity. This study examines the role of IL-22 in Rheumatoid arthritis (RA) and Psoriatic Arthritis (PsA) and its relationship to clinical parameters in response to biologic therapy.

Method: Serum was collected from RA (n=59), PsA (n=27) and normal controls (n=11). In a subgroup of patients serum was obtained pre and 3 months post anti-TNF therapy. Anti-CCP titre and smoking history was collected. At arthroscopy RA synovial tissue (ST) was obtained (n=6) to establish *ex-vivo* whole tissue ST explant cultures which closely reflect the joint environment. RA ST was stimulated with IL-22 (100ng/ml). MMP2 and MMP9 were measured by zymography. Mann-Whitney test was performed and results are expressed as median (range).

Results: Serum IL-22 was significantly higher in Inflammatory Arthritis 17.07pg/ml (0-83.5) compared to normal controls 3.38pg/ml (0-11.17) ($p<0.01$). IL-22 was significantly higher in RA 17.46pg/ml (0-83.5) compared to PsA 14.65pg/ml (0-39.54) ($p<0.05$). IL-22 was significantly higher in smokers compared to both non-smokers and ex-smokers. Similarly, IL-22 was significantly higher in anti-CCP positive patients compared to anti-CCP negative patients ($p<0.05$). IL-22 was decreased 3/12 post anti-TNF therapy in 15 of 33 patients from 14.5pg/ml (3.98-69.19) to 9.04pg/ml (0-66.09). IL-22 significantly increased both MMP-2 and MMP-9 ($p<0.05$).

Conclusion: IL-22 is increased in inflammatory arthritis and may regulate the pro-inflammatory response in specific patients. IL-22 expression is associated with smoking and anti-CCP antibody, both risk factors for RA, this further suggests an important role for IL-22 in specific Inflammatory Arthritis patients.

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Synovial Fluid and Synovial Tissue Biomarkers of the Response to Intra-Articular TNF-α Blockade in Psoriatic Arthritis. U. Fiocco[1], P. Sfriso[1], F. Oliviero[1], P. Roux-Lombard[2], F. Lunardi[1], F. Calabrese[1], R. Nardacchione[3], E. Scagliori[1], L. Cozzi[1], M. Vezzù[1], B. Molena[1], A. Scanu[1], J. M. Dayer[2] and L. Punzi[1], [1]University of Padova, Padova, Italy, [2]University Hospital of Geneva, Geneva, Switzerland, [3]Abano Terme Hospital, Padova, Italy

Purpose: To identify synovial fluid (SF) and synovial tissue biomarkers of the response to intra-articular (IA) TNF-α blockade.

Methods: SF cytokine/chemokine levels and synovial tissue histology were assessed during a perspective study of repeated IA etanercept injections in the knee joint of 14 patients affected by psoriatic arthritis (PsA) and resistant knee joint synovitis (KJS) (1). SF was aspirated from the knee joint before each IA injection of 0.5 ml of etanercept (E) (12.5mg) once every two weeks, for 12-weeks. IL-1β, IL-1Ra, IL-6, IL-8, IL-17, IL-22, TNF-α, IFN-γ, MCP-1, MIP-1α and MIP-1β were measured on SF samples, obtained at baseline and after the last IA-E injection, by a commercially available multiplex beads immunoassay, based on the Luminex platform (Fluorokine MAP Multiplex Human Cytokine Panel A, R&D Systems, Minneapolis, USA) according to supplier's instructions. Normal values were established in 50 healthy blood donors. Characterization of synovial mononuclear cell infiltrate and synovial vessels was carried out by staining for CD45, CD3, CD68, CD31 and CD105 of serial sections of synovial biopsies obtained from 11 knees before the baseline IA-injection and repeated after the last injection. All parameters were measured by computer-assisted morphometric analysis (Image Pro-plus version 5) and a 2 mm^2 area was evaluated (7 random fields at x 40). The nonparametric Wilcoxon rank test was used to compare SF cytokine levels and synovial tissue infiltrating cells before and after IA-E treatment. For correlation analysis Spearman's rank correlation test was used.

Results: Before IA-E treatment, IL-6 correlated significantly with IL-1Ra, IL-1-β, MIP-1α SF level. Moreover, CD31+ synovial tissue cells were significantly correlated with both IL-1β and IL-6 SF level; CD45+ cells with IL-1β and CD3+ cells with MIP-β SF level, respectively.

IA TNF-α blockade induced a reduction in IL-1β, IL-1Ra, IL-6, IL-22 SF level (Tab I), as well as in CD45+ and CD31+ synovial tissue cells ($p<0.05$). After IA-E, a significant correlation was observed between IL-17 and IL-6 SF level and between IL-1Ra and IL-1β, IL-8, IL-6.

Table I: Comparison of synovial fluid cytokine levels in psoriatic arthritis before and after intra-articular knee joint etanercept treatment

SF-ILs	Pre (M±SD)	Post (M±SD)	p (Wilcoxon rank test)
TNF-α	25±44	27±37	ns
IL-1-β	8±10	4±1	0.014
IL-1Ra	10876±10491	5015±6011	0.004
IL-6	4596±5322	1770±3255	0.016
IL-8	753±1257	622±939	ns
MCP1	413±320	296±168	ns
MIP1- α	99±62	128±151	ns
MIP1- β	80±72	84±135	ns
IL-17	23±73	18±26	ns
IL-22	13±8	5±3	0.039

Conclusion: IA-TNF-α blockade has shown early down-regulation of either IL-1-β and IL-6 in resistant knee joint synovitis, not already reported following systemic anti-TNF-α treatment. The correlations observed after IA-E treatment between IL-1ra and IL-8, as well IL-6 and IL-17, suggest the modulation of the local cytokine balance following TNF-α signal attenuation. IL-22 SF expression in PsA, suggests an underlying role for the Th17 system in both skin and joint involvement.

References:
1. Fiocco U., P. Sfriso, R. Nardacchione, F. Sovran, E. Scagliori, L. Cozzi, M. Vezzù, D. Bertolini, F. Oliviero, C. Botsios, A. Piccoli, A. Di Maggio, L. Rubaltelli, L. Punzi. Evaluation of the Efficacy and Safety of Repeated Intra-Articular Etanercept Injections in Resistant Knee Joint Synovitis. Arthritis Rheum 2007; 56(9):S592

Disclosure: U. Fiocco, None; **P. Sfriso**, None; **F. Oliviero**, None; **P. Roux-Lombard**, None; **F. Lunardi**, None; **F. Calabrese**, None; **R. Nardacchione**, None; **E. Scagliori**, None; **L. Cozzi**, None; **M. Vezzù**, None; **B. Molena**, None; **A. Scanu**, None; **J. M. Dayer**, None; **L. Punzi**, None.

1347

Glatiramer Acetate (GA), the Immunomodulatory Drug, Inhibits Inflammatory Mediators and Collagen Degradation in OA Cartilage. Mukundan Attur, Mandar Dave, Hayf Al-Mussawir, Jyoti Patel, Glyn Palmer and Steven B. Abramson, NYU - Hospital for Joint Diseases, New York, NY

Purpose: Glatiramer acetate, the generic name for Copaxone, an immunomodulatory agent used in the treatment of multiple sclerosis, has been to shown induce interleukin-1 receptor antagonist (IL-1Ra) production in macrophages and microglial cells. In osteoarthritis, the production of inflammatory mediators, particularly IL-1, by chondrocytes may be important in the pathogenesis and progression of OA. We therefore tested the effects of glatiramer acetate or co-polymer on the catabolic activities of chondrocytes in OA cartilage explants cultures.

Method: Human OA cartilage samples and chondrocytes were isolated from patients undergoing knee replacement surgery as approved by IRB. IL-6, IL-8, proMMP-13 and active MMP-13 ELISA were performed as per manufacturer's recommendations (R&D Systems).

Results: We have previously shown that OA cartilage explant cultures spontaneously release inflammatory mediators such as nitric oxide, Prostaglandin E2 (PGE2), interleukins including IL-1beta, IL-6, IL-8 and matrix metalloproteinase (MMPs). Addition of GA (1mg/ml) inhibited 1) IL-6 (25.19 + 13.27 to 15 + 8.5 ng/ml;$p<0.05$) and IL-8 (30.5 + 9.2 to 15.1 + 6.1 ng/ml;$p<0.01$) production; 2) inhibited spontaneous proMMP-13 production (35.6+ 14 to 18.5 + 5.1ng/ml;$p<0.01$); 3) inhibited MMP-13 activity by more than 30-50% ($p<0.01$); 4) inhibited collagen degradation as assayed by CTX II ELISA (7.4 + 1.7 to 4.5 + 1.9 ng/ml; $p<0.05$). GA also increased significantly ($p<0.001$) IL-1Ra production by OA cartilage explant ex vivo cultures.

Conclusion: Glatiramer acetate is a complex heterogeneous mixture of polypeptides that exhibits "chondroprotective" properties in OA cartilage, inhibiting the production of cytokine/chemokines production as well as MMP-13 expression/activation. The data suggest that these effects may be due to upregulation of IL-1Ra. Based on these studies, we propose that glatiramer acetate may have potential for disease modifying properties in OA and should be evaluated in vivo animal studies.

Disclosure: M. Attur, None; **M. Dave**, None; **H. Al-Mussawir**, None; **J. Patel**, None; **G. Palmer**, None; **S. B. Abramson**, None.

1348

Cytokine Quantification and Microarray Assessment Differentiate "CIAS1 Mutation Positive and Negative" Patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID). T.H. Pham[1], N. Plass[1], D. Stone[1], D. Chapelle[1], M. Gadina[1], H.W. Sun[1], W. Fury[2], I. Dozmorov[3] and R. Goldbach-Mansky[1], [1]NIH | NIAMS, Bethesda, MD, [2]Regeneron, Tarrytown, NY, [3]OMRF, Oklahoma City, OK

Purpose: Only about 60% of NOMID patients have mutations in *CIAS1*/ *NLRP3*/ *NALP3*, a gene associated with the activation of IL-1β. Mutation positive (MP) and mutation negative (MN) patients do not differ in their clinical phenotype nor in their response to treatment with anakinra, a recombinant IL-1 blocking agent, indicating that the organ specific pathology is IL-1 cytokine driven. We evaluated cytokine production and compared gene expression profiles in both patient groups.

Methods: Whole blood from mutation positive (MP) (n=13) and negative (MN) (n=7) NOMID patients and controls (n=26) were either spun and plasma collected, cells washed and treated with lipopolysaccharide (LPS) for 3 hours at 37°C or extracted for RNA. For cell treatment experiments, ATP was used as second stimulus, while oxidized ATP (oATP) or caspase-1 blocker (YVAD) was added as inhibitors. Cytokines were quantified using ELISA. Gene expression from microarray analysis using a cDNA profile of 54,000 random genes was assessed.

Results: LPS treated cells from MP patients significantly produced IL-1β (range 53 to 6.9ng/mL), however this is not seen in MN patients and controls ($p<0.001$). When a second stimulus was added to cell cultures only MN patients and controls further secreted IL-1β: LPS treatment alone (range 7 to 0.3ng/mL and 6 to 0.4ng/mL, respectively) to ATP addition (range 26 to 1ng/mL and 69 to 0.6ng/mL, respectively) ($p<0.05$), while IL-1 levels did not change with additional treatment in MP patients' cells. Also, IL-18 was significantly produced in treated cells of MP patients compared to MN patients and controls ($p<0.002$). However, IL-1 and IL-18 secretion were significantly blocked with oATP and YVAD in MP patients ($p<0.05$). MN patients and controls produced increased levels of IL-6 and TNF-α in plasma compared to MP patients ($p\leq0.05$). Of the 54,000 genes that correlated with IL-1 expression, 37 genes correlated well in MP but not MN patients, and 47 genes correlated well in MN vs MP patients. Among the differentially correlated genes, those highly correlated with IL-1 in MN but not MP patients included: ATP-binding cassette ($r=0.94$ for MN and $r=0.07$ for MP), annexin, P2XR, NLRP, while those most correlated with MP but not MN patients were ATPase, ADPRF, TLR1, IRAK, and PDK.

Conclusion: MP NOMID patients are hypersensitive to LPS and maximally produce IL-1β without the need for a second stimulus such as ATP. IL-1 and IL-18 were successfully inhibited in MP patients using YVAD and oATP. Evaluation of protein secretion from cell treatment studies demonstrated differential cytokine production among NOMID patients with and without the *CIAS1* mutation. Microarray analysis in patients demonstrated a set of genes that are differentially expressed in MP and MN patients. This further supports the notion that IL-1 mediated disease in MN NOMID patients may be due to mutation in genes other than *CIAS1*.

Disclosure: T. H. Pham, None; **N. Plass**, None; **D. Stone**, None; **D. Chapelle**, None; **M. Gadina**, None; **H. W. Sun**, None; **W. Fury**, Regeneron, 3 ; **I. Dozmorov**, None; **R. Goldbach-Mansky**, None.

1349

IL-27 Inhibits IL-1b and TNF-a, but the Anti-Inflammatory Function of IL-27 Is Abrogated within the Inflammatory Microenvironment. George D. Kalliolias, Rachael Gordon and Lionel B. Ivashkiv, Hospital for Special Surgery, New York, NY

Purpose: TNF-a and IL-1b are implicated in the pathogenesis of Rheumatoid arthritis (RA). Recently it was shown that IL-27, a new member of the IL-6/IL-12 family, is expressed in RA synovium. IL-27 is a pleiotropic cytokine with both anti-inflammatory and pro-inflammatory functions. In Collagen-induced arthritis IL-27 was beneficial by restraining Th17, while in Proteoglycan-induced arthritis and in Adjuvant-induced arthritis it was proven pathogenic by inducing Th1. Whether in human RA IL-27 is pathogenic or protective remains an open question.

Method: CD14+ cells were isolated with positive selection from peripheral blood of healthy donors and synovial fluids (SF) of RA patients. Activation of signaling pathways and gene expression following stimulation with cytokines were measured by immunoblotting and qRT-PCR respectively.

Results: Pretreatment with IL-27 of peripheral blood CD14+ cells derived from healthy donors, inhibited activation of MAPK signaling pathways (ERK and p38) downstream to IL-1b and TNF-a. IL-27 inhibited the induction of IL-1b- target genes (including IL-8, IL-1 and IL-6), suppressed the expression of IL-1RI and induced IL-1Ra in these cells. Surprisingly, we observed that, in stark contrast to CD14+ cells derived from healthy donors peripheral blood, SF CD14+ cells from RA patients were not responsive to IL-27 (there was no activation of Jak-STAT signaling pathway and no induction of target genes). Interestingly, we found that overnight pre-incubation of healthy donors peripheral blood CD14+ with TNF-a or IL-1b inhibited IL-27 signaling and this inhibition was abrogated by etanercept and anakinra. We also found that IL-1b, but not TNF-a, downregulated the cell surface expression of the gp130 subunit of the IL-27 receptor. In the presence of a p38 inhibitor, the inhibitory effect of TNF-a on IL-27 function was abrogated.

Conclusion: In human monocytes, IL-27 exerts anti-inflammatory effects by inhibiting both IL-1b and TNF-a. IL-27 inhibits IL-1b potentially by downregulating IL-1RI and inducing IL-1Ra. On the other hand, IL-1b suppresses the anti-inflammatory function of IL-27 by downregulating gp130. TNF-a also inhibits IL-27 functions in a p38-dependent manner. Our results indicate that in the inflammatory microenviroment the anti-inflammatory function of IL-27 is abrogated.

Disclosure: G. D. Kalliolias, None; **R. Gordon**, None; **L. B. Ivashkiv**, None.

1350

IL-27 Inhibits Human Osteoclastogenesis. George D. Kalliolias[1], Baohong Zhao[2], Antigoni Triantafyllopoulou[3], Kyung-Hyun Park-Min[1], Rachael Gordon[1] and Lionel B. Ivashkiv[1], [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, [3]Hospital for Speical Surgery, New York, NY

Purpose: IL-27 has both stimulatory and regulatory immune functions and is expressed in rheumatoid arthritis synovium. We investigated the effects of IL-27 on human osteoclastogenesis to determine whether IL-27 can stimulate or attenuate osteoclast-mediated bone resorption that is a hallmark of rheumatoid arthritis.

Method: Osteoclasts were generated by culturing blood-derived human CD14+ cells in the presence of MCSF and RANKL. The effects of IL-27 on osteoclast formation were evaluated by counting the number of TRAP+ multinucleated cells and measuring expression of osteoclast-related genes using real time RT-PCR. The induction of NFATc1 and the activation of signaling pathways downstream of RANK were measured by immunoblotting. The expression of key molecules implicated in osteoclastogenesis (including NFATc1, RANK, costimulatory receptors and ITAM-harboring adaptors) was measured by real time RT-PCR. Murine osteoclast precursors were obtained from bone marrow and a similar approach was followed.

Results: IL-27 inhibited human osteoclastogenesis, suppressed the induction of NFATc1, downregulated expression of RANK and TREM-2, and inhibited RANKL-mediated activation of ERK, p38 and NF-κB in osteoclast precursors. In contrast to human cells, IL-27 only minimally suppressed murine osteoclastogenesis, likely due to low expression of the IL-27 receptor subunit WSX-1 on murine osteoclast precursors.

Conclusion: IL-27 inhibits human osteoclastogenesis by a direct mechanism that suppresses responses of osteoclast precursors to RANKL. Our findings suggest that in addition to its well-known anti-inflammatory effects, IL-27 plays a homeostatic role in restraining inflammatory bone erosion.

Disclosure: G. D. Kalliolias, None; **B. Zhao**, None; **A. Triantafyllopoulou**, None; **K. H. Park-Min**, None; **R. Gordon**, None; **L. B. Ivashkiv**, None.

1351

The Role of the Atypical Chemokine Receptor D6 in Collagen-Induced Arthritis. Chris Hansell, Lindsay MacLellan, Iain B. McInnes, Robert J.B. Nibbs and Carl S. Goodyear, University of Glasgow, Glasgow, United Kingdom

Purpose: Chemokines direct leukocyte migration into inflamed tissue. The chemokine receptor D6 is expressed by a subset of leukocytes in the inflamed human synovium. D6 can bind at least 10 inflammatory CC chemokines but appears not to transduce signals. Instead it acts as a chemokine scavenger and progressively internalizes large quantities of it ligands, which it targets for destruction. As a result D6-deficient mice show a marked predisposition to exaggerated inflammation in a wide variety of experimental in vivo systems. In addition it appears that D6 facilitates the migration of DCs from the inflamed tissue to draining lymph nodes for optimal T cell priming. This underpins the decreased susceptibility of D6-deficient mice to experimental autoimmune encephalomyelitis. The aim of this study was to investigate the role of D6 in the murine models of rheumatoid arthritis (RA).

Methods: D6-deficient mice were back-crossed to DBA/1 mice for 12 generations and then intercrossed to obtain D6+/+ and D6-/- mice. In all experiments, age-matched male littermates at 8-10 weeks age were used. Collagen-induced arthritis (CIA) was induced by immunizing with collagen type-II (CII)/CFA at the base of the tail on day 0 and boosting on day 21 i.p. with CII/PBS. Collagen antibody-induced arthritis (CAIA) was induced by injecting 2 mg of the CII specific monoclonal antibody cocktail i.v. on day 0, and 50µg of LPS i.p. 72h later. Mice were scored for clinical arthritis severity based on joint inflammation and ankle thickness, using standard methods. On day 35, serum, lymph nodes, patella and legs were harvested for determination of anti-Collagen antibodies, recall responses, joint cytokine and chemokine secretion and histology respectively.

Results: D6-/- mice had a small but significant increase in disease severity in CIA. This was associated with an increase in total lymphocyte numbers in the draining lymph nodes, and increased proliferation and secretion of IL-17 in response to antigen. However, no difference was observed in the CAIA studies.

Conclusion: Contrary to expectations, T cell priming in the D6-deficient mice was sufficient to induce clinical disease. In fact, the small increase in antigen-specific proliferation and IL-17 production by LN cells may account for the slight exacerbation of the clinical scores. The results also suggest that, unlike in other tissues, D6 does not play a major role in suppressing inflammation in the joint.

Disclosure: C. Hansell, None; **L. MacLellan**, None; **I. B. McInnes**, None; **R. J. B. Nibbs**, None; **C. S. Goodyear**, None.

ACR/ARHP Poster Session C

Education

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1352

A Rheumatology Curriculum That Is Successful in Preparing Internal Medicine Residents for the Rheumatology Portion of the Internal Medicine in-Service Examination and the American Board of Internal Medicine Certification Examination. Alan R. Erickson[1], Amy C. Cannella[2], Gerald F. Moore[3], T. R. Mikuls[4], Lynell W. Klassen[5] and James R. O'Dell[4], [1]UNMC Physicians - Brentwood, LaVista, NE, [2]University of Nebraska Med Ctr, Omaha, NE, [3]Univ Nebraska Med Ctr, Omaha, NE, [4]U Nebraska, Omaha, NE, [5]Univ of Nebraska Med Ctr, Omaha, NE

Purpose: Teaching internal medicine residents is an important responsibility of academic rheumatologists. At the University of Nebraska Medical Center (UNMC) there is a long-standing and well-developed curriculum for all residents who rotate through rheumatology. In addition to regular teaching rounds, this curriculum includes a didactic lecture series, a computer based x-ray and photographic case series, and 2 distinct and separate 200 question closed book pre- and post-tests. The pre-test answers with explanations are given after the testing to use as a study guide. Using the results of the Internal Medicine(IM) in-training examination and the American Board of Internal Medicine (ABIM) certification examination as a surrogate marker for educational success, our hypothesis is that a well developed rheumatology

curriculum prepares third year internal medicine residents and graduating internal medicine residents for the rheumatology portion of these examinations.

Method: Subjects include 84 third year internal medicine residents at UNMC from July 2003 through June 2009 that completed the IM in-training examination and all graduating internal medicine residents from 1999-2008. Composite results of the in-training examination completed by third year internal medicine residents and ABIM certification examination results of graduating internal medicine residents were reviewed for each year. A manual count was competed of the number of UNMC third year internal medicine residents who had completed our rheumatology rotation prior to the in-service examination. All internal medicine residents complete our rheumatology rotation prior to graduation and thus prior to the ABIM certification examination. For the IM in-service examination we looked at our national percentile rank. For the ABIM certification examination we looked at our percentile ranking for first time takers.

Results: The majority of third year internal medicine residents (65%) completed our rheumatology rotation prior to completing the third year in-training examination. Compared to all program's third year IM in-training examination scores, our program ranked in the top 10th percentile for each year from 2003 to 2008. From 1999-2008, 99% of our residents released their ABIM certification scores to our internal medicine program director. On average, our internal medicine residents' scores ranked among the top 30% of first time test takers in the rheumatology subsection (average decile 7.4).

Conclusion: These results suggest that a well developed curriculum prepares internal medicine residents for the IM in-training examination and the ABIM certification examination. Limitations in this study include the lack of comparative data on other rheumatology curricula and difficulty in generalizing ABIM internal medicine certification board results.

Disclosure: A. R. Erickson, None; **A. C. Cannella**, None; **G. F. Moore**, None; **T. R. Mikuls**, None; **L. W. Klassen**, None; **J. R. O'Dell**, None.

1353

Creation of a Bedside Teaching Atlas. Lori J. Albert[1], Kelsey Mills[2] and Nancy Roper[3], [1]The Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Patient Partners in Arthritis, Toronto, ON

Purpose: Recognition of key physical findings is an essential component of diagnosing rheumatic diseases. Students and residents often have very limited opportunities to learn physical examination on patients having rheumatic diseases. Frequently, these patients have achieved good disease control on medication, and may not show any characteristic changes on examination. Thus, a significant proportion of trainees do not understand what they are looking for on physical exam. We describe the development of a Bedside Teaching Atlas of physical findings in the rheumatology examination. The purpose of this Atlas is to demonstrate the appearance of characteristic or diagnostic changes at the time that physical examination is taught, even when the patient's examination is normal.

Method: Photographs were obtained of key physical findings that can be observed in the rheumatic diseases such as joint effusions, joint deformities, nailfold changes and skin findings. Pages were spiral bound for "flip chart" style use. Descriptive information for each photo was placed on the back of the preceding page to face the instructor. This was done to encourage thoughtful "inspection" of the photo by the student, while permitting non-expert teachers to have information regarding the picture. The number of photos was limited to ensure portability and ease of use. A pilot version of the Atlas was circulated to rheumatologist clinician teachers as well as non-specialist teachers and non-physician teachers (such as Patient Partners in Arthritis®) . Trainees were given a questionnaire following sessions where the Atlas was used. Feedback was also obtained from the teachers using the Atlas.

Results: Qualitative surveys indicated a high level of trainee satisfaction with use of the Atlas during teaching sessions. The Atlas was rated highly for the variety of photos available and for the fact that many of the findings shown had not been seen before, or were not seen in the patient being examined. Importantly, the majority of trainees agreed that the Atlas helped them to recognize changes of early arthritis. Almost all trainees surveyed felt that the Atlas enhanced the learning experience. Free-text comments reflected enthusiasm over observing and understanding rheumatologic findings "for the first time". Many students commented that using the Atlas would promote more careful and informed examination of their own patients in future.

Conclusion: It is predicted that demonstration of key physical findings using the Bedside Teaching Atlas, in the context of teaching rheumatology physical exam, will enhance recognition of these findings in clinical situations and improve the diagnostic acumen of trainees. It is also predicted that use of the Atlas will enhance the effectiveness of physical exam teaching by physicians as well as non-physician teachers.

Disclosure: L. J. Albert, Pfizer Inc, 9 ; **K. Mills**, None; **N. Roper**, None.

1354

Integrating the Teaching and Learning of Compassionate Care Into a Rheumatology Outpatient Clinical Skills Exercise. Robert A. Kalish[1] and MA Blanco[2], [1]Tufts Medical Center, Boston, MA, [2]Tufts University School of Medicine, Boston, MA

Purpose: Medical education recognizes the need to balance trainees' competency in clinical knowledge and skills with the principles and practice of humanistic care. This study examined the outcomes of a videotaped medical student-patient partner exercise aimed at promoting the teaching and learning of both clinical skills and compassionate care in an outpatient rheumatology clinic setting.

Method: Twenty-two third-year medical students rotating at a tertiary care academic medical center during their internal medicine clerkship participated. Each student performed a complete medical history, which was videotaped, and a complete joint examination on a volunteer rheumatology outpatient who was presented as an unknown diagnosis; the student's task was to determine the rheumatologic diagnosis. The student repeated the joint examination with the preceptor present, received feedback from both preceptor and patient, and requested laboratory and radiographic data.

Subsequently, students viewed their videotape, tagged segments to identify strengths and weaknesses in their rheumatologic history taking and compassionate care skills, and completed a Compassionate Care Interactions and Rheumatologic History-taking Skills Rating Form. The preceptor reviewed the videotape and the student's tags, provided tagged feedback, and independently completed the same rating form. Sixteen patients completed a questionnaire rating the student's interpersonal and compassionate care skills. Within the week, preceptor and student met to discuss differential diagnosis and reinforce physical examination skills through preceptor observation of designated joint examination maneuvers. Students evaluated the exercise through an online questionnaire. Quantitative and qualitative methods of data analysis were employed.

Results: Self-assessment and preceptor assessment through the videotape allowed students to identify weaknesses in history taking skills, including temporal sequencing, symptom details, and question clustering. Students gained confidence in examining joints in subsequent patients during the clerkship. The exercise also increased students' recognition of opportunities to demonstrate compassionate care. No statistically significant differences between student and preceptor ratings of history taking or compassionate care skills were found though a trend to higher preceptor scores for compassionate care skills was noted. Patients unanimously agreed that students demonstrated compassionate care. Five students indicated the experience increased the likelihood they would consider a career in rheumatology.

Conclusion: This educational initiative successfully and efficiently combined the teaching and learning of humanistic and clinical skills in an outpatient rheumatology patient-partner exercise. Videotaping the student-patient encounter was an effective tool for promoting students' self-assessment and reflection, and enhancing the preceptor's feedback.

Disclosure: R. A. Kalish, Abbott Pharmaceuticals, 9 ; **M. Blanco**, None.

1355

Elective Rheumatology Program with a Primary Health Care Focus. E. L. M. Bezerra, M. J. Vilar and G. D. Azevedo, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil

Purpose: Rheumatic conditions are very common in primary care. However most general doctors do not have the required expertise to deal with the rheumatic diseases they are likely to encounter in clinical practice. This fact reflects the poor undergraduate Rheumatology curriculum in the majority of medical schools, where its teaching is developed mainly in hospital settings (terciary care) by using traditional methods. Student-selected component (SSC), an innovative teaching method, is an optional program within the medical curriculum first used in UK. Its specific aims include the development of students' skills in self-directed learning, the ability to study areas outside the core curriculum in depth and development of confidence in their own skills and abilities. Thus, the objective of this pilot study was the implementation of SSC in a traditional curriculum to develop Rheumatology skills related to primary care.

Method: Twelve medical students in the clerkship (5^{th} and 6^{th} year) voluntarily participated in this program. They already had applied for a mandatory Rheumatology discipline, with 60 hours of time available, at the 4^{th} year of UFRN regular curriculum.

The SSC program consisted of ten 3-hour weekly sessions, from April to June 2009. The activities developed were the following (S = Session):

S 1- Introduction to module and setting of goals. Use web-based scientific material to highlight the importance of rheumatological primary care.

S 2- Students interviewed general practitioners from the "Family Health Program" (primary care level) on more prevalent rheumatic diseases in the community and access to diagnostic and therapeutic methods.

S 3- Small groups of clinical cases discussions on osteoarthritis and rheumatoid arthritis.

S 4- Small groups of clinical cases discussions on low back pain and shoulder pain.

Note: Pre-class review of the topics were required, both for S 3 and 4.

S 5- A physiotherapist and a psychologist discussed their roles in dealing with patients with long-term chronic pain and debilitating conditions.

S 6 and 7- Primary care of rheumatic patients by students, with supervision of rheumatologists.

S 8- Written assessment (short-answer questions).

S 9- Practical assessment (OSCE with standardized patients).

S 10- Feedback session and program evaluation (semi-structured interview).

Results: All of the students achieved good performance on assessments (grade 8 or above, in a scale ranging from 0 to 10). After completing the program, students surveyed (12/12) stated their confidence for diagnosing and treating rheumatic disease had improved either greatly (90%) or somewhat (10%). Students unanimously indicated that active formats were preferred over lectures and that practical training in Rheumatology primary care was a very rich experience.

Conclusion: This study showed that SSC was an effective learning strategy for development of Rheumatology skills and abilities in undergraduate medical students. These observations deserve further study with a larger number of participants and the results comparison with a control group of clerkship students.

Disclosure: E. L. M. Bezerra, None; **M. J. Vilar**, None; **G. D. Azevedo**, None.

1356

Team-Based Learning in Rheumatology Education of Internal Medicine Residents. Karina D. Torralba[1], Ron Ben-Ari[1], Francisco P. Quismorio Jr.[1] and Beatrice A. Boateng[2], [1]Keck School of Medicine, University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [2]University of Arkansas for Medical Sciences, Little Rock, AR

Purpose: Team-based learning (TBL), a structured approach to classroom instruction has gained acceptance in health professions. It leads to improved student attendance, interest in subject matter and work performance. We studied the effectiveness and outcomes of using TBL in Rheumatology core curriculum learning sessions (CCLS) for Internal Medicine (IM) residents over an initial period of 12 months.

Methods: A needs assessment conducted among PGY1-PGY3 residents in May 2008 determined improvements in scope of topics, and teaching methods. Reorganization for 2008-2009 led to TBL-formatted CCLSs on Evaluation of Joint Pain, Back Pain, Rheumatologic Emergencies, Inflammatory Myopathies, Spondyloarthropathies, Rheumatoid Arthritis and Osteoarthritis. To assess receptiveness to TBL format, a 5-point Likert scale survey was anonymously filled out by residents at end of each session. To evaluate perception of collaborative learning, a Value of Teams Survey (VOTS) was filled out at the end of the CCLS series. As an independent outcomes measure, we compared in-training exam (ITE) scores of TBL vs non TBL participants. An independent t-test was conducted to determine differences in ITE scores between groups.TBL was modified to include 1) accessible learning materials pre-CCLS, 2) individual followed by group in-class readiness assurance testing with an Immediate Feedback Assessment Tool, and 3) team case application exercises. Answers were discussed within and between teams with faculty instructor.

Results: Although TBL participation is voluntary, more residents participated in the TBL sessions (68 vs 53). Across 7 CCLSs, majority (60-100%) agreed-strongly agreed that TBL was conducive for use during CCLSs based on time allocation, organization of activities, quality of learning and interaction between teammates and with instructor. For VOTS, 81% (n=44) agreed cooperation with peers is necessary for success; 87% agreed working with peers is a valuable skill, an effective way to learn, and is needed for better decision-making. Although the average ITE score for TBL participants and all PGY levels (m = 54.4, sd = 12.91) was higher than non-TBL participants (m = 50.7 and sd=11.84) within the study period, differences were not significant (t(119)=1.633, p=1.10). ITE scores by PGY level showed a significant difference in PGY 1 resident scores (t(55)=2.157, p=0.03). No significant differences were found in PGY2 and 3.

Conclusion: IM residents are receptive to the use of TBL for CCLS, and have favorable perceptions of collaborative learning. Additionally, results provide information on potential impact of TBL on available assessments such as the ITE. Evaluating its impact begins the process of determining the place of TBL in Rheumatology education.

Disclosure: Funding for this project was provided by the American College of Rheumatology Research and Education Clinician Scholar Educator Award.

Disclosure: K. D. Torralba, American College of Rheumatology-Research and Education Foundation , 2, 9 ; **R. Ben-Ari**, None; **F. P. Quismorio**, None; **B. A. Boateng**, None.

1357

Workshop Using Simulators to Teach Medical Students Large Joint Injections. Aasim Rehman, Vanessa C. Osting, Ashley G. Sterrett, John D. Carter, Priya Reddy, Louis Ricca, Joanne Valeriano-Marcet and Helen E. Bateman, University of South Florida, Tampa, FL

Purpose: To teach medical students the proper technique of large joint injections and assess the effect of such a workshop on their comfort levels when performing these procedures.

Method: All 4th year medical students attend the joint injection workshop at the beginning of their rheumatology rotation. The workshop consists of a teaching didactic session followed by the joint simulator injection session. The simulators are pre-wired anatomical models of the knee and shoulder. A pre and post workshop self assessment survey is given regarding student's comfort level with examination and injection of knee and shoulder joints, on a scale of 1 to 5 (1= not comfortable to 5= fully comfortable).

Results: A total of 68 4th year medical students completed the workshop. 23 students had performed knee injections, 6 had performed shoulder injection and 10 students had performed other musculoskeletal injections prior to attending the workshop. Results are shown in table 1.

Table 1: Pre and post workshop comfort levels. (N=68)

	Pre-Workshop Mean Comfort Level (+/- SD)	Post-Workshop Mean Comfort Level (+/- SD)	p-value*
Knee Palpation	2.81 (+/- 0.90)	3.93 (+/- 0.74)	<0.0001
Detecting Knee Effusion	2.75 (+/- 0.90)	3.51 (+/- 0.91)	<0.0001
Knee Injection	1.87 (+/- 1.02)	3.66 (+/- 0.84)	<0.0001
Shoulder Palpation (sub-acromial)	2.59 (+/- 0.85)	3.88 (+/- 0.86)	<0.0001
Shoulder Injection	1.44 (+/- 0.63)	3.59 (+/- 0.83)	<0.0001
Selection of Corticosteroid Preparation	1.55 (+/- 0.68)	3.15 (+/- 1.10)	<0.0001

* Paired t-test of post-workshop comfort level compared with pre-workshop comfort level.

Conclusion: Our joint injection workshop using simulators increases the comfort level of 4th year medical students when performing large joint injections.

Disclosure: A. Rehman, None; **V. C. Osting**, None; **A. G. Sterrett**, None; **J. D. Carter**, None; **P. Reddy**, None; **L. Ricca**, None; **J. Valeriano-Marcet**, None; **H. E. Bateman**, None.

1358

Teaching Residents Arthrocentesis and Soft-Tissue Injection Procedures: Practice Outcomes for Internal Medicine Residents in Outpatient and Hospitalist Careers. Catherine J. Bakewell[1] and Gregory C. Gardner[2], [1]Univ of Washington, Seattle, WA, [2]University of Washington, Seattle, WA

Purpose: In 1994 the University of Washington designed a half-day arthrocentesis course for internal medicine residents, followed by a month-long musculoskeletal rotation for primary care residents in 2002. Purpose of this study was to evaluate the impact of the course and rotation on primary care internist graduates of the program and to utilize the data to improve our procedure curriculum.

Method: Surveys were mailed to 2002 – 2006 internal medicine graduates who went into primary care or hospitalist careers. The surveys were designed to provide feedback on resident education in musculoskeletal procedures as well as characterize current clinical application of these procedures. This data was added to a previously collected survey of residents pre-and post arthrocentesis course from 2002.

Results: There were 52 responses from 82 surveys mailed to recent primary care graduates (64% response rate). Thirty-two respondents were practicing outpatient medicine (OPM). Twenty respondents worked only in an inpatient setting (IPM). The most common procedures performed were the knee followed by subacromial bursa, then trochanteric bursa. OPM graduates did 1054 procedures at 11 different sites per year. IPM graduates performed 44 procedures at 9 sites.

Physicians practicing OPM were more comfortable than IPM with procedures. IPM graduates had an average comfort level with knee arthrocentesis of 3.1 (1 = not comfortable, 5 = very comfortable), and performed an average of 1.5 procedures per year, compared to an average comfort level of 4.3 for those practicing OPM, who averaged of 9.9 knee arthrocenteses per year ($p < .05$ for both).

There was non-significant trend favoring increased comfort and number of procedures done for those respondents who took either the R1 arthrocentesis and injection course or the musculoskeletal month as an R2 over those who did not. OPM graduates felt training in residency is necessary in a wide variety of procedures while IPM graduates suggestions were more restricted. Even with training provided in residency and general comfort level of those practicing OPM, almost half of the respondents who practice OPM referred 6 or more musculoskeletal procedures per year to another clinician.

Conclusion: Our 2002 survey found that a focused arthrocentesis course had a significant impact on resident comfort level for up to 6 months. Once an individual enters the job force, their practice environment seems to be the single largest determinant in the practitioner's comfort level and number of procedures performed. Based our results we suggest:

1) Medicine R1s should receive training in aspiration/injection of the knee, subacromial bursa, and trochanteric bursa, as these comprise > 75% of all injections performed in clinical practice.

2) Once an internal medicine resident identifies a career path in primary care, we recommend more comprehensive training in arthrocentesis and soft tissue injection techniques tailored to their future career.

Disclosure: C. J. Bakewell, None; **G. C. Gardner**, None.

1359

The Development of An Interactive Web-Based Rheumatology Teaching Module. Michelle Batthish[1], Ereny Bassilious[2], Nicholas Blanchette[2], Gordon Soon[2], Nadia Luca[2], Rosanne St Bernard, Teddy Cameron[3], Tamara Bahr[3], Avi Hyman[3], Gordon Tait[3], Brian Feldman[1], Rayfel Schneider[1] and Shirley ML Tse[2], [1]The Hospital for Sick Children, Toronto, ON, [2]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, [3]Academic Computing, University of Toronto, Toronto, ON

Purpose: We previously demonstrated that an interactive web-based rheumatology teaching module would be both accessible and well utilized by paediatric residents. Our objective is to develop an interactive web-based teaching module to improve resident learning and problem solving about rheumatology ("POINTER": Paediatric Online Interactive Teaching in Rheumatology).

Method: We developed interactive case scenarios and patient simulators around commonly encountered rheumatologic topics. This will enable residents to work through modules at their convenience and receive consistent and timely feedback.

Results: POINTER was created on the University of Toronto Portal website with a unique login and password for each user. POINTER consists of two parts. Part I Interactive case-based scenarios: this is a dynamic module that starts with a common clinical stem but based on a random assignment feature the computer generates pathways to different diagnoses, hence promoting its multiple use. Throughout, learners are presented with multi-media and clinical "pearls" of information. Part II Patient simulator: Learners work through a case with total autonomy, selecting relevant history, physical exam maneuvers, and investigations and are ultimately provided with a final diagnosis. The simulator tracks and assigns a time and cost expenditure to the user's interventions. No feedback on performance is provided until a final diagnosis is submitted at which time the learner receives feedback on diagnostic accuracy, time and cost expenditure.

Conclusion: Following development of POINTER, we will evaluate the feasibility, effectiveness and satisfaction of this module by randomizing a group of residents to using the POINTER website or reviewing pre-selected articles. Each group will complete an information based pre and post multiple choice test and a teaching modality satisfaction questionnaire. In addition, we will track POINTER usage, including frequency of use, length of time spent online and time of day POINTER is most accessed.

Disclosure: M. Batthish, None; **E. Bassilious**, None; **N. Blanchette**, None; **G. Soon**, None; **N. Luca**, None; **R. St Bernard**, None; **T. Cameron**, None; **T. Bahr**, None; **A. Hyman**, None; **G. Tait**, None; **B. Feldman**, None; **R. Schneider**, None; **S. M. Tse**, None.

1360

The Carolinas Fellows Collaborative (CFC): An Educational Model for Rheumatology Training Programs. Beth L. Jonas[1], Lisa G. Criscione-Schreiber[2], Marcy B. Bolster[3] and Kenneth S. O'Rourke[4], [1]Univ of North Carolina, Chapel Hill, NC, [2]Duke University Med Ctr, Durham, NC, [3]Medical Univ of South Carolina, Charleston, SC, [4]Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: The ACGME Outcome Project was approved in 1999 and changed the focus of program evaluation from a process oriented assessment to an evaluation of outcomes assessment. Over the last decade there has been an exponential increase in the requirements for training programs and training program directors in all the specialties of Medicine and Surgery in response to the ACGME Outcome Project. Development and implementation of the continually evolving requirements presents a particular challenge to small programs with limited financial and administrative support.

Method: Previously, each of our programs presented a summer core lecture series for the new rheumatology fellows. Beginning in 2004, the program directors from the four programs in our region combined resources and faculties to provide a July weekend retreat for rheumatology fellows in which the summer core lecture series was covered in three days. This conference was extremely well-received and led the following year to the addition of a winter conference program. This series of biannual retreats rotates among institutions and takes advantage of the particular expertise at each institution. The program directors meet at least twice annually to develop curricula, goals and objectives, evaluation tools, educational research projects, and to discuss issues important to training rheumatology fellows.

Results: In a collaborative fashion, the program directors have successfully developed the curriculum and hosted 5 summer and 4 winter rheumatology fellows' conferences. The July program includes a cadaver lab on joint aspiration and injection techniques. For each of the 4 winter conferences, we have developed and implemented a Rheumatology Objective Structured Clinical Examination. Since its inception, the CFC has worked to develop competency based goals and objectives for all the rheumatology learning activities, and competency- based assessment tools in accordance with the ACGME Outcome Project. In addition, the program directors serve each other as peer mentors who share successful educational tools, collaborate on educational research, help address program problems and together develop strategies to address them. Moreover, fellow interaction at the twice yearly conferences has led to inter-institutional clinical research and publication.

Conclusion: Regional collaboration of rheumatology training program directors serves to combine limited resources for education of rheumatology fellows in the environment of increasing regulation and requirements. Other important advantages of this collaboration include exposure of the fellows to a wider faculty with unique expertise, development of collegial and research relationships among the fellows at different institutions, and opportunities for peer mentoring among the training program directors.

Disclosure: B. L. Jonas, None; **L. G. Criscione-Schreiber**, None; **M. B. Bolster**, None; **K. S. O'Rourke**, None.

1361

Competency Based Goals, Objectives, and Evaluations for Rheumatology Training Programs: A Standardized Template of Learning Activities From the Carolinas Fellows Collaboration (CFC). Lisa G. Criscione-Schreiber[1], Marcy B. Bolster[2], Beth L. Jonas[3] and Kenneth S. O'Rourke[4], [1]Duke University, Durham, NC, [2]MUSC, Charleston, SC, [3]Univ of North Carolina, Chapel Hill, NC, [4]Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: Each ACGME accredited Rheumatology training program must have written goals and objectives (G&O) for each learning activity (LA). Evaluation of each LA should measure whether rotation objectives are met. Rheumatology training programs nationally will benefit from access to pre-written goals and objectives.

Method: In three working meetings we composed G&O and evaluations for each LA of rheumatology training programs, anticipating that individual programs could modify documents as necessary. G&O were written collaboratively, and objectives feature appropriate verbs based on Bloom's taxonomy. Draft documents were peer reviewed by faculty at the four institutions and by members of the ACR Clinician Scholar Educator Group. Evaluations for each LA were adapted from these competency-based objectives. By consensus, we limited evaluation scores to: superior performance, meets objective, or does not meet objective.

Results: We completed competency-based G&O for 7 core rotations, 8 elective rotations and 7 conferences. LA goals detail progressive fellow performance improvement by educational level. G&O documents include teaching methods and list how progress toward meeting objectives is evaluated. Specific objectives in each competency are mirrored in the evaluations (Figure).

Figure. Sample Evaluation of Medical Knowledge Objectives for the Outpatient Continuity Clinic

Check (1) the appropriate overall assessment, and (2) specific objectives for improvement

MEDICAL KNOWLEDGE	Does not meet expectations	Meets Expectations	Superior Performance	Insufficient Observation

- o Describe pathogenesis & clinical expression of the rheumatic diseases encountered
- o Summarize an approach to evaluation of multi-organ inflammatory disorders
- o Discuss mechanisms of action, uses, and side effects of pharmacologic agents used
- o Identify therapy-related complications
- o Distinguish non-rheumatic disorders from rheumatic diseases
- o Interpret diagnostic tests
- o Critically appraise and cite literature pertinent to the evaluation of outpatients
- o Describes the structure and function of musculoskeletal tissues and joints
- o Discuss the roles of physical and occupational therapy
- o Specify the role of orthopedic surgery in the care of patients with musculoskeletal conditions

Conclusion: We produced detailed competency-based G&O for each potential LA of a rheumatology training program. We propose adoption of these G&O by the ACR, with access available to all US training programs. Evaluation forms that mirror stated objectives ensure that trainees are assessed using standardized measures and are aware of the learning expectations. These documents are now used by the four CFC training programs and are easily modifiable for use by all US rheumatology programs.

Disclosure: L. G. Criscione-Schreiber, None; **M. B. Bolster**, None; **B. L. Jonas**, None; **K. S. O'Rourke**, None.

1362

Joint Simulator Workshop as a Teaching Tool for Joint Injections: Do Rheumatology Subspecialty Residents Benefit? Vanessa C. Osting, Aasim Rehman, Ashley G. Sterrett, Christopher Koltz, Priya Reddy, Helen E. Bateman, Louis Ricca, John D. Carter and Joanne Valeriano, University of South Florida, Tampa, FL

Purpose: To assess the effect of a joint injection workshop on the comfort levels of rheumatology subspecialty residents in identifying joint anatomy and performing intraarticular injections.

Method: A joint injection workshop consisting of both didactic teaching and interactive joint models was offered to rheumatology subspecialty residents to enhance their knowledge and comfort with the anatomy and injection of the knee, shoulder (sub-acromial), wrist, elbow and ankle joints. A self-assessment survey was administered before and after the workshop to assess comfort levels on a scale (1-5: 1 = not comfortable; 5 = fully comfortable) in performing 3 tasks for each joint: palpating bony structures, selecting a corticosteroid preparation and performing joint injections.

Results: 15 rheumatology subspecialty residents from various institutions participated in the workshop. None of the rheumatology subspecialty residents had prior formal joint injection workshop training. Results are shown in Table 1.

Table 1: Pre and post workshop comfort levels (N=15)

	Pre-Workshop Mean Comfort Level (+/- SD)	Post-Workshop Mean Comfort Level (+/- SD)	p-value*
Knee Anatomy	3.87 (+/- 0.92)	4.67 (+/- 0.49)	0.0004
Knee Effusion	3.60 (+/- 1.12)	4.20 (+/- 0.77)	0.0140
Corticosteroid Preparation for Knee	4.00 (+/- 1.00)	4.73 (+/- 0.46)	0.0032
Knee Injection	4.00 (+/- 1.00)	4.60 (+/- 0.63)	0.0070
Shoulder Anatomy	3.07 (+/- 0.70)	4.13 (+/- 0.92)	0.0013
Corticosteroid Preparation for Shoulder	3.27 (+/- 0.80)	4.20 (+/- 0.68)	0.0005
Shoulder Injection (sub-acromial)	3.27 (+/- 1.03)	4.07 (+/- 0.80)	0.0004
Ankle Anatomy	2.87 (+/- 0.99)	3.80 (+/- 0.77)	0.0054
Corticosteroid Preparation for Ankle	3.20 (+/- 1.08)	4.00 (+/- 0.76)	0.0281
Ankle injection	2.33 (+/- 1.11)	3.53 (+/- 0.99)	<0.0001
Elbow Anatomy	2.87 (+/- 0.83)	4.07 (+/- 0.88)	<0.0001
Corticosteroid Preparation for Elbow	3.20 (+/- 0.94)	4.13 (+/- 0.92)	0.0011
Elbow injection	2.47 (+/- 1.19)	3.53 (+/- 1.06)	0.0045
Wrist Anatomy	2.67 (+/- 0.82)	3.87 (+/- 0.92)	0.0004
Corticosteroid Preparation for Wrist	3.00 (+/- 0.93)	3.93 (+/- 0.88)	0.0011
Wrist injection	2.13 (+/- 1.19)	3.47 (+/- 1.19)	0.0018

***** Paired t-test of post-workshop comfort level compared with pre-workshop comfort level.

Conclusion: Our joint injection workshop improves the comfort levels of rheumatology subspecialty residents in identifying joint anatomy and performing intraarticular injections

Disclosure: V. C. Osting, None; **A. Rehman**, None; **A. G. Sterrett**, None; **C. Koltz**, None; **P. Reddy**, None; **H. E. Bateman**, None; **L. Ricca**, None; **J. D. Carter**, None; **J. Valeriano**, None.

1363

Rheumatology Practice Profiles in Teaching and Community Settings: Implications to Fellowship Training. Amarie M. Negrón, Leyda M. Díaz-Correa, Angel M. Mayor, Salvador Vilá and Luis M. Vilá, University of Puerto Rico Medical Sciences Campus, San Juan, PR

Purpose: Specialty and subspecialty medical training programs must provide trainees a wide and balanced exposure to clinical entities. Although university-based programs usually allow residents to learn the evaluation and management of unusual and difficult cases, they do not always provide the required experience to manage common and less complicated medical conditions which are usually seen at community-based medical facilities. Few studies have addressed these concerns. The aim of this study was to compare the rheumatology practice profiles of a university setting and two community-based rheumatology practices.

Methods: Claim forms submitted from rheumatology practices to healthcare insurance companies in 2007 were evaluated. The university and community settings were located in the same geographic region of a United States city. The university setting has an accredited Rheumatology Training Program by the Accreditation Council for Graduate Medical Education and fellows had clinical exposure to all rheumatology services provided by the institution. Demographic parameters, primary diagnoses (per International Classification of Diseases, Ninth Revision), type of patient visit and rheumatologic procedures (per Current Procedural Terminology-4) were examined. Variables were analyzed by chi-square and Student's *t* tests.

Results: A total of 8,153 claim forms were evaluated; 1,893 from the university setting and 6,260 from the community practices. The demographic features, type of patient visit, rheumatologic procedures and primary diagnoses are shown in the table below.

Feature	**University (n = 1,893)**	**Community (n = 6,260)**	**p value**
Age, mean years (SD)	45.4 (15.3)	55.7 (16.2)	<0.001
Gender, % women	88.3	88.5	0.002
Office visit, %	89.9	99.7	<0.001
Emergency room visits, %	0.5	0.0	<0.001
Hospital visits, %	9.2	0.2	<0.001
Joint injections, %	3.0	10.4	<0.001
Soft tissue injections, %	1.7	5.3	<0.001
Rheumatoid arthritis, %	17.2	11.4	<0.001
Systemic lupus erythematosus, %	39.6	14.0	<0.001
Scleroderma, %	3.4	0.6	<0.001
Sjögren's syndrome, %	0.4	2.2	<0.001
Inflammatory muscle disease, %	2.4	0.4	<0.001
Polymyalgia rheumatica, %	0.3	1.2	<0.001
Unspecified connective tissue disease, %	3.0	8.1	<0.001

Vasculitic syndromes, %	2.6	0.8	<0.001
Spondyloarthropathies, %	1.4	0.9	0.047
Osteoarthritis, %	10.1	19.3	<0.001
Gout, %	1.4	0.2	<0.001
Fibromyalgia syndrome, %	2.0	7.0	<0.001
Regional rheumatic pain disorders, %	1.5	8.0	<0.001
Low back pain, %	0.4	5.8	<0.001

Conclusion: Several differences were found in the rheumatology practice profile among patients seen at the university and community settings. This study suggests that efforts should be undertaken to provide a more rounded and diversified patients' exposure to rheumatology fellows at this institution.

Disclosure: A. M. Negrón, None; **L. M. Díaz-Correa**, None; **A. M. Mayor**, None; **S. Vilá**, None; **L. M. Vilá**, None.

1364

Rheumatology Telemedicine in Rural Australia. Simon Burnet[1], Tim Kelly[2], Alison Marrinan[3], Peter Donohoe[3] and Tori Wade[4], [1]Adelaide, Australia, [2]Crystal Brook Hospital, [3]Adelaide to Outback GP Training Programme, [4]University of Adelaide

Purpose: This pilot study examines the feasibility of interns on rural placements facilitating specialist services to rural areas via an innovative e-health approach. The project was designed to enhance educational opportunities for junior doctor training, as well as increase rural access to specialist services, while providing optimal patient care.

Method: The study involved interns at a rural general practice performing follow-up rheumatology consultations in collaboration with a metropolitan based specialist via videophone broadband link-up. The process replaces the rheumatologist's usual follow-up consultations.

Results: Three telemedicine clinics were evaluated from the patient, intern and Rheumatologist's perspective. We found multiple benefits from this novel approach including;Interns gaining improved rheumatology clinical skills and communication skills;Enhanced understanding between general practice and other specialties;Interns and consultants working together in this way provides a high level of service otherwise not possible; and Reduced travel time and cost savings for both patients and consultants.

Conclusion: Experience in this pilot study indicates potentially unlimited applications for dynamic broadband video link-up to enhance junior doctor training with specialists in general practice. One limitation is Rheumatologist's inability to formally examine patients. It showcases junior doctors gaining valuable high-level learning via technology appropriate to Y-generation learning styles. It offers a solution to overcome rural geographic isolation from specialist care.

Disclosure: S. Burnet, None; **T. Kelly**, None; **A. Marrinan**, None; **P. Donohoe**, None; **T. Wade**, None.

1365

PANLAR Recommendations and Guidelines for Musculoskeletal Ultrasound Training in the Americas. Carlos Pineda and The PANLAR Ultrasound Study Group, Instituto Nacional de Rehabilitacion, Mexico City, Mexico

Purpose: To develop guidelines for Musculoskeletal Ultrasound (MSUS) training in the Americas for Pan American League of Associations for Rheumatology (PANLAR) courses.

Method: Twenty-six Rheumatologists from 19 countries of the American Continent participated in a consensus-based interactive process using two consecutive electronic questionnaires. The first questionnaire included the following: the relevance of organizing courses to teach

MSUS to Rheumatologists; determination of the most effective educational course model; trainee levels; educational objectives; requirements for passing the course(s); course venues; number of course participants per instructor, and percentage of time spent in hands-on sessions. The second questionnaire consisted of questions that did not achieve consensus (> 65%) in the first questionnaire, topics, and pathologies to be covered at each course level. In addition, two meetings were held, to present and discussed the results from the two questionnaires and the questions that did not achieve consensus, to review and approved the final recommendations and guidelines for MSUS training courses in the Americas.

Results: Ninety six percent of the participants answered the first and 100% the second questionnaire. The group agreed that MSUS is an essential diagnostic and procedural tool for the practicing clinical rheumatologist. General consensus was obtained for the courses to be divided into three educational levels: basic; intermediate, and advanced. These courses should be taught using a theoretical-didactic and hands-on model. In addition, the group established the minimum requirements for attending and passing each MSUS course level, the ideal number of course participants per instructor (four participants/instructor), and the specific topics and musculoskeletal pathologies to be covered. In the same manner, the group concluded that 60–70% of course time should be focused on hands-on sessions.

Conclusion: A multinational group using a consensus-based questionnaire established PANLAR recommendations and guidelines for MSUS course training in the Americas. The PANLAR Ultrasound Study Group urges that these recommendations be adopted in the future by both national and regional institutions involved in the training of Rheumatologists for the performance of MSUS.

Disclosure: C. Pineda, None.

1366

Peer to Peer Mentoring: Facilitating Individuals with Early Inflammatory Arthritis to Manage Their Arthritis. M. Bell[1], Paula Veinot[2], Gaya Embuldeniya[3], Romy Cho[3], Phedias Diamandis[3], Lopamudra Das[3] and Chris Tran[3], [1]Univ of Toronto, Toronto, ON, [2]U of T, Toronto, ON, [3]U of T, ON

Purpose: Inflammatory arthritis (IA) is a major cause of long-term disability. Peer support has been used in various chronic conditions and may assist individuals with early IA (EIA) to make informed decisions and better manage their disease. Existing peer support programs may not meet the needs of persons newly diagnosed with IA. The purpose of this study is to identify educational preferences as well as informational, emotional and appraisal support needs of individuals with EIA from the perspectives of patients, family and friends, and health care providers (HCPs).

Methods: Semi-structured, one-on-one interviews with individuals were performed with a purposive sample. Themes were identified through constant comparative analysis.

Results: Interviews were conducted with patients with EIA (n=11), family and friends (n=6), and HCPs (n=9). *Individuals with EIA* reported using a variety of information sources (books, Internet, physicians) with informational needs evolving over time. Peer support was thought to be a viable option for support. Disease stage, personal qualities and one-on-one vs. group format were important considerations.

Data from *family and friends* suggested that the general public lacks awareness of EIA. HCPs, the Internet and colleagues who are HCPs were important informational sources. A network of emotional support was reported to be valuable to cope with and learn about EIA. Peer support was a much-lauded approach for informational and emotional support.

From the *HCP* perspective, findings support an arthritis care model that begins with a focus on “therapy initiation” through improved education from HCPs and a later transition to “medication adherence” aided through peer support. Peers were thought to play an important role in helping new patients make lifestyle modification choices and to cope once therapy had begun.

Across the three categories of participants, there was a desire for peer support (learning preferences, delivery method) to be context-driven (e.g., importance of sharing similar socioeconomic status, disease status), and for having choice as to whether or not to participate. Interviews are ongoing to examine whether culture may have an impact on learning needs.

Conclusion: Peers may be considered an instrumental part of decision support and stress management and an adjunct to clinical care for persons with EIA.

Disclosure: M. Bell, None; **P. Veinot**, Paula Veinolt, 5 ; **G. Embuldeniya**, Gaya Embuldeniya, 5 ; **R. Cho**, None; **P. Diamandis**, None; **L. Das**, None; **C. Tran**, None.

1367

Are Fewer Workshop Sessions as Effective as the Classic ASMP? Jean Goeppinger[1], Kate R. Lorig[2], Ziya Gizlice[1], Philip Ritter[2] and Teresa J. .Brady[3], [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Stanford University, Palo Alto, CA, [3]Centers for Disease Control and Prevention, Atlanta, GA

Purpose: To determine the effectiveness of a shorter version of the classic six-week Arthritis Self Help Course/Arthritis Self-Management Program (ASHC/ASMP) workshop. We asked if a shorter workshop would have the same positive outcomes as the six-week workshop while – potentially – increasing enrollment and decreasing the financial and personnel barriers experienced by disseminating organizations.

Method: Based on the findings of a needs assessment of persons with arthritis, clinicians, and program providers, we developed a two-week, six hour, lay-led workshop that included the content deemed most important: principles of self-management and pain management, goal-setting/action planning, problem-solving steps and feedback, exercise/fitness, difficult emotions, medication usage, and community resources. Workshop Leaders were trained to facilitate activities focusing on each of these areas. Program participants were recruited at Stanford (N=378) and UNC-Chapel Hill (N=357) and randomized individually (Stanford) and by cluster (UNC-Chapel Hill) to immediately receive (1) the High Resource Intervention: a two-week/six hour workshop with supplementary materials including The Arthritis Helpbook, a self-test, exercise and relaxation CDs, and a "Community Resource" Tip Sheet, (2) the Low Resource Intervention: a two week/six hour workshop with only a supplementary booklet of Tip Sheets, and (3) a four month wait list control group. At the end of four months controls were offered a workshop. All participants were followed in a longitudinal study for 12 months. Self-administered measures included health status, health behavior, arthritis self-efficacy, medical care utilization, and demographic variables. Analyses, including Analysis of Covariance controlling for randomization method, were conducted for participants at both sites.

Results: At four months, comparing all intervention subjects with randomized wait list controls, there were few and inconsistent improvements in health status, health behavior, arthritis self-efficacy, and medical care utilization outcomes at either Stanford or UNC. One out of 16 outcome variables showed statistically significant improvements at Stanford, while two out of 16 showed statistically significant improvements at UNC. There were also few differences between participants in high and low exposure interventions at either site. The twelve month longitudinal study findings were even weaker than those at four months.

Conclusion: The results of this attempt to develop a less time and resource intensive version of the ASHC/ASMP must be considered negative. The improvements subsequent to the two-week interventions were minimal, particularly when comparing the results of the randomized study to six-week small-group, Mailed Tool Kit, and internet interventions.

Disclosure: J. Goeppinger, None; **K. R. Lorig**, Bull Publixhing Company, 7 ; **Z. Gizlice**, None; **P. Ritter**, None; **T. J. .Brady**, None.

ACR/ARHP Poster Session C

Epidemiology and Health Services Research III

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1368

Osteoporosis Care in a Community-Based Cohort of Patients with Systemic Lupus Erythematosus. Gabriela Schmajuk[1], E.H. Yelin[2], E.F. Chakravarty[3] and J. Yazdany[2], [1]Stanford University, San Francisco, CA, [2]UCSF, SF, CA, [3]Stanford Health Services/Blake Wilbur Clinic, Palo Alto, CA

Purpose: Osteoporosis and fragility fractures are associated with significant morbidity for patients with systemic lupus erythematosus (SLE). Quality indicators (QI) published in 2009 advise the use of calcium, vitamin D, and bone mineral density testing (BMD) among SLE

patients using ≥ 7.5 mg of prednisone daily for ≥ 3 months. Our objective was to evaluate the quality of osteoporosis prevention and care in a community-based cohort of patients with SLE.

Methods: Data were derived from an ongoing longitudinal study of patients with confirmed SLE. Respondents participate in an annual telephone survey and are queried regarding demographic, clinical, and other healthcare-related variables. In 2008, questions regarding bone health (calcium, vitamin D, and BMD use) were posed to 779 subjects. Patients with incomplete data for predictors or outcomes of interest were excluded (n=35). Multiple logistic regression was used to adjust for demographic and healthcare-related covariates.

Results: 744 subjects were analyzed: 92% were female, with mean (standard deviation) age 50.7 (12.6) years and Systemic Lupus Activity Questionnaire score 11.7 (7.8). 76.1% had seen a rheumatologist within the past year. In addition to the full cohort, we examined 2 subgroups: (1) all current steroid users (n=427), (2) current steroid users who met eligibility criteria for the QI (n=127). Proportions of patients reporting calcium, vitamin D, and BMD use are described in Table 1. In all groups, fewer than 50% of patients reported receiving all 3 outcomes. In multivariate analyses, older age, female sex, and seeing a rheumatologist predicted the receipt of appropriate osteoporosis care in the full cohort and among all steroid users. Similar findings were observed among the smaller subgroup of steroid users who met criteria for the QI, although the findings did not reach statistical significance.\

Conclusion: Osteoporosis care in this community-based cohort of SLE patients is suboptimal. Even among patients at highest risk (≥ 7.5 mg of prednisone daily for ≥ 3 months), the proportion of patients fulfilling the SLE osteoporosis QIs is low. Quality-improvement efforts should address osteoporosis prevention and care among all SLE patients, especially those taking moderate-dose, prolonged steroids.

Table 1.

	All patients	**All steroid users**	**QI steroid users***
Outcome	**n=744**	**n=427**	**n=127**
Calcium use	466 (62.6)	293 (68.6)	92 (72.4)
Vitamin D use	411 (55.2)	263 (61.6)	79 (62.2)
BMD within 3 years	428 (57.5)	282 (66.0)	83 (65.4)
All outcomes	270 (36.3)	180 (42.2)	52 (40.9)

* QI steroid users: patients using ≥ 7.5 mg of prednisone daily for ≥ 3 months within the past year

Disclosure: G. Schmajuk, None; **E. H. Yelin**, None; **E. F. Chakravarty**, None; **J. Yazdany**, None.

1369

Disparities in Outcomes Among Persons with Rheumatoid Arthritis From University-Affiliated Clinics. E.H. Yelin[1], J. Barton[2], Laura Trupin[1], L. J. Julian[1], J. Yazdany[1], Mary E. Margaretten[2], Vladimir Chernitskiy[3], Jonathan Graf[2] and John Imboden[2], [1]UCSF, SF, CA, [2]UCSF, San Francisco, CA, [3]University of California, San Francisco, CA

Purpose: This project assesses disparities in outcomes by race/ethnicity, immigrant status, and socioeconomic status among persons with rheumatoid arthritis (RA) sampled from the rheumatology clinics at a public hospital and tertiary-care facility that were designed to serve diverse populations in an urban environment.

Methods: Data are derived from the Rheumatoid Arthritis Cohort Study (RACS). RACS enrolls the universe of persons with RA presenting to rheumatology clinics at an urban county hospital and a tertiary care facility both affiliated with a university. Once enrolled, all data from clinical encounters, including laboratory tests, are entered into a database. RACS also includes an annual structured telephone survey about demographic characteristics, health care utilization, and standardized measures of patient-reported outcomes conducted in English, Spanish, or Cantonese/Mandarin.

Results: Derive from the initial 176 RACS participants with completed interviews for whom encounter data are also available. Outcome measures assessed include Disease Activity Score 28 (DAS 28) and the Health Assessment Questionnaire (HAQ), a measure of functional status, from clinical encounters, and pain rating (0-100) and global RA status (0-100) from the telephone survey. Disparities are assessed by race/ethnicity (Asian/Pacific Islander [API], Hispanic [HISP], African-American [AA], and Non-Hispanic White [WHT); education level (less than high school [<HS], high school or some college [HS/SC], and college graduate or beyond [BA]); and whether individual is an immigrant. We used ordinary least squares to regress the outcome measures on age, gender, duration of RA, a composite measure based on rheumatoid factor positivity, anti-CCP positivity, or the presence of erosions, and, separately, race/ethnicity, education level, and immigrant status.

RACS participants average 55 years of age (range 19-81). 82% are female, 35% WHT, 36% HISP, 23% API, and 6% AA. 54% are immigrants. 44% speak languages other than English at home, of these only 16% can speak English fluently. 31% have <HS-, 36% have HS/SC-, and 33% have BA-level educations. Average duration of RA is 11 years (range 0-53). The table below shows significant disparities in all outcome measures by race/ethnicity, education level, and immigrant status.

Conclusion: Even in medical settings with a history of serving diverse populations, pronounced disparities by race/ethnicity, education level, and immigrant status are observed in all outcomes.

		DAS-28	Pain Rating	RA Global	HAQ
		Adjusted mean (95% CI)			
Race	API	3.7 (3.2,4.2)	45 (36,55)	50 (40,60)	1.1 (0.9,1.4)
	HISP	4.0 (3.7,4.4)	48 (41,56)	47 (39,55)	1.5 (1.4,1.8)
	AA	3.2 (2.4,4.1)	29 (18,47)	48 (29,66)	1.2 (0.7,1.8)
	WHT	2.8 (2.4,3.2)	28 (20,36)	30 (21,38)	0.9 (0.7,1.1)
Educ	<HS	4.3 (3.9,4.6)	53 (45,61)	54 (46,62)	1.5 (1.3,1.8)
	HS/SC	3.5 (3.2,3.9)	35 (27,42)	41 (34,49)	1.2 (1.0,1.4)
	BA	2.6 (2.3,3.0)	30 (22,38)	29 (22,37)	0.9 (0.7,1.1)
Immigrant	No	2.9 (2.5,3.2)	29 (22,36)	33 (27,40)	1.0 (0.8,1.2)
	Yes	3.9 (3.6,4.2)	46 (40,52)	47 (41,53)	1.4 (1.2,1.6)
All variables significant at p<.05					

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Mortality Impact of Extra-Articular Manifestations of Rheumatoid Arthritis: Observations From a Population-Based Patient Cohort. Elena Myasoedova[1], Cynthia S. Crowson[1], Carl Turesson[2], Sherine E. Gabriel[1] and Eric L. Matteson[1], [1]Mayo Clinic, Rochester, MN, [2]Malmö, Sweden

Purpose: To compare the trends in mortality and examine impact of development of a second extra-articular manifestation of rheumatoid arthritis (ExRA) during the period 1995-2007 to the previous decade, and to examine the possible risk factors for these outcomes.

Method: We conducted a retrospective medical record review of incident ExRA features from an incident population based cohort of patients with RA (1987 ACR criteria first met between 1/1/1995 and 1/1/2008). Patients were followed from 1/1/1995 until 1/1/2009 or death. The date of ExRA incidence was recorded and ExRA were classified according to the predefined criteria (Ann Rheum Dis 62:722-727, 2003). Cox proportional hazards models were used to assess the association of ExRA with mortality and with the development of a second ExRA. Time-dependent covariates were used to model ExRA and risk factors, which developed over time. Patients with ExRA prior

to incidence date were excluded from each analysis. Mortality rates were compared to those reported for the previous decade (incident RA cases between 1/1 1985 and 12/31/1994 from the same population base, followed through 12/31/2000 (J Rheumatol 29:62-67, 2002).

Results: The study population included 463 RA patients with incident RA (mean age 55.6, 69% female) followed up for a median of 5.8 years, during which 53 patients died. Rheumatoid factor (RF) was present in 306 (66%) patients. During the follow-up period, 159 patients developed an incident ExRA (22 with severe ExRA) and 37 developed a second ExRA. There were significantly fewer second ExRA in the 1995-2007 cohort than in the 1985-1994 cohort (hazard ratio [HR] 0.5; 95% confidence interval [CI] 0.3, 0.9). Potential predictors of second ExRA (age, sex, calendar year, smoking, RF positivity, joint erosions/destructive changes, subcutaneous nodules as the first ExRA and exposure to antirheumatic drugs) failed to reveal any significant associations. ExRA was a significant predictor of premature mortality (HR 2.0, 95% CI 1.1, 3.6) after adjusting for age, sex and calendar year. In contrast with previous findings, severe ExRA did not confer a greater mortality risk than overall occurrence of ExRA (HR 2.1, 95% CI 0.8, 6.0, vs no severe EXRA). Similarly, development of a second ExRA did not further increase mortality risk (p=0.33). While not reaching statistical significance, the mortality rates compared to the 1985-1994 decade after occurrence of ExRA (HR 0.7, 95% CI 0.4, 1.4) and after severe ExRA (HR 0.6, 95% CI 0.2, 2.1), suggested improved survivorship in these patients compared to the 1985-1994 decade.

Conclusion: ExRA was significantly associated with decreased survivorship in RA. Patients diagnosed with RA during the 1995-2007 period were half as likely to have a second ExRA compared to RA patients in the previous decade, and a second ExRA was not associated with higher mortality. Survival following ExRA may be improving compared to the previous decade.

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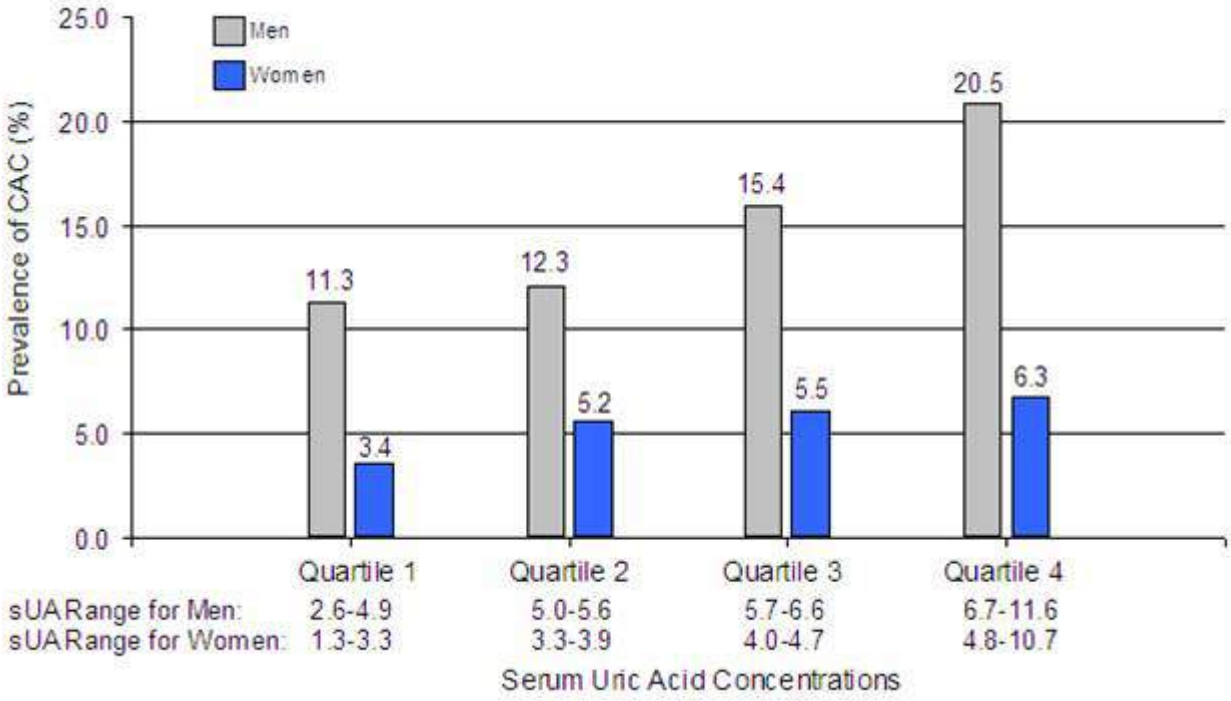
Hyperuricemia Is Associated with Subclinical Coronary Atherosclerosis. E. Krishnan[1], M. Bennett[1], L. Chung[1], M. Lyon[1], B. J. Pandya[2] and O. Dabbous[2], [1]Stanford University School of Medicine, Palo Alto, CA, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL

Purpose: To test the hypothesis that asymptomatic hyperuricemia (serum uric acid [sUA] >7.0 mg/dL) is a risk for subclinical coronary atherosclerosis, independent of other known risk factors.

Method: Subjects (n=2,997) without cardiovascular disease participated in a 15-year prospective observational study (the Coronary Artery Risk Development in Young Adults Study, CARDIA) that included 1,374 men (mean age 40.2 years) and 1,623 women (mean age 40.3 years). All subjects underwent clinical and laboratory tests for cardiovascular risk assessment at baseline and year 15. Presence of coronary artery calcification (CAC), defined as an Agatston score >0, was the indicator of subclinical atherosclerosis. Statistical analysis examining the relationship between presence/absence of CAC and sUA concentrations was performed using logistic regression models where the potential confounding effects of age, gender, race, body mass index, low- and high-density lipoproteins, triglyceride, hypertension, diabetes, smoking, alcohol use, and renal disease as measured by serum creatinine and albuminuria were addressed.

Results: Overall, 9.6% (15% men and 5% women) had developed CAC at year 15. Among men and women, the prevalence of CAC approximately doubled among those with the highest quartile of sUA at year 15 compared with those in the lowest quartile (Figure; $P<0.001$). In multivariate analyses adjusting for the risk factors significant in bivariate regressions, sUA >7.0 mg/dL at year 15 was associated with an odds ratio (95% confidence interval [CI]) of 1.67 (1.13-2.48) compared with sUA ≤7.0. When the 15-year change in sUA was the metric of interest, each unit increase in sUA was associated with an odds ratio (95% CI) of 1.18 (1.06-1.32) overall. These results did not change in the subanalyses that excluded individuals with metabolic syndrome.

Conclusion: The risk of subclinical atherosclerosis appears to rise with increasing sUA concentration in young adults in the general community. This trend remains even after controlling for important confounders including the presence of metabolic syndrome. The concept that asymptomatic hyperuricemia is a benign condition deserves to be revisited.



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Self-Reported Arthritis Increases Fracture Risk: Results From the Women's Health Initiative. Nicole C. Wright[1], Jeffrey R. Lisse[1], Charles B. Eaton[2], Brian T. Walitt[3] and Zhao Chen[1], [1]University of Arizona, Tucson, AZ, [2]Alpert Medical School of Brown University, Pawtucket, RI, [3]Washington Hospital Center, Washington, DC

Purpose: To study the association between arthritis, a leading cause of disability in the US, and fracture, a major public health concern in elderly populations.

Methods: The relationship between arthritis and fracture was examined in the Women's Health Initiative (WHI), a nationwide multi-ethnic cohort of postmenopausal women. Using self-reported baseline medical questionnaire data, women were classified into three arthritis categories: no arthritis, osteoarthritis (OA), and rheumatoid arthritis (RA). Only those RA cases with report of one of the RA therapeutic agents at baseline were included. Incident fractures were captured through periodic medical update. Trained WHI physicians adjudicated all fractures reported by women participating in the clinical trials component and all reported hip fractures. Age-adjusted fracture rates by arthritis category were generated, and Cox proportional hazards model was used to test the association between arthritis and fracture. Models were adjusted for study assignment and potential confounders such as age, lifestyle characteristics, and medications known to alter bone metabolism.

Results: Of the 161,809 enrolled in the WHI, 52% did not report an arthritic condition and 39.9% reported OA. Medication use could only be verified on 874(11%) of the initial self-reported RA cases. As of March 2008, the women were followed for a mean of 7.83 years. During this time, 26,940 fractures were reported including 2,898 (10.8%) spinal fractures and 1,921 (7.1%) hip fractures. Age-adjusted fracture rates were highest in the RA group and lowest in the non-arthritic group for each fracture type. Based on the adjusted Cox models,

report of arthritis is associated with an increased risk for fracture, with the RA group having the highest risk. For example, compared to the non-arthritis group, the OA and RA groups had 14% and almost 3-fold increase risk of hip fracture (T able).

Conclusion: Report of arthritis is associated with increases in fracture risk. The significant fracture risk increase seen in the OA group suggests that there is an association between bone quality and OA. This study confirmed the association between RA and fracture, consistent with the hypothesis that systemic inflammation may have an adverse effect on bone quality.

Table 1: Adjusted* Hazard Ratio (95% CI) of Fractures by Arthritis Status

	No Arthritis (n=84,168)	**OA (n=64,551)**	**RA (n=874)**
Total (n=26,940)	Ref.	1.10 (1.06, 1.14)	1.53 (1.29, 1.82)
Spine (n=2,898)	Ref.	1.17 (1.06, 1.29)	1.99 (1.31, 3.03)
Hip (n=1,921)	Ref.	1.14 (1.01, 1.29)	2.89 (1.86, 4.50)

* Adjusted for age; race; height; weight; physical activity; assignment in the HT trial, DM trial, and CaD trial; hospitalizations; falls; smoking ; hormone use; parental fracture >age 40; calcium & vitamin D intake; depression score; years since menopause; diabetic treatments; calcium regulating drugs; general health score; and fracture >55

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Physician Visits for SLE: Impact of Individual, Neighborhood, and Healthcare Delivery System Characteristics. Chris Tonner[1], Laura Trupin[2], J. Yazdany[2], L. J. Julian[2], Patricia Katz[2], Lindsey A. Criswell[3] and E.H. Yelin[2], [1]University of Califorina, San Francisco, CA, [2]UCSF, SF, CA, [3]University of California, San Francisco

Purpose: To assess the impact of overall health status, sociodemographics, nature of health insurance, characteristics of local community, and variation among local health care markets for hospital services (HSAs) on utilization of physician services among persons with SLE (MDSLE).

Methods: Data are derived from the Lupus Outcomes Study (LOS), a U.S. cohort of 755 persons with confirmed SLE diagnoses, recruited from clinical and non-clinical sources. Principal data collection is from an annual structured telephone interview covering demographics, SLE symptoms and activity, overall health status, and health care utilization. Present analysis includes 2926 person-years of observation from the 2003-2007 interviews. Using geocoded addresses, contextual data were appended for neighborhood socioeconomic characteristics (source: 2000 Census), subspecialists per capita in the county (source: Area Resource File), and HSAs (source: Dartmouth Health Care Atlas). We used a linear mixed model to estimate the impact of fixed effects for education, health care access, and living in a neighborhood with a high proportion of persons below poverty and random effects for the HSA on MDSLE, after adjusting for other sociodemographic characteristics and SLE severity and overall health status.

Results: LOS respondents reported a mean of 11.2 (95% CI 10.3-12.1) MDSLE. Persons with SLE with a high school education or less, living in areas of concentrated poverty and receiving care from HMOs and generalist physicians had significantly fewer MDSLE (Table). Those with a combination of ≤ high school education and who lived in poverty areas had only 74% as many MDSLE as the remainder; those with a combination of HMO and generalist MDs had only 63% as many as the remainder (both results were statistically significant). In addition, there was a statistically significant impact of HSAs on MDSLE, indicating that healthcare markets have an effect on utilization beyond individual and neighborhood characteristics.

Conclusion: Personal, health care system, and community characteristics each contribute independently to MDSLE. Low levels of education, living in areas of concentrated poverty, receiving care from a generalist and being in an HMO reduce MDSLE. The healthcare market also affects MDSLE.

Adjusted Number of MD Visits for SLE in Year Prior to Interview, by Education, Poverty Area, HMO Status, and Specialty of Main SLE MD			
Education		**HMO**	
≤ HS	10 (9,11)*	No	12 (11,12)*
Some College	12 (11,12)	Yes	11 (10,11)
≥ College Grad	12 (11, 13)	**Main SLE MD**	
Poverty Area		Generalist	8 (7,9)
No	12 (11,12)*	Specialist	12 (11,12)*
Yes	10 (9, 11)		
*p < .05			

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Population-Based Association of Sickle Cell Disease with Gout. Allan C. Gelber, Sophie Lanzkron, Janet Maynard and Carlton Haywood Jr., Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Gout is a leading cause of inflammatory arthritis. Hematologic disorders comprise a subset of the secondary causes of gout, including myeloproliferative (e.g. polycythemia) and lymphoproliferative (e.g. tumor lysis) disorders. Inherited hemoglobinopathies, including sickle cell disease [SCD], may contribute to hyperuricemia and gout, via increased nucleic acid production, accelerated hemolysis and impaired renal function. In the 1960s, the association of SCD with gout was described in several case series. A large scale examination, at the population level, has not occurred. If confirmed, identification of SCD as a risk factor for gout would contribute meaningfully to the care of patients with SCD with moderate-severe joint pain.

Method: We examined the 2004 Nationwide Inpatient Sample. For each hospital stay, one primary and 14 secondary ICD-9 diagnoses were recorded, as well as age, gender, race, socioeconomic status (SES) measures of health insurance and median household income. Hospital size and teaching status were recorded. We ascertained all hospital stays with a primary or secondary diagnosis of SCD or gout. A co-morbidity profile of coexistent obesity, renal insufficiency or hypertension was identified. Our analyses were restricted to 26 states with race as a demographic code, to hospital stays among African Americans, and to age 18-59, the adult age range when SCD-related admissions are most prevalent. Using logistic regression, we examined the independent association of SCD with gout.

Results: A total of 463,318 hospital stays met inclusion criteria. There were 12,070 (2.6%) hospitalizations in which SCD and 3,785 (0.8%) in which gout was recorded. Overall, the study population was 63% female, 37% receiving Medicaid, 54% with household income <$36,000, 8% obesity, 34% hypertension, and 3% with renal failure. These admissions were comprised of 60% urban teaching hospitals; 54% in the South, 26% in Northeast. Mean (±SD) age among SCD was 31.7 ± 9.9 years, and 49.9±7.5 in those with gout. The risk of gout among those with SCD, is as follows:

Model	Odds Ratio (95% Confidence Interval)
Age, gender-adjusted	2.4 (1.8 – 3.3)
Age, gender, SES-adjusted	2.2 (1.6 – 2.9)
Age, gender, SES, Co-morbidity-adjusted	3.1 (2.3 – 4.2)
Age, gender, SES, Co-morbidity, Hospital profile-adjusted	3.1 (2.3 – 4.2)

Conclusion: In a broadly representative 2004 sample of US hospitalizations, SCD was associated with a greater than three-fold increase in risk of coexistent gout. Clinicians evaluating hospitalized patients with SCD who manifest joint pain, in young and mid-adult life, ought to consider coexistent gout, in addition to sickle crisis and septic arthritis in the evaluation and management of these acutely ill patients.

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Markers of Disease Severity Predict New-Onset Heart Failure in Rheumatoid Arthritis. Soko Setoguchi[1], J. Greenberg[2], Jeffrey R. Curtis[3], Marc C. Hochberg[4], George Reed[5], Peter Tsao[1], Michael E. Farkouh[6], Joel M. Kremer[7] and Daniel H. Solomon[1], [1]Brigham & Women's Hospital, Boston, MA, [2]NYU, New York, NY, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of Maryland School of Medicine, Baltimore, MD, [5]University of Massachusetts, Worcester, MA, [6]Mount Sinai Medical Center, New York, NY, [7]Albany Medical College, Albany, NY

Purpose: Patients with rheumatoid arthritis (RA) have an increased risk of heart failure (HF) that may not be explained by traditional cardiovascular (CV) risk factors. However, the independent contribution of markers of RA severity to HF, especially in the presence of the RA treatments has not been well understood.

Method: We conducted a cohort study using a multicenter prospective longitudinal registry of RA from the US. The outcome of interest was subjectsreports of new onset HF confirmed by treating rheumatologists. When records were available, HF was positively adjudicated in 75% of HF cases. We assessed potential predictors of HF at baseline including demographic, life style, CV risk factors, RA treatment, and markers of RA severity (Table). We used Cox proportional hazard regression to conduct multivariate analyses. The discriminatory power of the Cox models including various factors was assessed by calculating the concordance probability (CP) (analogous to c-statistics in logistic regression models).

Results: Among 8,483 RA patients with no previous HF with mean age of 59, 75% women, and 93% white, we observed 33 cases of HF during a median follow-up of 23 months. The incidence rate of HF was 19 (95% CI 13– 26) per 10,000 patient-years. After adjusting for demographic, life style, CV risk factors, and treatment for RA, the risk of HF increased significantly by 180% with 1 unit increase in modified Health Assessment Questionnaire. There was a marginally significant increase in HF (10%) with 5 year increase in the duration of RA. We observed 5 fold increase in the risk of HF with NSAID use and 4 fold increase with oral steroid use >7.5mg (Table). Adding markers of RA severity and RA treatment to the model with demographic and life style factors improved the CP by 0.03 (0.79 to 0.82). The CP improved by another 0.02 by adding CV risk factors (0.82 to 0.84).

Conclusion: In the large sample of RA patients, markers of RA severity were strongly associated with the risk of new onset HF even after controlling for RA treatment and CV risk factors. More functional limitations, moderate dose steroids, and NSAIDs all elevated the risk for new onset HF in patients with RA. Increased HF surveillance may be considered in patients at elevated risk of HF.

Table

	Univariate Analysis			**Multivariate analysis***		
	HR	**95% CI**		**HR**	**95% CI**	
Markers of RA Severity						
Duration of RA (per 5 year)	**1.3**	1.2	1.5	**1.1**	1.0	1.3
Extraarticular manifestations	**2.1**	0.99	4.4	**1.2**	0.5	2.7

mHAQ (per 1 unit)	**3.9**	2.3	6.4	**2.8**	1.6	4.9
Seropositivity	**0.8**	0.4	1.5	**0.7**	0.3	1.3
RA Treatment						
Any DMARD	**0.8**	0.4	1.8	**0.7**	0.3	1.6
Daily prednisone dose						
None vs. 1 ~ 7mg	**1.2**	0.6	2.8	**1.0**	0.4	2.3
None vs. > 7.5mg	**3.1**	1.3	7.6	**4.0**	1.5	10.6
NSAID use	**2.8**	0.7	11.6	**5.2**	1.1	23.6

*Adjusted for age, gender, race, life style factors (BMI, smoking, and exercise), and CV risk factors (coronary artery disease, diabetes, hypertension, hyperlipidemia, and stroke).

HR: hazard ratio, CI: confidence interval, mHAQ: modified Health Assessment Questionnaire

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Serum 25(OH) Vitamin D Level and Rheumatoid Arthritis-Related Autoantibody: Analysis in a Population-Based U.S. Sample.

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Purpose: Rheumatoid arthritis (RA)-related autoantibody such as rheumatoid factor (RF) precedes to RA development. Immunomodulatory effect of vitamin D may play an important role in the presence of RA-related autoantibody. To assess the relationship between serum vitamin D levels and RA susceptibility, we compared 25(OH) vitamin D levels between unaffected RF+ subjects and RF- controls in a representative U.S. population-based sample from the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994).

Method: We identified subjects aged 60 and older who did not meet the criteria for RA (previously described) or did not take DMARDs. Serum 25(OH) vitamin D levels were compared among non-RA subjects with RF+ and RF-. We used multivariable linear regression models to compare 25(OH) vitamin D levels adjusting for relevant covariates (age, gender, body mass index, race, season of blood draw, resion of residence, tobacco use, alcohol, daily calcium and vitamin D intake, serum creatinine, and serum calcium level). Categorical 25(OH) vitamin D levels (<25 nmol/L, 25-50 nmol/L, >50 nmol/L) were also examined in multivariable ordinal logistic regression model. **Results:** Among 4,463 non-RA subjects with mean age of 71.8 years old, 49.9% female, 58.6% Caucasian, we identified 262 (5.9%) RF+ subjects and 4,201 (94.1%) RF- controls. Mean age, gender, and race were similar between RF+ subjects and RF- controls. We found no significant difference in the mean body mass index, % current smoker, daily vitamin D intake, season of measurement, and resion of residence between subjects with RF+ and RF- (Table). In multivariable linear regression, the serum 25(OH) vitamin D levels were not significantly different between RF+ subjects and RF- controls after adjusting for predictors of vitamin D level and RF (Table). Analysis using categorical vitamin D levels revealed similar results.

Conclusion: In this US representative sample aged 60 and older, non-RA subjects with RF+ did not reveal significantly different serum 25(OH) vitamin D levels compared to RF- controls. Our findings failed to show a link between vitamin D levels and RA susceptibility.

Characteristic	RF negative (n=4,201)	RF positive (n=262)
Body mass index (kg/m2), mean (SD)	26.9 (5.0)	26.2 (4.6)
Current smoker, % (N)	15.3 (643)	16.8 (44)
Season of blood draw (winter), % (N)	28.2 (1,183)	24.4 (64)
Resion of residence (northeast), % (N)	15.4 (648)	14.1 (37)
Daily vitamin D intake (IU), mean (SD)	191.9 (2.7)	187.5 (22.0)
Serum 25(OH) vitamin D level (nmol/L)		
Unadjusted	65.5 (65.1, 65.9)	63.0 (61.4, 64.6)
Fully adjusted*	65.6 (65.2, 66.0)	63.9 (62.5, 65.3)

*age, gender, body mass index, race, season of blood draw, resion of residence, tobacco use, alcohol, daily calcium and vitamin D intake, serum creatinine, and serum calcium level

Disclosure: M. Kinjo, None; **S. Setoguchi**, NIH, 2 ; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 .

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A Low Physical Education Grade Predicts Middle Age Musculoskeletal Disease in Women but Not in Men. Simon Timpka[1], Ingemar F. Petersson[1] and Martin Englund[2], [1]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, [2]Lund University, Lund, Sweden

Purpose: Musculoskeletal disorders are common in the general population and chronic pain is one of the most prevalent complaints, especially in women. Directed primary prevention is possible if high risk groups are identified at an early stage. One goal of Physical Education (PE) is to serve as the foundation for a future healthy lifestyle. However, very little is known about the association between PE grade and musculoskeletal disease later in life.

In this study, we focused on “Disorders of the musculoskeletal system and connective tissue” (ICD-10 chapter XIII, code M) and the subgroup “Other soft tissue disorders, not elsewhere classified” (M79), which contains pain diagnoses such as Unspecified Rheumatism (M79.0) and Fibromyalgia (M79.7).

Method: For a historical cohort study, we identified all the 2298 subjects (48.6% women), born in 1957–1962, who in 1974–1976 graduated from secondary school in a municipality in Southern Sweden. The PE grade and the subjects' 10-digit personal identification number were retrieved from municipal records. We ensured via the Population Register that subjects were still resident in the county in the period 2003–2007, and linked our data to the Skåne Health Care Register (SHCR), a regional register covering both in-and outpatient heath care of the population of the southernmost county of Sweden. Data on occupation and education were collected from Statistics Sweden. All clinic visits with a main diagnosis of our focus in 2003-2007 were identified. For the analysis, we used a logistic regression model adjusted for level of

education and having an occupation associated with high prevalence of musculoskeletal disorders. An average PE grade was used as reference group.

Results: 530 individuals did not reside in the county during the whole study period while 56 did not receive a PE grade and were therefore excluded, 1712 (74.5%) remained eligible (48.8% women). In women, a low PE grade was associated with a higher Odds Ratio (OR) for both "Disorders of the musculoskeletal system and connective tissue" and "Other soft tissue disorders, not elsewhere classified". In men, no association between PE grade and future disease was found.

Odds Ratio (OR) for Musculoskeletal Disorders in the Middle Age by Physical Education (PE) Grade Compared to an Average Grade Adjusted for Occupation and Education

	PE Grade	Disorders of the musculoskeletal system and connective tissue (M)			Other soft tissue disorders, not elsewhere classified (M79)		
		c/n	OR	95 % CI	c/n	OR	95 % CI
Women	Low	81/186	**1.49**	(1.01-2.19)	34/186	**2.14**	(1.23-3.72)
	Average	103/333	1		27/333	1	
	High	107/316	1.24	(0.88-1.74)	33/316	1.47	(0.86-2.53)
Men	Low	69/252	0.76	(0.52-1.11)	17/252	0.71	(0.37-1.37)
	Average	98/321	1		25/321	1	
	High	83/304	0.87	(0.61-1.24)	22/304	0.95	(0.52-1.74)

c/n= Number of cases/Total number of individuals with grade
Code of diagnosis according to WHO's ICD-10.

Conclusion: In women, a low PE grade in adolescence predicts musculoskeletal pain disorders three decades later. No such association was found in men.

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Predictors of SF36 Scores in a New Lupus Cohort in Southern California. Janina Cervera[1], Mariko L. Ishimori[1], Dilrukshie Cooray[2], Meenakshi Jolly[3], Emmanuel Katsaros[4], Ioana Moldovan[4], Shuntaro Shinada[5], Karina D. Torralba[5], Daniel J. Wallace[1], Joel A. Block[3], Michael H. Weisman[1] and Perry Nicassio[6], [1]Cedars-Sinai Med Ctr, LA, CA, [2]Harbor UCLA Med Ctr, Torrance, CA, [3]Rush University Med Ctr, Chicago, IL, [4]Loma Linda Univ Med Ctr, Loma Linda, CA, [5]USC LAC Med Ctr, LA, CA, [6]UCLA, LA, CA

Purpose: To evaluate the contributions of demographics, disease and psychosocial factors to patient reported health outcomes in a new cohort of Hispanic and Caucasian systemic lupus erythematosus (SLE) patients in Southern California.

Methods: SLE patients age ≥18, meeting revised ACR criteria, self-identified as Caucasian/fluent in English or Hispanic/fluent in Spanish were recruited from 4 academic medical centers in the PATROL (Patient-reported Outcomes in Lupus) study. Subjects were evaluated by SLE disease activity index (SLEDAI) and self-administered questionnaires. Patient reported health outcomes were measured by Short Form 36 (SF-36). Depression, helplessness and internality were assessed by Patient Health Questionnaire-9 (PHQ9) and Rheumatology Attitudes Index (RAI) respectively. Hierarchical multiple regression analysis was performed for the dependent variables of SF36 Physical Functioning and Mental Health domains to evaluate the stepwise contribution of the following independent variables: ethnicity, age, education and income in step 1, SLEDAI and systemic lupus activity questionnaire (SLAQ) in step 2, and depression (PHQ9), helplessness and internality (RAI) in step 3.

Results: 58 Hispanic and 45 Caucasian SLE subjects were enrolled. In step 1, only age had a statistically significant effect on Physical Functioning. After adjusting for age, the second step of the model showed an association only between lower self reported SLAQ scores (β-0.37, p=0.001) with higher Physical Functioning. In the last step, less helplessness and higher internality on RAI were associated with less Physical Functioning (β=-0.38, p=.001 and β=0.22, ,p=0.046), but PHQ-9 scores did not have a significant effect. The model accounts for 43.5% of the variance in Physical Functioning. For Mental Health scores, only age was a significant factor. After adjusting for age, step 2 of the analysis showed that only lower SLAQ score was highly predictive of greater Mental Health (β =-0.50, , p=0.000). In the last step

depression was inversely associated with Mental Health (β=-0.47,I p=.000); RAI scores did not contribute. The model accounts for 36.6% of the variance in Mental Health.

Conclusion: Ethnicity was not found to be a significant predictor of SF 36 Physical Functioning or Mental Health in our cohort. There was a significant correlation between lower self-reported disease activity but not physician-assessed SLEDAI score, and better Physical Functioning and Mental Health. Less helplessness and higher internality contributed to better Physical Function; less depression to better Mental Health. These findings suggest that successful treatment of SLE patients may need to address not only physical manifestations of disease, but also psychosocial factors that contribute to patients' perception of their disease.

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1379

Non-Melanoma and Melanoma Skin Cancer Risk in a National Cohort of Veterans with Rheumatoid Arthritis. Wassila Amari[1], Angelique L. Zeringue[2], Jay R. McDonald[2], Liron Caplan[3], Fran Cunningham[4], Seth A. Eisen[2] and Prabha Ranganathan[1], [1]Washington University, St Louis, MO, [2]St. Louis Veterans Affairs Medical Center, St. Louis, MO, [3]Univ of CO Denver School of Med, Aurora, CO, [4]VA Pharmacy Benefits Management, Hines, IL

Purpose: Although previous studies have examined the risk of malignancy, including skin cancer, in patients with rheumatoid arthritis (RA), only one prior study has looked primarily at skin cancer risk. Our aim was to determine the incidence and risk factors for non-melanoma (NMSC) and melanoma skin cancer (MM) in a national cohort of veterans with RA treated with non-biologic versus tumor necrosis factor (TNF) antagonist DMARDs.

Methods: We examined a retrospective cohort of 16,829 patients with an International Classification of Disease, Version 9, (ICD-9) diagnosis of RA from the Department of Veterans' Affairs (VA) national administrative databases enrolled between October 1, 1998 and September 30, 2006. The cohort was divided into 2 medication groups: patients treated with non-biologic and those treated with anti-TNF DMARDs. Skin cancer was defined as the first occurrence of an ICD-9 code for NMSC and MM after initiation of a DMARD. Outcome risk was described using hazard ratios with Cox proportional hazards regression for time-to-event analysis and logistic regression. Chart review was performed to validate the diagnosis of both cancer types.

Results: Of the 16,829 RA patients, 3,096 were on anti-TNF treatment. The incidence of NMSC was 25.9 per 1000 patient-years in patients on TNF antagonists and 19.6 per 1000 patient-years in those on non-biologic DMARDs. Patients on anti-TNF agents had a higher risk of developing NMSC than those on non-biologic DMARDs with a hazard ratio of 1.34 (95% CI 1.15-1.58; $p<0.0001$). Factors that increased the risk of NMSC included older age, male gender, glucocorticoid use, a history of prior malignancies, and duration of anti-TNF therapy. The incidence of MM was 3.7 per 1000 patient-years in patients on TNF antagonists and 2.6 per 1000 patient-years in those on non-biologic DMARDs. Patients on anti-TNF agents had a higher risk of MM with a hazard ratio of 1.5 (95% CI 1.01-2.24; $p<0.05$). Risk factors for MM included a history of previous malignancies. The increased risk of both NMSC and MM was a drug class effect and not associated with individual TNF antagonists. There was substantial agreement between diagnosis by ICD-9 codes and chart review for NMSC ($\kappa=0.61$) but only moderate agreement for MM ($\kappa=0.45$).

Conclusion: Anti-TNF therapy in veterans with RA is associated with an increased risk of NMSC. Although our data suggest an association with MM, the modest agreement between the ICD-9 codes for MM and chart validation precludes a firm conclusion. Other risk factors for NMSC in RA include older age, male gender, a history of prior malignancies, glucocorticoid use and duration of anti-TNF therapy. These results should prompt rheumatologists to carefully evaluate the use of TNF antagonists in RA patients with such risk factors who may be more prone to develop skin cancer.

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Frequency of Lipid Testing in Patients with Rheumatoid Arthritis: A Retrospective Database Analysis. J. R. Curtis[1], A. John[2] and O. Baser[3], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Roche, Nutley, NJ, [3]University of Michigan Health Systems, Ann Arbor, MI

Purpose: Cardiovascular disease is associated with systemic inflammation and dyslipidemia and contributes to excess mortality among patients with rheumatoid arthritis (RA). The objective of this study was to determine the proportion of pts with RA that received any lab testing for dyslipidemia and to assess whether they were less likely to be tested than pts with osteoarthritis (OA).

Method: A retrospective analysis was conducted using medical and pharmacy claims from a national commercial administrative claims database. Adult pts had at least 2 physician diagnoses of RA or OA at least 2 months apart from April 2005 to March 2008, had continuous medical and pharmacy benefits for at least 18 months, and did not have any other inflammatory disease at baseline. Baseline was defined as 6 months before RA/OA diagnosis. Propensity score matching and multivariate regression analysis were used to control for baseline differences between groups. After matching, we evaluated the risk-adjusted differences in the proportion of RA and OA pts receiving any dyslipidemia testing, and also compared the mean number of total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG) tests performed.

Results: There were significant baseline differences between eligible RA and OA pts (RA, N=30,586; OA, N=107,534). Pts in the RA (vs OA) group were younger (50 vs 56 mean years), and more were women (74.1% vs 58.3%; $p<0.0001$, both comparisons). Pts in the RA (vs OA) group had a higher mean Charlson Comorbidity Index (1.07 vs 0.94) and lower rates of diagnosed diabetes (6.2% vs. 9.7%), obesity (2.2% vs 4.1%), and hypertension (23.1% vs 38.4%; $p < 0.0001$, all comparisons). Fewer pts in the RA (vs OA) group used lipid-lowering therapy at baseline (11.7% vs 25.0%; $p<0.0001$). Over a median observation period of 2.3 years, significantly fewer pts in the RA (vs OA) group had at least 1 lipid test ordered (Table). Given that a pt was tested (and after adjusting for baseline factors), the average number of TC tests was 2.0 for the RA group and 2.9 for the OA group ($p<0.0001$). Similarly, pts in the RA group underwent an average of 1.8 HDL, 1.9 LDL, and 2.0 TG tests, and pts in the OA group underwent an average of 2.7 HDL, 2.9 LDL, and 2.9 TG tests ($p<0.0001$, all comparisons).

Conclusion: This real-world analysis indicates that pts with RA receive suboptimal rates of testing for dyslipidemia and also receive testing less often than pts with OA. In light of the increasingly recognized cardiovascular burden associated with RA, physicians should monitor and manage dyslipidemia and other cardiovascular risk factors in RA pts and educate them about the risk associated with the disease.

Table. Proportion of RA and OA Patients for Whom Lipid Tests Were Performed

At Least Once (Median Observation Period of 2.3 Years)

	RA Group N=30,586 %	OA Group N=107,534 %	*p*
Total cholesterol	59.8	69.0	<0.0001
High-density lipoprotein	57.2	66.4	<0.0001
Low-density lipoprotein	58.6	68.4	<0.0001
Triglycerides	59.1	68.4	<0.0001

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Quality Adjusted Life Expectancies in Patients with Rheumatoid Arthritis – A Comparison of the EQ-5D, SF-6D and 15D. Louise Linde[1], Jan Sørensen[2], Mikkel Østergaard[3] and Merete L. Hetland[4], [1]Department of Rheumatology, Hvidovre Hospital, Hvidovre, Denmark, [2]University of Southern Denmark, Odense, Denmark, [3]Department of Rheumatology, Copenhagen University Hospital at Gentofte and Hvidovre, Denmark, [4]DANBIO, Hvidovre Hospital, Hvidovre, Denmark

Purpose: Cost-effectiveness analyses of health interventions may be based on outcomes derived from patient-reported utility-based health status measures, such as the EQ-5D, SF-6D and 15D instruments. It is unclear to which degree the outcomes vary depending on the instrument used. We explored differences in index scores and quality-adjusted life expectancies (QALexp) obtained by the above-mentioned three instruments in patients with rheumatoid arthritis (RA).

Method: Health status (EQ-5D, SF-6D, 15D), disease activity score based on 28 joint count and C-reactive protein (DAS28) and Health Assessment Questionnaire (HAQ) regarding patients with RA in routine care were collected cross-sectionally. Individuals with complete health status data were included in the analysis. Danish population based survival data were aggregated into five-year age groups and the expected survival from age 20 to 79 was calculated. The QALexp were estimated as the product of the mean index score and the expected population based survival in each age interval. Data were stratified to compare the QALexp in subgroups according to gender, DAS28 and HAQ assuming that these factors did not impact the mortality.

Results: 1689 patients were available for analysis (73% women, 76% IgM rheumatoid factor positive, mean (SD) DAS28: 3.06 (1.21), HAQ: 0.67 (0.63)). The mean index scores were: EQ-5D: 0.732, SF-6D: 0.709 and 15D: 0.874 ($p<0.01$ for pairwise comparisons (paired t-test)), see Figure. The differences in index scores were reflected in the estimated QALexp, see Table. The EQ-5D and SF-6D index scores and estimated QALexp were largely similar, while the 15D values were consistently higher. For all three instruments, the QALexp differed according to gender, DAS28 and HAQ subgroups. However, the magnitude of the differences varied according to the instrument used: The EQ-5D yielded the largest QALexp differences: men vs women: 2.1; DAS28<3.2 vs DAS28≥3.2: 7.8; HAQ<1 vs HAQ=1-2: 7.3; HAQ=1-2 vs HAQ>2: 6.3, while the 15D yielded the smallest differences.

Conclusion: We have identified methodological challenges in the interpretation of cost effectiveness analyses in RA studies. In this large study of 1689 patients investigated with both the EQ-5D, SF-6D and 15D, substantial variation in the index scores and quality-adjusted life expectancies was observed depending on the instrument used. Comparison of cost-effectiveness analyses should only be performed between studies that have applied the same instruments.

Figure.

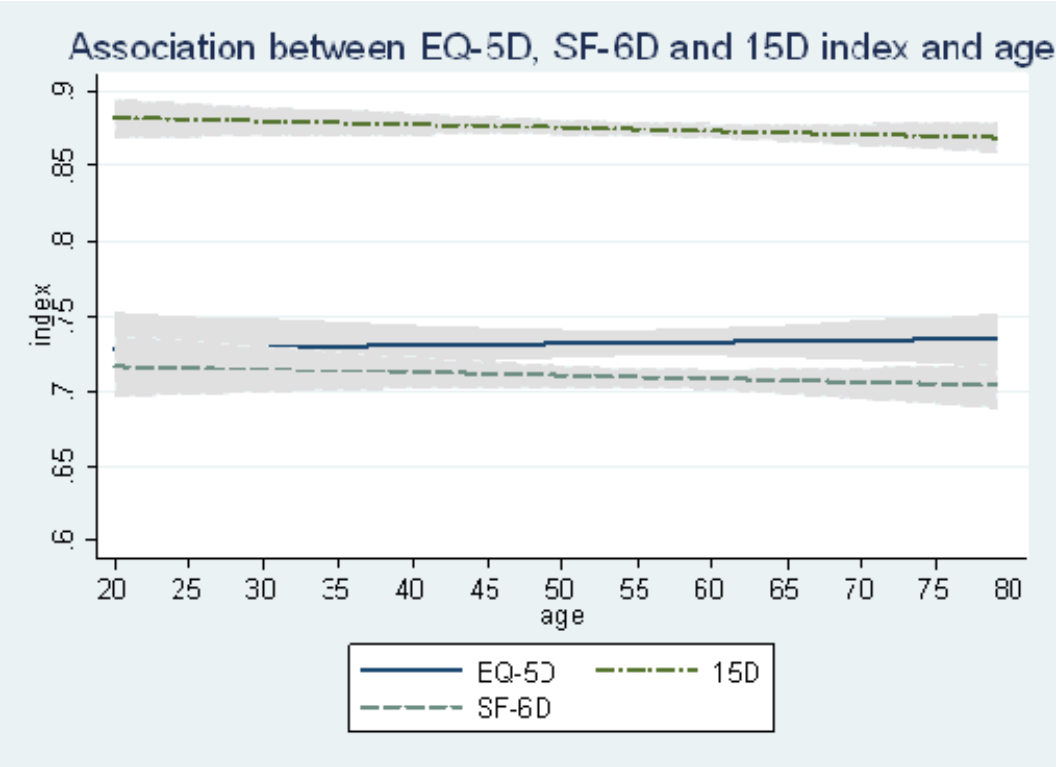

Table. Quality adjusted life expectancies for a 20 year old until 79 years for the EQ-5D, SF-6D and 15D assuming mortality as for the general population.

	n	EQ-5D	SF-6D	15D
Whole sample	1689	40.2	39.0	48.0
Women	1240	39.8	38.6	47.9
Men	449	41.9	39.5	48.3
DAS28 <3.2	704	44.9	42.7	50.2
DAS28 ≥3.2	985	37.1	36.6	46.6
HAQ <1	965	40.9	39.2	48.2
HAQ = 1-2	327	33.6	33.4	44.6
HAQ >2	72	27.3	30.4	41.6

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Remission of Rheumatoid Arthritis (RA): Benefits From Socioeconomic and Quality of Life Perspectives. Helga Radner[1], Josef S. Smolen[2] and D. Aletaha[1], [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria

Background: RA is a disease with a considerable socio-economic burden. This burden is mediated through impairment of physical function, which in turn is mostly dependent on the level of RA disease activity. While the ultimate therapeutic target is achievement of disease remission, it is unclear to what extent the socioeconomic burden of RA is reduced as patients improve in the activity of their disease.

Purpose: To understand the punctual relationship of disease activity states with the socioeconomic burden of RA.

Methods: In 350 consecutive RA patients seen in routine clinical care we obtained data on work productivity using the Work Productivity and Activity Impairment Questionnaire (WPAI), on quality of life using the Short Form-36 (SF-36), and on health states (utility) using the Euroqol-5D (EQ-5D). Patients were then divided into four groups according to their disease activity state by the Clinical Disease Activity Index (CDAI): remission (REM), low, moderate, and high disease activity (LDA, MDA, and HDA). The socioeconomic data were then compared across the four disease activity groups.

Results: The physical component summary measure (PCS) of the SF-36, the EQ-5D, and the work productivity (by the WPAI) were significantly worse if higher levels of disease activity were present ($p<0.01$ by ANOVA, **Table**). Subsequent pairwise comparisons indicated for all measures that the achievement of REM was superior to achievement of LDA ($p<0.01$, Student's t-test).

Table. Quality of life, utility and work productivity (mean values ± SD) at different levels of disease activity defined by Clinical Disease Activity Index (CDAI)

	Total	**REM**	**LDA**	**MDA + HDA**	**p-value (ANOVA)**	**p-value (t-test REM vs. LDA)**
N	350	89	148	113		
SF-36 MCS (range 0-59.1)*	48±12	48.9±11.8	49.4±12	45±12	p=0.021	p=0.75
SF-36 PCS (range 0-70.4)*	37.7±11.2	46±8.8	38.3±10.3	30±8.7	p<0.0001	p<0.0001
EQ-5D (range -0.13-1)*	0.77±0.19	0.89±0.12	0.79±0.15	0.65±0.21	p<0.0001	p<0.0001
WPAI % impairment while working**	27.8±26.9	9±17.6	28.1±23	47.9±29.5	p<0.0001	p=0.001
WPAI % overall activity impairment**	35.3±26.4	18±20.5	33.1±22.8	53.2±24.6	p<0.0001	p<0.0001

Abbreviation: SF-36 MCS /PCS (Short Form 36 mental component summary measure / physical component summary measure); EQ-5D (Euro-Qol 5D); WPAI (Work Productivity and Activity Impairment Questionnaire; REM (remission; CDAI ≤ 2.8); LDA (low disease activity; 2.8<CDAI≤10); MDA+HDA (moderate to high disease activity; CDAI>10); * higher values better; ** higher values worse

Conclusion: While more impairment of work productivity, quality of life, and health states were seen with higher levels of disease activity, even in LDA these measures were significantly worse when compared to REM. This suggests that even in patients with LDA therapeutic adaptations to attain remission are worthwhile and warranted.

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Disclosure: H. Radner, UCB, 2 ; **J. S. Smolen**, UCB, 2 ; **D. Aletaha**, UCB, 2 .

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Utility Differences in RA and Knee OA Patients. L. M. Manheim, D. D. Dunlop and R. W. Chang, Northwestern University, Chicago, IL

Purpose: Cost Effectiveness analysis relies on utility measurement, a community based assessment of health, to evaluate the relative effectiveness of many arthritis interventions. We examine health utility in persons with rheumatoid arthritis (RA) and Knee Osteoarthritis (KOA) to address the following questions: how does overall health-related utility differ for persons with RA and KOA; are factors related to utility the same for OA and RA patients; and what factors that have potential for interventions significantly associated with utility?

Methods: This study uses baseline data from 107 RA and 91 KOA subjects enrolled in the Increasing Motivation for Physical Activity in Arthritis Clinical Trial (IMPAACT) study, a randomized controlled trial to evaluate an individually tailored physical activity intervention. Prior to randomization each person completed a set of baseline questionnaires including the SF-36 used to derive the SF6-D utility measure, (the outcome) and explanatory factors: physical activity assessed by accelerometer, demographics, BMI, disability, and comorbidity based on prescription drug use. The outcome measure SF6-D utility is a weighted (by community preferences) average of six SF-36 dimensional scores reflecting: physical functioning, role, social, pain, mental health, and vitality. Utility is normally distributed around its mean and predicted values do not exceed 1 or show ceiling effects. Multiple regression was used to examine whether any of these factors explained differences in utility between RA and KOA patients.

Results: Mean SF6-D utility is greater for KOA than for RA (0.752 vs. 0.697, $p<.001$). This utility difference between RA and KOA is approximately the same at the 25^{th}, 50^{th}, and 75^{th} percentiles, suggesting a simple shift of the curve with RA lower by .05 points at all points along the curve. Each of the subcomponents of the utility index is lower for RA than for KOA. Interestingly the largest (and only statistically significant) differences among subscales was in mental health (RA subscore 51% less than KOA:-.033 vs. -.022, $p<.01$) and social role (RA subscore 33% less for RA: -.035 vs. -.017, $p<.01$) subscales, while physical functioning (6.5% less for RA) and pain (9.4% less for RA) show the least differences. Older age, being male, greater physical activity, not being overweight, lack of disability, and fewer comorbidities are all significantly related to better utility. The only significant interactions with disease indicated that greater comorbidity and age impact more negatively on utility for RA than for KOA subjects.

Conclusion: Persons with RA have significantly lower utility levels than persons with KOA. While lower scores for RA are apparent across all global health-related dimensions making up the utility score, they are most pronounced for psycho-social rather than pain and functioning dimensions. Levels of physical activity and being overweight or obese show independent significant effects on utility suggesting areas for intervention to improve health-related quality of life.

Disclosure: L. M. Manheim, NIH, 2, Arthritis Foundation, 2 ; **D. D. Dunlop**, NIH, 2, Arthritis Foundation, 2 ; **R. W. Chang**, NIH, 2, Arthritis Foundation, 2.

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Serum Urate and Its Relationship with Alcoholic Beverage Intake in Men and Women: Findings From the Coronary Artery Risk Development in Young Adults (CARDIA) Cohort. Angelo L. Gaffo[1], Jeffrey M. Roseman[2], David R. Jacobs Jr.[3], C. Lewis[4], James M. Shikany[2], T. R. Mikuls[5], Pauline E. Jolly[2] and Kenneth G. Saag[2], [1]Birmingham VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Minnesota, Minneapolis, MN, [4]UAB, Birmingham, AL, [5]U Nebraska, Omaha, NE

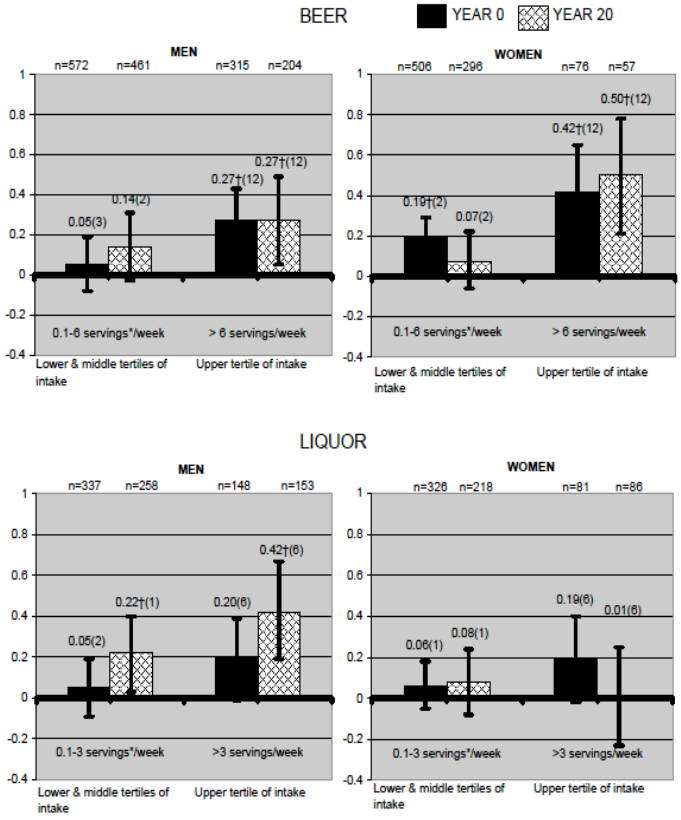
Purpose: Choi and colleagues have previously reported differential effects of beer, liquor and wine on serum urate (SU) concentrations in older adults. We examined these relationships in a bi-racial cohort of young men and women enrolled in the CARDIA study.

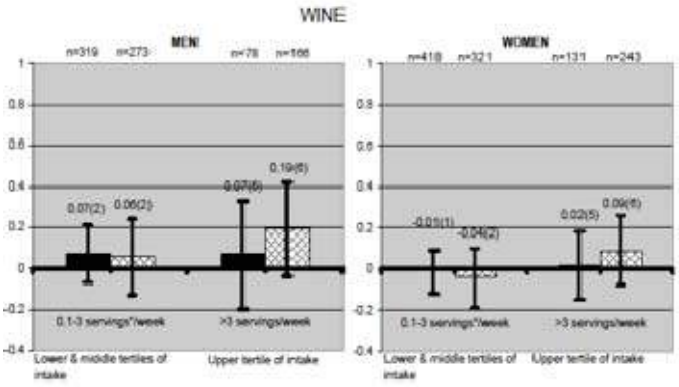
Method: Data from 3123 participants at baseline (recruited in 1985-6) and follow-up at 20 years were utilized, with balanced proportions of Caucasians and African Americans. The relationships of SU with categories of beer, liquor, wine, and total alcohol intake referent to no intake were examined in sex-stratified cross-sectional and multivariable-adjusted longitudinal regression analyses.

Results: Mean age at entry was 25.1 years. On multivariable analyses and referent to non-drinkers, a significant positive association between SU concentration and beer intake was observed among men and women, being more pronounced and consistent in the latter. A positive association between liquor intake and SU concentration was observed only for men at the year 20 evaluation. Wine intake was not associated with SU changes in either sex at either time point (Figure). Total alcohol intake was positively associated with SU concentrations in both men and women. The magnitude of the associations between alcoholic beverage intake and serum urate was modest (less or equal than 0.03 mg/dL per serving, effect size < 0.11).

Conclusion: Following previous findings in older adults, an association between higher SU concentrations and greater beer intake was found among young women and men, being stronger in the former. No associations were found with wine intake. Small increases in SU associated with alcohol intake in young adults could have clinical implications on gout and cardiovascular disease that deserve further study.

Figure. Multivariable adjusted SU difference (in mg/dL) by categories of alcoholic beverage intake and compared with non-drinkers (referent group). Numbers above the error bars represent the exact SU difference, numbers in parentheses represent the median alcoholic beverage intake for each category in servings per week Significantly different from non-drinkers (P<0.05).





Disclosure: A. L. Gaffo, None; **J. M. Roseman**, None; **D. R. Jacobs**, None; **C. Lewis**, None; **J. M. Shikany**, None; **T. R. Mikuls**, None; **P. E. Jolly**, None; **K. G. Saag**, Regeneron, Novartis, Takeda, 2, Takeda, Savient, Novartis, 5 .

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Predicting Absence or Work Stoppage Among Patients with Early Rheumatoid Arthritis. Wei Zhang[1], Huiying Sun[1], Reiko Sato[2], Amitabh Singh[2], Bruce Freundlich[2], Paul Emery[3], Chung-Tei Chou[4] and Aslam H. Anis[5], [1]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, [2]Wyeth Pharmaceuticals, Collegeville, PA, [3]University of Leeds, Leeds, United Kingdom, [4]Taipei Veterans General Hospital, Taipei 112, Taiwan, [5]Univ of British Columbia, Vancouver, BC

Purpose: To assess the association between baseline clinical and patient-reported outcomes parameters and work absence or stoppage during the12 weeks immediately following baseline among employed people with early rheumatoid arthritis (RA).

Method: Data from the COmbination of Methotrexate and ETanercept trial, a double-blind randomized clinical trial, was used. Patients working full-time or part-time at baseline were included in the analysis. The outcomes were work stoppage and work absence that occurred during the first 12 weeks period. Stepwise logistic regression was used to assess the association, including age, gender and treatment variable (etanercept and methotrexate vs. methotrexate alone) for all analyses. Model selection was first conducted within 4 blocks of independent variables: I. demographics, II. medication and medical history, III. baseline clinical variables (pain, fatigue, Disease Activity Score, total swollen joints, total tender joints (TTJ), patient global assessment, physician global assessment, Health Assessment Questionnaire, morning stiffness, disease duration), and IV. baseline quality of life measures (EuroQol [EQ-5D] utility, EQ-5D VAS, SF-36 Mental component summary and Physical Component Summary [PCS]). The clinical and quality-of-life measures were categorized into poor, moderate, and good based on tertiles. The final multivariate model selection was constructed only among the variables selected in each block at the first step using entry criterion p=0.1 and stay criterion p=0.2.

Results: Among the 205 included in the analysis, 69% were females, the mean age was 45 years and the mean RA duration was 8.7 months. 8.5% stopped working and 18.5% missed work between baseline and week 12. First, as per selection criteria, previous NSAID use, neurologic, cardiovascular and psychiatric history in block II, fatigue and TTJ in block III, and EQ-5D VAS in block IV were selected for work stoppage. Caucasian in block I, neurologic history in block II, TTJ in block III, and SF-36 PCS in block IV were selected for work absence. Neurologic (odds ratio [95% confidence interval]: 7.6 [1.6-35.5])history, psychiatric history (4.4 [0.9-21.5]), and fatigue (8.0 [1.5-42.8] for poor vs. good status) were retained in the final multivariate logistic regression for work stoppage, while Caucasian (3.2 [0.8-12.6]), neurologic history (5.4 [1.6-18.8]) and TTJ (5.1 [1.9-13.9] for poor vs. good status) were retained for work absence.

Conclusion: Our results suggest that baseline comorbidities, fatigue, and tender joint counts could predict work stoppage and absence over the subsequent 12 week period in early RA. Measures associated with near-term work stoppage and absence can differ and may suggest that separate factors contribute to distinct work outcomes.

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The Increased Risk of Incident Gout in Obese Patients Enrolled in a Community-Based Cohort: Campaign against Cancer and Heart Disease (CLUE II). Mara A. McAdams[1], Janet W. Maynard[2], Alan N. Baer[2], Anna Kottgen[1], Sandy Clipp[1], Allan C. Gelber[2] and Josef Coresh[1], [1]Johns Hopkins School of Public Health, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Community-based cohorts are useful for epidemiologic studies to identify risk factors for chronic diseases. Previous studies have primarily focused on anthropometric risk factors for gout in men. We evaluated the risk of incident gout in men and women by obesity status using the community-based cohort, Campaign Against Cancer and Heart Disease (CLUE II).

Method: The CLUE II cohort contains 26,147 individuals, aged 13 to 87 years, who resided within or surrounding Washington County, Maryland in 1989. The mean age was 47.4 years in 1989), and 99% self-reported white race. At baseline (1989), participants were asked to self-report sex, race, age, height, weight, weight at age 21, education, treatments for high cholesterol and blood pressure, hormone use, and menopausal status. Follow-up questionnaires through 2007 included a question about ever having received a gout diagnosis by a healthcare professional. This study included over 12,000 CLUE II participants who returned at least one follow-up questionnaire after 2000. Incident gout cases were restricted to the participants who self-reported the onset of gout after 1989 based on self-reported age or year of gout onset. We assessed the eighteen-year risk of incident gout in obese participants (BMI >30 kg/m2 at baseline) with cumulative incidence rate ratios (RR) from Poisson regression. We modeled the RR of incident gout using female-specific risk factors in models restricted to female participants.

Results: Of the study population (12,391 participants), 416 had incident gout. The prevalence of obesity at baseline was 16% of the study population. Gout patients were more likely to be male, older age, and treated for high cholesterol and blood pressure at baseline. The 18-year risk of developing gout was increased for every five-unit increase in BMI. The risk of gout was higher in obese participants compared to non-obese participants and this risk was also seen for participants who were obese at age 21. The categorical risk of incident gout was similar in participants whose baseline BMI was 30-35 and those with a BMI greater than 35.

	Model 1: **Adjusted RR of gout***		**Model 2:** **Adjusted RR of gout****	
	RR	CI	RR	CI
Five unit (kg/m^2)	1.55	1.44, 1.66	1.45	1.37, 1.56
Categorical BMI				
<25	1		1	
25-30	2.08	1.61, 2.67	1.94	1.51, 2.50
30-35	3.70	2.81, 4.89	3.18	2.39, 4.24
35+	3.46	2.29, 5.23	2.73	1.78, 4.17
Obesity at baseline	2.38	1.94, 2.91	2.05	1.65, 2.54
Obesity at age 21	2.01	1.31, 3.08	1.68	1.09, 2.60

* Adjusted for baseline age, race and sex

** Additionally, adjusted for baseline treated blood pressure and cholesterol

Conclusion: In a community-based cohort we found that obesity was associated with an increased risk of gout over 18 years of follow-up. Obesity appears to be a strong risk factor for gout. Gout should be considered in the differential diagnosis of acute joint pain in obese patients.

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Past Fractures Increase Risk for Subsequent Fractures at Multiple Sites: Global Longitudinal Study of Osteoporosis in Women (GLOW). Kenneth G. Saag[1], Andrea LaCroix[2], Stuart L. Silverman[3], Steven Boonen[4], Juliet Compston[5], J. Coen Netelenbos[6], Johannes Pfeilschifter[7], Philip Sambrook[8], Nelson B. Watts[9], Gordon FitzGerald[10] and Silvano Adami[11], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Fred Hutchinson, Seattle, WA, [3]Cedars Sinai/UCLA, Beverly Hills, CA, [4]University of Leuven, Leuven, Belgium, [5]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [6]VU University Medical Center, Amsterdam, Netherlands, [7]Alfried Krupp Krankenhaus, Essen, Germany, [8]University of Sydney-Royal North Shore Hospital, Sydney, Australia, [9]University of Cincinnati, Cincinnati, OH, [10]UMass Medical School, Worcester, MA, [11]University of Verona, Verona, Italy

Purpose: The ability of a past fracture to predict subsequent fractures is an important criterion in defining a fracture as attributable to osteoporosis. Although some data from large cohorts suggest that fractures at most anatomic sites are associated with future fractures, the specific types of fractures that predispose to future fracture are controversial. We examined the risk of incident fracture based on initial fracture site in a large international study.

Method: The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational, longitudinal study of women 55+ recruited by 615 primary physician practices (17 sites, 10 countries). Self-administered questionnaires were mailed at baseline and at 12 months (2:1 over-sampling of women ≥65). Self-reports of fractures at 10 anatomic locations after age 45 were collected at both baseline and follow-up. The odds of any incident fracture at 1 year were determined based on site of past fracture and after multivariable adjustment for age and other fracture sites (in women with multiple fractures).

Results: Among the 47,939 women for whom 1-year data were available (79% of baseline cohort), 1167 (2.4%) had fractures. For women with no previous fracture the incidence was 1.8% (661/36,846) vs 4.6% (506/11,093) for those with a prior fracture ($p<0.001$). The unadjusted odds ratios were significantly elevated for all 10 sites (range 1.8-3.3). After adjustment for age and other fracture locations, the risk of incident fractures was attenuated but remained significant for the rib, hip, wrist, spine, upper arm and ankle (Table).

Table. Incidence of any fracture at 1 year given previous fracture and adjusted odds ratio for any fracture at 1 year vs women without prior fracture

Fracture site	Previous fracture prevalence n (% of overall fractures)	Any incident fracture*, given initial fracture site n (%)	Adjusted OR (95% CI)
Rib	1991 (18)	139 (7.0)	2.4 (2.0-2.9)
Hip	806 (7.3)	56 (7.0)	1.7 (1.3-2.3)
Wrist	4101 (37)	204 (5.0)	1.7 (1.4-2.0)
Spine	1057 (9.5)	66 (6.2)	1.6 (1.4-3.0)
Upper arm	1344 (12)	70 (5.2)	1.4 (1.1-1.9)
Ankle	2923 (26)	119 (4.1)	1.3 (1.1-1.6)
Lower leg	1186 (11)	56 (4.7)	1.3 (1.0-1.7)
Upper leg	419 (3.8)	26 (6.2)	1.3 (0.8-2.0)
Clavicle	626 (5.6)	32 (5.1)	1.2 (0.8-1.7)
Pelvis	479 (4.3)	27 (5.6)	1.0 (0.6-1.5)

*Any incident fracture consists of the 10 categories in the 1st column

Conclusion: In a large practice-based international cohort, the risk of incident fracture at 1 year varied by site of past fracture and was significantly associated with 6 of 10 previous fracture locations. These findings help to define fractures that may be most strongly attributed to osteoporosis.

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Long Term Mortality Is Increased in Male as Patients. Gunnstein Bakland[1], Jan Tore Gran Sr.[2] and Hans Nossent[3], [1]University Hospital Northern Norway, Tromsø, Norway, [2]Oslo University Hospital, Rikshospitalet, Oslo, Norway, [3]Tromsø, Norway

Purpose: To report very long term gender specific mortality rates in a population of AS patients compared to a control population. Although increased standardized mortality rates (SMR) have been described in AS patients, no significant increase in mortality was seen in an AS inception cohort in northern Norway during the first twenty years of disease (2). Earlier radiation therapy has been considered an important contributor to early death in AS (1).With increased periods of observation and closer and expanded matching to a control population, we now report the updated estimates of mortality as well as predictors and causes of death in AS.

Method: We identified all AS patients fulfilling the modified New York criteria who had been registered in our hospitals records after 1978. Each case was assigned three controls matched for gender, age and area of residency. The onset of low back pain was defined as the point of debut of AS. All data were entered to and analyzed in SPSS v 16.0. Overall mortality was analyzed using a Log Rank-test (Mantel-Cox). Causes of death were determined through record review where available.

Results: A total of 677 patients were included in the analysis and matched to 2031 controls. As expected the male-to-female ratio was about 3:1. Mean age at symptom debut was 23.7 years (median 22.2) and mean diagnostic delay was 9.0 years (median 7.0). At the time of last follow-up, the crude mortality rate in the patient group was 14.5 % (n=98) as compared to 7.2 % in the control group (OR 2.18 [1.66-2.87]). Overall comparison adjusted for gender (Mantel-Cox) showed a highly significant increased mortality in the patient group ($\chi 2$=48.75, p<0.0009). Standardized mortality rate (SMR) [95% confidence interval] in the patient group was 1.61 [1.29-1.93]. In gender specific analyses, male AS patients had significantly increased mortality (SMR =1.63 [1.29-1.97]), while SMR was not increased for female patients (SMR=1.38 [0.48-2.28]. In time dependent analyses, the increase in mortality among male patients became only apparent more than 15 years after diagnosis, whereas mortality increased slightly though not significantly among female patients after 35 years. Cause of death was established in only 29 of 89 cases, and malignancy was the most prevalent cause (10) followed by infections (5).

Conclusion: The long term risk of mortality is increased in male AS patients with an estimated SMR 1.63. The increased risk become manifest about 15 years after diagnosis in male patients. A non-significant trend towards increased mortality risk in female patients appeared about 35 years after diagnosis.

Disclosure: G. Bakland, None; **J. T. Gran**, None; **H. Nossent**, None.

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Scaling Properties of the OAKHQOL Questionnaire for Hip and Knee Osteoarthritis: A Rasch Analysis. Christophe Goetz[1], Emmanuel Ecosse[2], Anne-Christine Rat[3], Jacques Pouchot[4], Joël Coste[2] and Francis Guillemin[1], [1]Nancy-University, Paris Descartes, Metz P Verlaine; Department of clinical epidemiology and evaluation, Nancy University Hospital, Nancy, France, [2]Nancy-University, Paris Descartes, Metz P Verlaine; Biostatistics and epidemiology unit, Hôpital Cochin, AP-HP, Paris, France, [3]Nancy-University, Paris Descartes, Metz P Verlaine; Department of clinical epidemiology and evaluation, Nancy University Hospital; Department of rheumatology, Nancy University Hospital, Nancy, France, [4]Nancy-University, Paris Descartes, Metz P Verlaine; Department of internal medicine, Georges Pompidou European Hospital, AP-HP, Paris, France

Purpose: The self-administered OAKHQOL questionnaire has been developed to assess health-related quality of life in lower limb osteoarthritis (OA). We used a Rasch analysis to further document its validity.

Method: The questionnaire contains 40 items divided in 5 domains: physical activities (PA), mental health (MH), pain (P) social support (SS) and social functioning (SF), and 3 independent items, with a scoring using numerical rating scales ranging from 0 to 10. Patients with knee or hip OA of various stages of severity completed it. For each of the 5 domains, responses to the items were analyzed using a partial credit model. Fit of data to model expectations and thresholds ordering were examined. The invariance of the scales was assessed by looking for differential item functioning (DIF) across gender, age and involved joint. Analyses were run using RUMM2020 software.

Results: Responses of 544 knee (n=237) and hip (n=307) OA patients were analyzed; 297 were treated in rheumatology and 247 were waiting for arthroplasty. Fit of data to initial models was low for all domains except for pain. Internal consistency was good to excellent (Person Separation Index ranging from 0.80 to 0.94). The thresholds of two items in PA and two in MH were not ordered and were rescored from 11 to 3 answering modalities. One item in SS with disordered thresholds was kept unchanged because this item showed misfit when rescored. Five items of PA domain demonstrated a DIF between knee and hip OA (Going down stairs, Climbing stairs, Dressing, Cutting toe-nails and Getting in and out a car), and one item a DIF for gender (Need help). Two items of MH domain showed a DIF for gender (Been afraid of being dependent on others and Feel aggressive and irritable) and one a DIF for age (Feel older than my years). After rescoring items with disordered modalities and splitting items with DIF, fit of data improved. Significant misfit was found in only one item in PA and one in MH. Removing items showing DIF or misfit did not significantly modified the person estimates (less than 0.02 logit), meaning there was no significant bias at the domain level.

Conclusion: The OAKHQOL questionnaire demonstrates satisfying scale properties for each of the five domains in patients with hip and knee OA under medical treatment or awaiting for surgery. Out of 40 items, 9 present DIF and 2 show misfit to the model, but the resulting bias is trivial at the domain level.

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Better Patient-Reported Physical Functioning Outcomes in Early Rheumatoid Arthritis Treatment with Adalimumab Plus Methotrexate Than Methotrexate Alone. Edward C. Keystone[1], Sanjoy Roy[2], Naijun Chen[2], Saeed Rasty[2], Benoît Guerette[3], Mary Cifaldi[2] and Robert Landewe[4], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Abbott Laboratories, Abbott Park, IL, [3]Abbott Laboratories, Rungis, France, [4]Maastricht University Medical Center, Maastricht, Netherlands

Purpose: Rheumatoid arthritis (RA) is a chronic, debilitating disease that impairs physical functioning. Global physical functioning in RA is commonly measured by the overall score on the patient-reported Health Assessment Questionnaire (HAQ). Analysis of the individual HAQ items may provide insight about how patients perceive various aspects of their own physical functioning, especially during RA treatment. This study evaluates patient-relevant aspects of physical functioning during treatment with a combination of adalimumab (ADA) and methotrexate (MTX) vs. MTX alone.

Methods: Study data were derived from PREMIER, a 2-year, multicenter, Phase III, randomized, double-blind, comparator-controlled trial of ADA for the treatment of MTX-naïve patients with early RA (<3 years). HAQ data at baseline, Week 52, and Week 104 were analyzed for patients randomized to receive ADA+MTX combination therapy or MTX monotherapy. On the HAQ, patients rated their ability to perform a variety of tasks on this scale: 0=without any difficulty, 1=with some difficulty, 2= with much difficulty, and 3=unable to do. Due to the ordered, categorical nature of the HAQ item responses, ordered logistic regression (OLR) techniques were adopted to estimate the effects of treatment on individual item responses in a proportional-odds model at baseline, Week 52, and Week 104 of the study. A similar

model was also used to estimate the effect of radiographic damage (using modified total Sharp scores [mTSS]) on individual HAQ item responses.

Results: A total of 525 patients (ADA+MTX=268; MTX=257) were included in this analysis. The treatment groups did not differ at baseline in their distributions of HAQ item responses. At both Week 52 and Week 104, the ADA+MTX group had lesser numeric responses (indicating better physical functioning) than the MTX group for 15 of 20 HAQ items (odds ratios: 1.77 to 2.78 at Week 52; 1.62 to 2.77 at Week 104; $p<0.05$ for each comparison). Patients in the ADA+MTX group were approximately 3 times more likely than patients in the MTX group to find it easier to open car doors and to cut their meat and approximately 2 times as likely to have better ability to do most of the remaining activities assessed by the HAQ. The effect of mTSS on HAQ was significant for 4 items at Week 52 and for 6 items at Week 104 (all comparisons $p<0.05$). Only 2 items (walking outdoors on flat ground; bathing) were affected by mTSS at both time points (both $p<0.05$).

Conclusion: For most aspects of physical functioning measured by the HAQ, patients with early RA treated with ADA+MTX had better self-reported outcomes than patients treated with MTX alone. The greatest benefits were experienced in activities involving the hands. Radiographic damage affected several aspects of physical functioning, with greater impact over time.

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A Comparison of Traditional Gout Risk Factors Between Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study. Janet W. Maynard[1], Mara A. McAdams[2], Alan N. Baer[1], Anna Kottgen[2], Allan C. Gelber[1] and Josef Coresh[2], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins School of Public Health, Baltimore, MD

Purpose: Gout is a major form of inflammatory arthritis in both men and women; yet, little is known about whether clinical risk factors for gout vary by gender. In the Atherosclerosis Risk in Communities (ARIC) Study, we evaluated the association of traditional risk factors for gout in women as compared to men.

Methods: ARIC is a population-based cohort study of 15,792 individuals (55% women) recruited in 1987-1989. Our study population consisted of African-American and Caucasian men and women with and without gout. A participant was considered to have gout if 1 or more of the following criteria were met: a) gout was self-reported, b) surveillance of hospital discharge summaries revealed an ICD-9 code for gout (274.0, 274.1, 274.8, or 274.9), or c) use of a medication taken primarily to treat gout at any study visit. We stratified by gender and used multivariable logistic regression to model the risk of prevalent gout. The multivariable models included baseline age, race, obesity, organ meat, animal protein, shellfish, and alcohol intake, diuretic use, hypertension, renal function, and diabetes. Obesity was classified as BMI >30. We generated models using interaction terms to see if gender modifies the relationship between traditional risk factors and gout.

Results: 399 women (4.8%) and 703 men (9.9%) have gout in the ARIC cohort. In women and men, African-American race, obesity, high alcohol intake, hypertension, and decreased kidney function were associated with an increased risk of gout. In women, but not in men, age and organ meat intake were associated with an increased risk of gout. In men, but not in women, diabetes was associated with an increased risk of gout. Gender modified the relationship between gout and three traditional risk factors: race, protein intake, and organ meat intake.

	Women OR (95% CI)	Men OR (95% CI)	P-value for interaction of gender
Age (per 1 year)	**1.04 (1.02, 1.07)**	1.01 (0.99, 1.03)	0.07
Race			
Caucasian (reference)	1	1	
African-American	**1.87 (1.46, 2.40)**	**1.47 (1.20, 1.80)**	**0.05**
Obesity	**2.43 (1.93, 3.06)**	**1.98 (1.66, 2.37)**	0.07

Protein (per 15gm)	1.05 (0.98, 1.13)	0.94 (0.89, 0.99)	**0.005**
Shellfish	0.99 (0.79, 1.25)	1.05 (0.89, 1.25)	0.96
Organ Meat	**1.28 (1.02, 1.61)**	0.85 (0.72, 1.02)	**0.002**
Alcohol			
No drinks/day (reference)	1	1	
1-2 drinks/day	0.98 (0.74, 1.32)	**1.24 (1.03, 1.50)**	0.36
>2 drinks/day	**2.01 (1.08, 3.72)**	**2.30 (1.82, 2.89)**	0.86
Diuretic use	**1.60 (1.22, 2.10)**	**1.44 (1.14, 1.80)**	0.87
Hypertension	**1.71 (1.29, 2.27)**	**2.34 (1.91, 2.86)**	0.44
Kidney function (per 10 mls/min/1.73m^2)	**0.84 (0.77, 0.92)**	**0.77 (0.72, 0.83)**	0.08
Diabetes	1.21 (0.92, 1.59)	**1.33 (1.06, 1.67)**	0.86

Key: OR=odds ratio; CI=confidence interval

Conclusion: Traditional risk factors, including African-American race, obesity, high alcohol intake, diuretic use, decreased kidney function and hypertension are associated with an increased risk of gout in both women and men. The relationship between certain risk factors, such as African-American race, protein intake, and organ meat intake varies by gender. Understanding how gender modifies traditional risk factors may allow for more targeted patient counseling and treatment strategies.

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The Significance of Self-Rated Health and Mental Well-Being in Predicting Outcomes Following TJR Surgery for OA. Anthony V. Perruccio[1], Elizabeth M. Badley[2], Sheilah Hogg-Johnson[3] and Aileen Davis[4], [1]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [2]Univ of Toronto, Toronto, ON, [3]Institute for Work and Health, Toronto, ON, [4]Toronto Western Research Institute, Toronto, ON

Purpose: Total joint replacement (TJR) is a frequently performed procedure for hip and knee OA. Studies of the determinants of TJR patient-reported outcomes and the scope of outcomes examined have typically been limited to aspects of physical health, in particular pain and physical function. What has been neglected is the concomitant consideration of patient-reported mental and social health status. Moreover, a number of studies have documented the predictive significance of self-rated health (SRH) for a number of health outcomes. However, SRH has not been fully considered in TJR patient-reported outcomes. The purpose of this study was to examine the predictive significance of physical, mental and social health and SRH for future health status in a cohort of individuals within 6 months of undergoing TJR surgery for hip or knee osteoarthritis (OA) and to simultaneously investigate the predictive significance of these health dimensions for SRH.

Method: Participants (hip: n=215; knee: n=234) completed measures pre-surgery and at 3 and 6 months post-surgery associated with physical: HOOS/KOOS (pain, physical function, sport/rec); mental: POMS (fatigue), HADS (anxiety and depression); and social health: LLFDI (disability limitation), passive/active recreation, community access. Using structural equation modeling, confirmatory factor analyses was used to investigate 3 latent health dimensions characterized as physical, mental and social health. These dimensions were regressed on prior health status and on prior SRH. As well, SRH was regressed on each of these dimensions both within and across time points. Measures of overall model fit were assessed.

Results: Hip group: age range from 31-86 years (mean=62) with 57% female; Knee group: age range from 35-88 years (mean=64) with 63% female. 90% of the sample completed the baseline questionnaire within 3 weeks prior to surgery. Significant improvements in health dimension scores were observed over time. Prior dimension status strongly predicted future status. And, with simultaneous adjustment for prior health dimension scores, comorbidity and sociodemographic characteristics, SRH significantly predicted future health status for all three of the health dimensions. Worse prior SRH predicted less improvement both at 3 and 6 months post-surgery. Mental well-being was the only health dimension to significantly predict SRH, both within and across time points. The effects of physical and social health on SRH were fully mediated through mental well-being.

Conclusion: As a significant predictor of future health status following TJR surgery, improving a patient's SRH appears to be critical for improving the rate of recovery. As the most proximal determinant of SRH, mental well-being should be incorporated as an essential constituent of any care, treatment and management strategy.

Disclosure: A. V. Perruccio, None; **E. M. Badley**, None; **S. Hogg-Johnson**, None; **A. Davis**, None.

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Influence of Industry Funding On the Outcome and Quality of Randomized Controlled Trials of Drug Therapy for Rheumatoid Arthritis. Nasim A. Khan[1], Juan I. Lombeida[1], Horace J. Spencer[1] and Karina D. Torralba[2], [1]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [2]University of Southern California, Los Angeles, CA

Purpose: To assess impact of industry funding on the outcome and quality of randomized controlled trials (RCTs) of drug therapy for rheumatoid arthritis (RA).

Method: MEDLINE and Cochrane Central Register of Controlled Trials databases were searched using terms *Rheumatoid Arthritis* or *Arthritis, Rheumatoid* with a limitation to C*linical Trials, English* and years *2002-3 & 2006-7*. Eligible studies were identified by screening the title and abstract for original, parallel-design, drug trials with clinical primary outcome(s) that randomly allocated patients to different treatment groups. Two reviewers independently assessed each RCT for source of funding [industry, non-profit or mixed/both), outcome type [positive (statistically significant result favoring experimental intervention for the primary outcome), or not positive], and reporting of aspects of methodology whose inadequate performance has been empirically shown to bias the assessment of treatment effect. RCTs with industry funding were compared with those without any industry funding using chi square test.

Results: A total of 107 RCTs were identified. Regarding funding, 61 (57%) RCTs were industry, 20 (18.7%) were non-profit source(s), and 6 (5.6%) were mixed source funded. No funding source was reported in 20 (18.7%) RCTs. Eighty-eight (82.2%) RCTs could be assessed for outcome. Trials excluded from analysis included those that had safety as the primary outcome (10), and those where interventions tested were treatment strategies with no a priori strategy declared as experimental (9). Industry-funded RCTs were not found have higher rates of positive outcomes [industry sponsored (38/51, 74%), non- profit (12/16, 75%), mixed (2/5, 40%), and unspecified source (13/16, 81%); p Value = 0.33]. Industry funded RCTs reported significantly more frequent performance of several quality measures such as double-blinding, adequate descriptions of withdrawals and dropouts during the study, and intention-to-treat analysis (Table).

Conclusion: Industry funded drug RCTs of RA did not differ in frequency of reporting positive outcome from non-industry funded RCTs and had better reporting of some key methodological aspects of RCTs.

	Industry funded (N=60), n (%)	Non-industry funded (N = 47), n (%)	p Value
Positive outcome*	40/56 (71.4)	25/32 (78.1)	0.33
Random sequence generation	23 (34.3)	14 (35)	0.55
Allocation concealment	21 (31.3)	11 (27.5)	0.42
Double-blinding	58 (86.6)	19 (47.5)	< 0.001
Description of withdrawal/dropouts	56 (83.6)	27 (67.5)	0.047
Intention-to-treat analysis**	47/58 (81)	21/39 (53.8)	0.004

*Excluding RCTs safety as primary outcome + strategy trials with no a priori designated "experimental" study group.

** Excluding RCTs safety as primary outcome.

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Causes of Hospitalization in Patients Treated with Anti-Tumor Necrosis Factor á Agents. Devy Zisman[1], Amir Haddad[1], Sharbel Hashoul[1], Arie Laor[2], Haim Bitterman[2], Itzhak Rosner[3], Alexandra Balabir-Gurman[4], Reuven Mader[5] and Uzi Milman[6], [1]Carmel Medical Center, Haifa, Israel, [2]Carmel Medical Center / Faculty of Medicine, Technion, Haifa, Israel, [3]Bnai Zion Medical Center / Faculty of Medicine, Technion, Haifa, Israel, [4]Rambam Medical Center / Faculty of Medicine, Technion, [5]Ha'Emek Medical Center / Faculty of Medicine, Technion, Afula, Israel, [6]Clalit Health Services

Purpose: To ascertain causes of hospitalization in patients with rheumatoid arthritis (RA), psoriatic arthritis (PSA), and ankylosing spondylitis (AS) treated with anti-tumor necrosis factor α (anti-TNF) agents compared to patients treated with traditional disease-modifying antirheumatic drugs (DMARDs).

Method: A retrospective cohort study of patients with RA, AS & PSA insured by Clalit Health Services in northern Israel between April 2002 and December 2007 was conducted. 354 treated with DMARDs only (group A) were compared to 322 anti-TNF-treated patients. The latter were assessed during their anti-TNF treatment period (group B) and compared to an equivalent period before anti-TNF initiation (group C). All hospitalization charts were reviewed and diagnoses, co-morbidities, concomitant medications and clinical course analyzed. Statistical analysis was performed using SAS 9.2 software.

Results: In the study period there were 142 hospitalizations in group A, 265 in group B, and 420 in group C with 61 infections requiring hospitalization during anti-TNF treatment compared to 39 before treatment and16 in the DMARDs group. The common relative risk (RR) controlled for age and gender between groups B and C was 4.5 (95% confidence interval 1.57-12.91). Mycobacterial infections (2 cases), multiple sclerosis like syndrome (3 cases), and hematological malignancies (4 cases) occurred exclusively during anti TNF treatment. In contrast, a major significant decrease was noted in hospitalizations due to disease flares and orthopedic admissions during anti-TNF treatment compared to the same patients before treatment (99, 255 and 15, 20, respectively). The common RR controlled for age and gender was 0.31 and 0.14 (95% confidence interval 0.18-0.51 and 0.05-0.4, respectively). No significant differences among the groups in hospitalization due to congestive heart failure or chronic lung disease exacerbations, cerebrovascular accidents nor surgical admissions were noted. One death occurred in group B due to a hematological malignancy

Conclusion: Rheumatic patients treated with anti-TNF agents had an increased risk of hospitalization due to infections compared with DMARD treated patients but the rate of hospitalization due to disease exacerbation and orthopedic admissions declined remarkably after anti-TNF treatment.

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1395

Norms-Based Assessment of Patient-Reported Outcomes Associated with Adalimumab Monotherapy in Patients with Ankylosing Spondylitis. Miriam Kimel[1], Chris Thompson[1], Katherine Gooch[2], Dennis Fryback[3], David Feeny[4] and Dennis Revicki[1], [1]United BioSource Corporation, Bethesda, MD, [2]Abbott Laboratories, Abbott Park, IL, [3]University of Wisconsin School of Medicine and Public Health, Madison, WI, [4]Kaiser Permanente Center for Health Research, Portland, OR

Purpose: Adalimumab monotherapy has been shown to improve signs and symptoms, physical function, and general health-related quality of life (HRQOL) for ankylosing spondylitis (AS) patients (pts). The interpretation of the HRQOL score change is not well established. We compared the HRQOL impact of AS with general United States (US) norms and the impact of adalimumab treatment on initial and sustained improvement in HRQOL for pts with active AS compared with general US norms and minimum clinically important differences (MCID) for each HRQOL measure.

Methods: Of 315 pts enrolled in the initial 24-week period of the ATLAS trial, 208 were randomized to adalimumab 40 mg SC every other week and 107 to placebo. HRQOL was assessed using the Short Form 36 (SF-36) Health Survey and the Health Utilities Index Mark 3 (HUI3). The HRQOL burden of AS was assessed by comparing baseline SF-36 (PCS, MCS, and SF-6D) and HUI3 scores with general US norms using National Health Measurement Study (NHMS) data. The impact of adalimumab treatment on HRQOL was assessed by comparing SF-36 and HUI3 scores at Weeks 12 and 24 with NHMS norms.

Results: At baseline, adalimumab and placebo group pts had comparable HRQOL scores for all measures (PCS, MCS, SF-6D, and HUI3); scores for both groups were significantly more impaired compared with the general US population (all $p<0.0001$). Compared with the general population, mean scores for trial pts were approximately 20, 10, 0.25, and 0.33 points less for PCS, MCS, SF-6D, and HUI3, respectively. At Week 12, adalimumab and placebo group scores were significantly worse than for the general population. Mean improvements in PCS (+6.5) and SF-6D (+0.08) scores from baseline to Week 12 were clinically relevant for adalimumab pts (based on MCIDs of 5 points for PCS and 0.03 points for SF-6D). Clinically meaningful differences in PCS and SF-6D scores were observed for adalimumab vs. placebo pts (improvements of 5.4 vs. 0.04 points). Similar within-group improvements and between-group differences in PCS and SF-6D scores were also observed at Week 24. In addition, based on an MCID of 0.03 points, clinically relevant within-group improvements (0.13 points) and between-group differences (0.08 points) were seen for HUI3 scores favoring adalimumab. Previous analyses of 3-year outcomes from ATLAS indicated that mean PCS scores increased from baseline to 43 and 44 points at 1 and 3 years, respectively. The NHMS US population norm for the PCS is 46 points.

Conclusion: After 6 months of therapy, AS pts receiving adalimumab had significantly improved health status. However, a longer duration of therapy may be required to improve health status to levels comparable to general population norms.

Disclosure: M. Kimel, United Biosource Corporation , 3 ; **C. Thompson**, United Biosource Corporation , 3 ; **K. Gooch**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **D. Fryback**, University of Wisconsin , 9 ; **D. Feeny**, Kaiser Permanente Center for Health Research , 3 ; **D. Revicki**, United Biosource Corporation, 3 .

1396

Costs Associated with Administration of Intravenous Infusion Therapy for Rheumatoid Arthritis. G.B. Kruse[1], Sanjoy Roy[2], Mary Cifaldi[2], D.C. Skonieczny[3] and B. Wong[1], [1]Bruce Wong & Associates Inc., Philadelphia, PA, [2]Abbott Laboratories, Abbott Park, IL, [3]Medical Present Value Inc., Austin, TX

Purpose: Biologic agents for the treatment of rheumatoid arthritis (RA) are administered either as subcutaneous injections or intravenous infusions. Whereas patients can self-inject subcutaneous drugs, infusion therapy requires drug administration by a health care provider. Although many factors influence the choice of the route of administration for biologic agents, the cost of administering these drugs has not been studied sufficiently. This study assessed the costs of administering infliximab, abatacept, and rituximab based on physician reimbursements for such services.

Methods: Provider claims data were analyzed from Medical Present Value (MPV), a large, longitudinal, national, provider contract-management database. Patients with an RA diagnosis and any claim including an infusion of a biologic agent between January 1, 2003, and December 31, 2008, were identified. Health Care Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes were used to identify infused drugs and administration costs.

Results: A total of 4,556 patients with RA receiving at least 1 infusion of infliximab, abatacept, or rituximab were identified. Of 33,354 infusion administration claims, 80% were for infliximab, 15% were for abatacept, and 5% were for rituximab. Mean (SD) total provider cost per infusion (in US $), including the drug, was $2,874 ($1,515) overall and $2,827 ($1,282) for infliximab, $1,827 ($622) for abatacept, and $6,057 ($1,689) for rituximab. The cost of administration was $226 (7.9% of total cost) overall and $224 (7.9) for infliximab, $171 (9.3) for abatacept, and $390 (6.4%) for rituximab.

In a subgroup of patients within the MPV database who received 12 doses of infliximab, the average infused dose increased from 389.7 mg to 428 mg from the first to the twelfth recorded dose. Similarly, the average cost of administering the drug increased from $214 to $241 in these patients.

Conclusion: Although drug cost is the single largest component of infusion therapy in RA, service costs of infusion administration add a significant amount to the total cost. These costs are frequently unrecognized when considering the drug cost effectiveness. Payors should

examine related financial implications when evaluating available options for providing optimal therapy for RA. This evidence is the first to show that the "dose creep" associated with infliximab increases the cost of infusion, potentially due to increased duration of infusion with greater doses. This is likely to be a major unrecognized cost because infliximab represents the largest share of biologic therapy in RA in this study database and has the longest history of use, which may exacerbate the effects of dose creep and related infusion costs.

Disclosure: G. B. Kruse, Bruce Wong & Associates Inc., 3 ; **S. Roy**, Abbott Laboratories, 3 ; **M. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **D. C. Skonieczny**, Medical Present Value, 3 ; **B. Wong**, Bruce Wong & Associates Inc., 3 .

1397

Methods to Improve the Triage Accuracy of Referrals for Possible Inflammatory Polyarthritis. Glen S. Hazlewood, Liam Martin and Susan G. Barr, University of Calgary, Calgary, AB

Purpose: The accurate triage of referrals for possible inflammatory polyarthritis is critical, particularly to avoid misclassification of non-inflammatory disorders and delays in appropriate therapy. We studied the accuracy of our triage process and the ability of clinical and lab markers of inflammation to correctly identify patients with inflammatory disorders.

Method: Data is collected prospectively on all referrals to our Central Referral Office. All referrals from Jan 2007- Dec 2008 with possible inflammatory polyarthritis, including patients with polyarthralgia, were analyzed. The working diagnosis based on referral data was compared to the final diagnosis after consultation with a rheumatologist. A convenience sample of 200 sequential referrals was reviewed for completeness of several key data elements, including joint distribution, duration of symptoms, morning stiffness (AMS), swelling, past medical history and medications, CBC, RF and either an ESR or CRP. The impact of a rheumatology specific referral form on completeness of information was assessed. The utility of joint swelling, AMS>30min, ESR>20, CRP>8 and RF>20 for identifying inflammatory disorders was determined by calculating likelihood ratios for positive (LR+) and negative (LR-) results. Low cutpoints were chosen to maximize sensitivity and minimize misclassification of patients as non-inflammatory.

Results: A working diagnosis was available for 8284/9182 (90%) of referrals. Polyarthritis was questioned in 3706 (45%). Of these, the working diagnosis was inflammatory arthritis (IA) in 49%, indeterminate (IND) in 21%, osteoarthritis (OA) in 19%, and fibromyalgia (FM) in 12%. A final diagnosis was available for 1832/3706 (49%). Of those with a working diagnosis of FM, 98% (179/182) had a final diagnosis of a non-inflammatory disorder, including 66% with confirmed FM. Referrals triaged as OA were non-inflammatory in 327/369 (89%), possible-IA in 23 (6.2%) and IA in 19 (5.1%). Referrals triaged as IND were diagnosed with IA/possible-IA in 157/432 (36.3%). Patients triaged as IA were confirmed to have IA in 525/849 (61.8%). Reported joint swelling, AMS >30 min. and RF were not able to distinguish inflammatory vs non-inflammatory disorders. An ESR>20 (LR+1.5[95% CI: 1.1-2.1], LR- 0.7[0.5-0.9]), or CRP>8 (LR+1.7[1.0-2.8], LR-0.8(0.7-0.96)] had minimal utility in isolation. However, a normal ESR, CRP and RF in combination, had a moderate LR- of 0.4 [0.3-0.8]. For OA, this would lower the probability of IA/possible-IA from 11% to 5%. The referral form improved the completeness of referral information from 49% to 69% ($p<0.001$). Of the 200 referrals reviewed, 62 (31%) were inadequate and additional data was requested to enable triage. Of these, 19 (31%) had abnormal labs (CBC, ESR, CRP, RF) or x-rays, and 8/19 (42%) were ultimately diagnosed as IA.

Conclusion: Inflammatory arthritis can be reliably excluded for referrals with a working diagnosis of FM. For other consults, a normal ESR, CRP and RF are helpful in lowering the probability of IA, while joint swelling and AMS are not. A referral form can help improve the reporting of key triage information.

Disclosure: G. S. Hazlewood, None; **L. Martin**, None; **S. G. Barr**, None.

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Utilization of VA Pharmacy Benefits Management Data and the VA Rheumatoid Arthritis Database to Demonstrate Reduced Disease Activity in Rheumatoid Arthritis Patients Adherent with Methotrexate. G. W. Cannon[1], BC Sauer[1], CL Hayden[1], A.M. Reimold[2], R.S. Hooker[3], G.S. Kerr[4], J.S. Richards[4], L. Caplan[5], D.S. Johnson[6] and T. R. Mikuls[7], [1]VA and University of Utah, Salt Lake City, UT, [2]VA and UTSouthwestern Medical Center, Dallas, TX, [3]VA, Dallas, TX, [4]VA and Georgetown University, Washington, DC, [5]VA and University of Colorado, Aurora, CO, [6]VA and University of Mississippi, Jackson, MS, [7]U Nebraska, Omaha, NE

Purpose: The linkage of pharmacy databases with objective clinical outcome measures provides an opportunity to evaluate rheumatoid arthritis (RA) therapies in real world clinical settings. This work merges information from the Veterans Affairs Rheumatoid Arthritis (VARA) registry initiated in 2003 and the VA Pharmacy Benefits Management (PBM) database with data from 1998 to determine if adherence with prescribed methotrexate (MTX) for the treatment of RA is associated with a reduction in RA disease activity.

Methods: VARA routinely collects 28 joint disease activity score (DAS28) on RA patients as part of this prospective multicenter observation cohort study. PBM data on these subjects were obtained during this observation period. For each MTX prescription, the estimated duration of the prescription, total dose of MTX dispensed, and anticipated date for refill of medication was recorded. The time gap between anticipated refill and actual refill of the next MTX prescription was calculated. MTX treatment course duration was defined as the time from the initial MTX prescription until the expected refill date for the last MTX prescription before a 90 day gap or discontinuation. The medication possession ratio (MPR), a measure of adherence, was calculated as the proportion of treatment time that the patient had drug available. Adherence was defined as an MPR $\geq$ 0.80. For each patient the average DAS28 over the course of therapy, prescribed MTX dose, and observed MTX dose were calculated. Patients included in this analysis were RA subjects who had at least one DAS28 score measured during their initial course of MTX therapy that was greater than 12 weeks in duration.

Results: Compared to non-adherent (MPR < 0.80) patients (n = 61), MTX adherent patients (n=329) had lower mean DAS28 score and ESR despite similar prescribed dose of MTX (Table). Other clinical chacteristics for these two groups were similar.

	Age	Disease Duration (yr)	RF (+)	aCCP (+)	Prescribed MTX dose (mg/wk)	Observed MTX dose (mg/wk)	DAS 28	ESR
MPR<80% (n=61)	65±11	9±10	82%	70%	16±4	11±3	4.1±1.4	30±25
MPR≥80% (n=329)	67±12	10±11	84%	74%	16±4	15±4	3.6±1.2	23±17
p-value	N.S.	N.S.	N.S.	N.S.	N.S.	<0.001	<0.02	<0.01

The impact of adherence on DAS28 was more pronounced after adjusting for weekly observed MTX dose. The results were unchanged after adjustment for age, disease duration, prescribed duration, and prescribed MTX dose.

Conclusion: RA patients in the VARA registry who were adherent with MTX therapy had significantly lower disease activity over follow-up in comparison to similar patients who were not adherent with therapy. This analysis demonstrates the potential for the use of data from these databases to evaluate clinical effectiveness of RA therapies in real world practice.

Disclosure: G. W. Cannon, None; **B. Sauer**, Dapartment of Veterans Affairs, 9 ; **C. Hayden**, None; **A. M. Reimold**, None; **R. S. Hooker**, None; **G. S. Kerr**, None; **J. S. Richards**, None; **L. Caplan**, None; **D. S. Johnson**, None; **T. R. Mikuls**, None.

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Lipoprotein Components Are Not Associated with Myocardial Infarction or Stroke in RA. Anne Grete Semb[1], G. Walldius[2], A. Aastveit[3], I. Jungner[4], T.K. Kvien[1] and I. Holme[5], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Karolinska Institute, Stockholm, Sweden, [3]Norwegian University of Life Sciences, Aas, Norway, [4]CALAB research, Stockholm, Sweden, [5]Ullevaal University Hospital, Oslo, Norway

Purpose: The striking contradiction concerning the high incidence of cardiovascular disease (CVD) in rheumatoid arthritis (RA) is low levels of lipids and at the same time there is an accelerated deposition of LDL-c, which is not explained by the traditional CV risk factors as hyperlipidaemia, smoking, diabetes, hypertension, and BMI. We aimed to describe the importance of lipids, apolipoproteins, and their ratios to predict future myocardial infarction (MI) or ischemic stroke (IS) in RA

Methods: In the AMORIS population 480 406 persons were followed for an average of 11.8 (7-17)(range) years. Of these 1 779 patients developed RA. A subgroup (n=150 443, of these were 505 persons with RA) volunteered blood samples, which were analyzed for total cholesterol (TC), triglycerides (TG), Apolipoprotein B (ApoB), apolipoprotein A1(ApoA-1). High and low density lipoprotein cholesterol (HDL-c, LDL-c) were calculated. Those who had any kind of cardiovascular disease at blood sampling were excluded. Cox regression models were used for statistical analyses.

Results: RA patients had lower lipids, apolipoproteins, and ratios than non RA. Despite this, the rate of AMI pr 1000 patient years was 3 fold higher in RA patients compared to the non RA persons in the total AMORIS population[1] ($p<0.001$). Similarly, The rate of IS was 3 times higher in RA patients compared to the non RA persons in the total AMORIS population[2] ($p<0.001$). Furthermore, females with RA were more prone to IS compared to male RA patients ($p<0.0001$). Hazard ratio of time from RA to first AMI or IS by 1 SD increase in lipoprotein components adjusted for age at RA disease onset , gender, hospital recorded diabetes and hypertension, showed that none of the lipid components or their ratios was significantly predictive for AMI or IS. At the same time, though, none of them was significantly different from the relationships found in the non-RA population.

Conclusion: Despite low levels of lipids and apolipoproteins, patients with RA have a higher rate of both AMI and IS compared a non-RA population. Lipoprotein components or their ratios are not predictive risk factors for MI or IS in RA.

References:
(1) Holme I, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2008; 264(1):30-38.
(2) Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Relationships between lipoprotein components and risk of ischaemic and haemorrhagic stroke in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2009;265(2):275-87.

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1400

Delay in Referral in Early Arthritis and Its Effect On Disease Outcome. Michael van der Linden[1], Saskia le Cessie[1], Karim Raza[2], Diane van der Woude[1], Tom W.J. Huizinga[1] and Annette H.M. van der Helm-van Mil[1], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom

Purpose: In Rheumatoid Arthritis (RA), rapid initiation of disease modifying drugs (DMARDs) is associated with a better disease outcome. Since DMARDs are rarely started before patients see rheumatologists, this suggests that delays in assessment by rheumatologists will affect outcome. We have assessed the relationship between delay in rheumatology assessment and [1] the rate of joint destruction as well as [2] the chance of achieving DMARD-free remission in RA. In addition, patient characteristics associated with patient-related and general practitioner (GP)-related delay in the entire early arthritis cohort were assessed.

Method: 1935 early arthritis patients from the Leiden Early Arthritis Clinic were studied and patient-related delay in presentation and GP-related delay in referral assessed. In 599 patients that fulfilled the 1987 ACR the criteria for RA during the first year after inclusion the association between the total delay and rate of joint destruction (median followup 4 years, max. 9 years) and achievement of DMARD-free remission were determined.

Results: In all early arthritis the median patient-related, GP-related and total delay were 2.7, 8.3 and 13.9 weeks. In the subgroup of RA-patients these delays were 3.4, 11.8 and 18.3 weeks respectively. Female gender, gradual symptom-onset, involvement of small joints and presence of autoantibodies associated with a longer total delay. Early arthritis patients that were diagnosed with RA had the longest delay in referral compared to all other diagnoses. Within RA-patients, a delay of <12 weeks associated with a significantly lower rate of joint destruction and more achievement of DMARD-free remission.

Conclusion: In RA, the time to referral is correlated with the chance of DMARD-free remission and the rate of joint destruction. Despite this correlation, among all early arthritis patients, those diagnosed with RA had the longest delay in referral. This implies that efforts to diminish the delay in visiting a rheumatologist may improve the disease outcome of RA-patients.

Disclosure: M. van der Linden, None; **S. le Cessie**, None; **K. Raza**, Wyeth Pharmaceuticals, 2 ; **D. van der Woude**, None; **T. W. J. Huizinga**, None; **A. H. M. van der Helm-van Mil**, None.

1401

Assessing HRQoL Burden of Disease and Comparison to the U.S. Population in Psoriatic Arthritis Patients Treated with Golimumab: Results From the GO-REVEAL Trial. A. Raju[1], G. Hammond[2], S. Parasuraman, J. Buchanan and T. Gathany[3], [1]Lincoln, RI, [2]Qualitymetric Inc., Lincoln, RI, [3]Johnson and Johnson Pharmaceutical Services, LLC, Malvern, PA

Purpose: Assess the burden of active psoriatic arthritis (PsA) on health-related quality of life (HRQOL) as measured by SF-36. Contrast proportions of individuals meeting or exceeding the age and gender adjusted pop norms.

Methods: Adult patients (n=405) were randomized to golimumab (GLM) 50 mg (tx 1), GLM 100 mg (tx 2), or placebo (tx 3). Inclusion criteria: diagnosis with PsA (for min. of 6 months), exhibition of at least 3 swollen and tender joints. A *t*-test was used to assess equivalence in continuous SF-36 scores between wk 24 trial and norm, disease means. Separate χ^2 tests were used to compare proportions of individuals meeting and exceeding pop norms at wk 24.

Results: At baseline and wk 24, despite improvement, GO-REVEAL means were significantly lower than age and gender-adjusted US population (pop) norms for all SF-36 domain scores, indicating marked health impairment (Table). At baseline, both disease specific norms means were significantly higher than trial means on 3 SF-36 physical scale scores (PF, RP, BP) and PCS summary scores (all *p*s<.05). Trial means were significantly higher than the depression specific norms on mental health scale and summary measures (VT, SF, RE, MH, and MCS) at wk 24, but were comparable on 3 of the physical health scales (RP, BP, GH) (Table). At wk 24, trial means were comparable to rheumatoid arthritis norms on all SF-36 domain scores (Table). At wk 24, 30.2% (tx 1) and 28.5% (tx 2) of individuals exceeded the pop. norms for PCS, relative to 7.6% for tx 3 (χ^2: 16.7 and 18.7, GLM 100, 50, vs. placebo, *p*s<.01). No difference was observed in the proportion of individuals meeting/exceeding the pop norms for MCS across treatments (χ^2: 2.6 and 2.5, GLM 100, 50, vs. placebo, *p*s>.10), although all mental health scales showed significant differences (VT, SF, RE, and MH, all *p*s<.05).

Conclusion: Trial means improved relative to the US pop norms, but all domain scores were still significantly below pop. norms at wk 24. SF-36 domain scores were comparable to those of the RA specific norms. Both GLM doses showed significant and meaningful improvement in both PCS and all 4 mental scales relative to placebo at wk 24, indicating an improvement in both mental and physical health scores.

	GO-REVEAL		**Norms**			**Comparisons**		
	Baseline	**wk 24**	**U.S. Pop.**	**Depression**	**Rheumatoid**	**U.S. Pop.**	**U.S. Pop.**	**Depression**
	(n=403)	**(n=388)**	**(n=2031)**	**(n=257)**	**(n=136)**	**(Baseline)**	**(wk 24)**	**(wk 24)**
Domain	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean Diff. (Comparator-Trial)**		
PF	**36.0**	**40.4**	**50.6**	**43.6**	**43.0**	14.6*	10.2*	3.2*
RP	**36.6**	**42.1**	**50.6**	**42.8**	**43.4**	14*	8.5*	0.7
BP	**36.0**	**43.3**	**50.0**	**43.2**	**41.1**	14*	6.8*	-0.1
GH	**39.0**	**42.2**	**50.2**	**40.4**	**41.2**	11.2*	7.9*	-1.8
VT	**42.5**	**47.1**	**50.6**	**40.9**	**45.7**	8.1*	3.5*	-6.3*
SF	**39.9**	**44.4**	**50.6**	**39.1**	**42.8**	10.7*	6.2*	-5.3*
RE	**42.0**	**45.8**	**50.6**	**39.2**	**44.5**	8.6*	4.7*	-6.7*
MH	**43.2**	**45.5**	**50.3**	**37.1**	**45.4**	7.1*	4.8*	-8.4*
PCS	**35.1**	**40.8**	**50.3**	**44.9**	**41.6**	15.2*	9.5*	4.1*
MCS	**45.2**	**47.8**	**50.4**	**37.1**	**45.9**	5.2*	2.7*	-10.6*

*: *p*<.01

Disclosure: A. Raju, None; **G. Hammond**, None; **S. Parasuraman**, JJPS, LLC, 3 ; **J. Buchanan**, JJPS, LLC, 3 ; **T. Gathany**, Johnson & Johnson, 3 .

ACR/ARHP Poster Session C

Fibromyalgia and Soft Tissue Disorders

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1402

What Pain Related Behaviour Tells the MD about a Patient with Fibromyalgia. MA Fitzcharles[1], Marta Ceko[2], Ann Gamsa[2], Mark Ware[2] and Yoram Shir[2], [1]MGH, Montreal, QC, [2]McGill University, Montreal, QC

Purpose: The entire clinical assessment of patients with fibromyalgia (FM) is subjective and depends upon patient report and interpretation of this report by the physician. There has been debate regarding the validity and reliability of the complaint of symptoms by patients with FM, who frequently report important functional impairment. Pain related behaviour (PRB) may be defined as overt demonstrations by an individual indicating the presence of important pain. These behaviours may be perceived by the health care professional as compatible with, or as an exaggerated response to the underlying condition. Some have even suggested that the presence of these behaviours may reflect a conscious effort by the patient to emphasise the severity of symptoms. We examined the frequency and associations of PRB in FM patients attending a specialized multidisciplinary FM clinic in a tertiary care centre.

Method: We evaluated 136 consecutively attending FM patients for the presence of PRB. These was defined as behaviours that occurred during the physician interview and examination, appeared out of proportion to that expected for the symptom complaint, and which conveyed the subjective impression of exaggeration of pain and discomfort. Associations with demographic variables, pain and mood measurements and functional status were explored using the following: McGill Pain Questionnaire (MPQ), Pain Catastrophizing Scale (PCS), Pain disability Index (PDI), the Arthritis Impact Measurement Scale (AIMS) and the Fibromyalgia Impact Questionnaire (FIQ),

Results: PRB was present in 28 (21%) vs. no PRB in 108 (79%). There were no differences between groups for age, gender, duration of symptoms or current employment status. Patients with PRB vs. no PRB scored higher on all pain assessments including MPQ vs. 39, (P=0.03), Affective component of MPQ 7.2 vs. 5.5 (p=0.04), pain VAS 7.2 vs. 6.2 (P=0.04), PDI 42 vs. 35 (P=0.03) and tended to be receiving disability compensation, 50% vs. 31% (P=0.06). There were no differences for pain catastrophizing (PCS), severity of depression and anxiety, presence of allodynia or FIQ.

Conclusion: PRB was observed in one in five of FM patients. All measurement of pain associated with the presence of these behaviours, but there was no association with mood disorders or functional impairment. Contrary to expectations, pain catastrophizing was not more prevalent in those with these overt behaviours. PRB may reflect a truly severe pain experience in FM, rather than a manifestation of attention seeking and histrionic behaviour.

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1403

Anxiety and Depression Subselects Fibromyalgia Patients: A Cluster Analysis with Treatment Implications. Juliana Barcellos de Souza[1], Serge Marchand[2], Mark A. Ware[3], Yoram Shir[3] and MA Fitzcharles[4], [1]University of Sherbrooke, QC, [2]Univ, QC, [3]McGill University, Montreal, QC, [4]MGH, Montreal, QC

Purpose: Successful management of fibromyalgia (FM) remains a challenge. Identification of parameters that could direct treatment approaches would be advantageous. We have previously identified 2 patient subgroups, without or with comorbid depression and anxiety, by hierarchical cluster analysis using the fibromyalgia impact questionnaire (FIQ), a well validated quality of life (QOL) assessment for FM. In the present study we report the validation of these subgroupings on a large population of FM patients in a tertiary care setting.

Method: The FIQs for 132 FM patients attending a tertiary care multidisciplinary pain clinic were analysed as follows: (A) patients were assigned to the respective cluster, FM-Type I (without depression and anxiety) and FM-Type II (with depression and anxiety), using the classification coefficient previously published (Souza et al., Rheum. Int. 2008) and; (B) the cluster analysis was reapplied with this new sample. To confirm the number of clusters with this new cluster analysis (B), we analysed progressive changes in the agglomeration coefficient. Positive and negative predictive values for clustering according to mood disorder, as well as specificity and sensitivity for both

models were calculated (A and B). Additional measures of pain and QOL included the McGill Pain Questionnaire (MPQ), Health Assessment Questionnaire (HAQ), Pain Catastrophizing Scale (PCS) and Pain Disability Index (PDI)

Results: Tertiary care FM patients were grouped into Type-I (n=28) and Type-II (n=104) groups with Type-II patients demonstrating higher values for pain, fatigue, stiffness, morning tiredness, anxiety, depression on the FIQ. Repeat analysis (B), identified 2 clusters dependent on mood. The inter-model analysis showed a sensitivity of 0.96, and specificity of 0.71; with positive predictive value of 0.41 and negative predictive value of 0.99. Type-I vs Type-II did not differ regarding duration of pain ($p=0.90$) or tender point count ($p=0.11$), but Type II were younger (47 vs 53 yrs $p<0.01$), and reported higher values for MPQ, HAQ, PCS and PDI (all $p<0.01$).

Conclusion: We have shown that the clustering of FM patients remained valid in a tertiary care setting, often considered to represent patients with more severe symptoms. There is therefore little doubt that different FM profiles exist, and may be identified by a single, comprehensive instrument, the FIQ. These clusters groups have implications regarding treatment approaches. Future studies should take these different patient groups into consideration in order to focus treatment interventions applicable to distinct patient groups.

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1404

Relevance of PROMIS Item Banks to Individuals with Fibromyalgia. David A. Williams[1], Stephen Schilling[1], Katrina N. Shibata[2], Lynn Zwinck[1], Lynne Matallana[2] and Lesley M. Arnold[3], [1]U. Michigan, Ann Arbor, MI, [2]National Fibromyalgia Association, Anaheim, CA, [3]U. Cincinnati College of Medicine, Cincinnati, OH

Purpose: In 2004, the NIH Roadmap initiative "Patient-Reported Outcomes Measurment Information System" (PROMIS) began its mission to develop the next generation of patient-reported outcomes measures (PROs) for chronic illnesses facilitated by the methods of item response theory (IRT) and computer adaptive testing (CAT). In practice, large banks of well-calibrated items can be drawn upon to measure a given outcome domain (e.g. function). While these item banks were developed to be applied with chronic illnesses generally, the current study sought to assess whether the items within the item banks were relevant to individuals with Fibromyalgia (FM).

Method: 80 females satisfying ACR criteria for FM (mean age=55.1 (sd=11.6)) were recruited from three sites (the Universities of Michigan and Cincinnati and the National Fibromyalgia Association (NFA). Groups of 20 participants were asked to review all items within one of four item banks: (1) Pain impact, (2) Fatigue, (3) Physical functioning, and (4) Emotional Distress (depression, anxiety, anger). Participants completed each item for themselves and then provided a relevancy rating on a 5-point Likert scale ranging from 1- "not at all relevant to FM" to 5-"very relevant to FM" for all items. Participants also completed open-ended questions soliciting suggestions for potential new items with relevance to FM.

Results: On average, the items contained within the Pain Interference and Fatigue banks were rated as being at least "Somewhat relevant" or better (i.e., ratings of 3,4,or 5) 87% of the time – the modal response for each of these banks was "very" relevant. The items within the physical functioning banks were rated as being at least 'Somewhat relevant" or better 64% of the time. For the negative mood banks, "Somewhat" relevant or better ratings were given to 73% of the depressive items, 67% of the anxiety items, and 55% of the anger items.

Conclusion: These data suggest that the majority of the pain and fatigue items already contained within the PROMIS item banks possess relevance for individuals with FM. The relevance of the items contained within the physical functioning and negative mood banks was more limited. In order to optimize PROMIS as a PRO measurement tool in FM, these item banks may require supplementary work.

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1405

Fluctuations in Baseline Clinical Pain Intensity Predict Therapeutic Response to Milnacipran in Patients with Fibromyalgia. Steven E. Harte[1], Lynn J. Zwinck[1], R. Michael Gendreau[2], David A. Williams[1], Daniel Clauw[3] and Richard E. Harris[1], [1]U. Michigan, Ann Arbor, MI, [2]Cypress Bioscience, Inc., San Diego, CA, [3]University of Michigan, Ann Arbor, MI

Purpose: Clinical experience and research indicate that the intensity of chronic pain fluctuates over time. Measures of pain variability that characterize these fluctuations may be useful in predicting treatment outcomes in clinical trials (Harris et al., Arthritis & Rheumatism 52, 2005). Patient electronic diaries (PEDs) that capture momentary pain ratings in real-time are a sensitive method of assessing pain variability. In this study, we used PED data to assess the relationship between pain variability and responsiveness to milnacipran treatment in fibromyalgia (FM) patients.

Method: Following a two week baseline (observational) period, FM patients were randomized to receive placebo (n = 223) or milnacipran (n = 665; 100 or 200 mg/day) for 6 months. Subjects carried Palm-based PEDs that prompted them at random intervals between 8 AM-10 PM to enter their current level of pain on a digital 0-100 numerical rating scale. Baseline pain variability was assessed for each participant as the standard deviation of all pain entries during the two week baseline period (pain variability index, PVI). Patient responsiveness to milnacipran was evaluated at 3 and 6 months using the Patient Global Impression of Change (PGIC) scale coded as a binary outcome measure: responder (very improved/improved) vs. non-responder (no change/worsing symptoms). Logistic regression analysis, adjusted for age and sex, was performed to assess the relationship between pain variability and treatment response. A logarithmic transformation was performed to better fit PVI to a normal distribution.

Results: The observed spread in baseline lnPVI values (mean ± SD 2.32 ± 0.48 [range -1.05 – 3.47]) indicates considerable variation in pain intensity across patients. Individuals with greater pain variability (higher lnPVI values) were more likely to be classified as responders to milnacipran when assessed after either 3 or 6 months of treatment (odds ratios ≥ 1.48, all $p < 0.05$). Participants randomized to placebo showed no significant relationships with lnPVI and responder status (all $p > 0.23$).

Conclusion: PEDs revealed that individuals with FM exhibit considerable fluctuations in pain intensity over time. Moreover, patients with greater baseline pain variability were more likely to respond to milnacipran than placebo. These data suggest that pain variability is predictive of treatment efficacy in chronic pain and should be considered in the design of clinical trials.

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1406

Tai Chi Is Effective in Treating Fibromyalgia: A Randomized Controlled Trial. Chenchen Wang[1], C. Schmid[1], R. Kalish[1], J. Yinh[1], Don L. Goldenberg[2], R. Rones[1] and T. McAlindon[1], [1]Tufts Medical Center, Boston, MA, [2]Newton-Wellesley Hosp, Newton, MA

Purpose: Fibromyalgia (FM) is a complex disorder best managed with multidisciplinary therapies. It is characterized by widespread musculoskeletal pain, sleep disturbances, functional limitation and poor quality of life. Tai Chi (TC) is an ancient Chinese exercise with an integrated mind-body approach to enhance both physical and mental health, and may be especially suited to the therapy of FM.

Methods: We conducted a 12-week, single-blind, randomized trial of TC (classical Yang style) vs. attention control (stretching and wellness education) for FM (ACR 1990 criteria). The 60-minute group sessions occurred twice-weekly. The primary endpoint was change in the FM Impact Questionnaire (FIQ) score at 12 weeks. Secondary endpoints included tender point count, patient and physician global assessments, sleep quality (PSQI), timed chair stand, 6-minute walk, grip strength, depression, self-efficacy and quality of life. We repeated these measures at 24 weeks to test durability of response. The TC and control groups were compared using an intent-to-treat analysis.

Results: The mean of the age of 66 subjects was 50y (SD 11), disease duration 11y (SD 7), BMI 33 kg/m^2 (SD 8), 85% were female, and 56% were white. There were no significant differences at baseline characteristics. Participants' baseline expectations of benefit from an exercise intervention were similar [TC=3.7 (SD 0.8), controls=3.9 (SD 0.7)]. At 12 weeks, patients assigned to TC exhibited significantly greater improvement in FIQ score [between-group change -17.9, 95% CI [-27.0 to -8.8]; P= 0.0006), patient global assessment, sleep quality, physical function, depression, and health status **(Table)**. The reduction in VAS pain intensity met the definition of a clinically-meaningful

improvement. At week 24, patients who continued TC exhibited durable benefits in FIQ score, sleep quality and quality of life. The two groups did not differ in medication usage. No adverse events were observed.

Conclusion: TC appears highly efficacious for treatment of both physical and psychological components of FM. TC may be a useful adjunctive treatment in the multidisciplinary management of this difficult disorder.

Table. Changes in Primary and Secondary Outcomes

Variables	Groups*	Baseline Mean (SD)	At 12 week Change (95% CI)	95% CI and P-value for Æ between group
FIQ (0-100)	TC AC	62.9 (15.5) 68.0 (11.0)	-28.6 (-36.5 - 20.8) -10.7 (-15.2, -6.2)	-17.9 (-27.0 to -8.8), P=**0.0006**
PSQI (0-21)	TC AC	13.9 (3.1) 13.5 (3.7)	-3.9 (-5.3, -2.5) -0.8 (-2.1, 0.4)	-3.0 (-4.9, -1.2) P= **0.004**
Patient Global (10-cm)	TC AC	5.8 (2.3) 6.3 (1.8)	-2.5 (-3.6, -1.5) -0.7 (-1.3, 0)	-1.9 (-3.2, -0.6) P=**0.004**
Physician Global (10-cm)	TC AC	5.6 (1.9) 5.6 (2.4)	-1.1 (-1.8, -0.3) 0 (-0.7, 0.7)	-1.1 (-2.1, -0.08) P=**0.08**
Chronic Pain Self-Efficacy (10-cm)	TC AC	5.2 (1.9) 4.6 (2.2)	1.6 (0.8, 2.4,) 0.5 (-0.4, 1.3)	1.1 (-0.05, 2.3) P=0.07
Chair stand test (sec)	TC AC	31.5 (12.3) 36.4 (14.4)	-8.9 (-12.9, -4.9) -7.9 (-11.2, -4.6)	-0.9 (-6.1, 4.2) P=0.9
Grip Strength, kg	TC AC	26.2 (7.8) 23.7 (5.9)	2.1 (0.6, 3.6) -0.4 (-2.5, -1.8)	2.5 (-0.03, 5.0) P=0.04
6 min walk test (yard)	TC AC	522.1 (102.7) 501.2 (106.6)	64.5 (39.4, 89.7) 18.5 (-7.4, 44.4)	46.0 (10.7, 81.4) P=0.01
SF-36: PCS (0-50)	TC AC	28.5 (8.4) 28.0 (7.8)	9 (5.5, 12.6) 1.6 (-1.1, 4.2)	7.5 (3.1, 11.9) P=0.003
SF-36: MCS (0-50)	TC	42.6 (12.2)	8.2 (4, 12.5)	6.4(0.4, 12.4)

	AC	37.8 (10.5)	1.8 (-2.6, 6.3)	P=0.02
CES-Depression (0-60)	TC AC	22.6 (9.2) 27.8 (9.2)	-8.6 (-11.9, -5.2) --2.6 (-5.5, 0.4)	-6.0 (-10.4, -1.6) P=0.02
AC=Attention Control *N=33 for each group at baseline.				

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1407

Baseline Characteristics of Fibromyalgia Patients in 4 Clinical Trials of Milnacipran. Robert H. Palmer[1], Daniel Clauw[2], Yves Mainguy[3], Yong Wang[1] and R. Michael Gendreau[4], [1]Forest Research Institute, Jersey City, NJ, [2]University of Michigan, Ann Arbor, MI, [3]Institut de Recherche Pierre Fabre, Labège, France, [4]Cypress Bioscience, Inc., San Diego, CA

Purpose: Milnacipran is approved in the US for the treatment of fibromyalgia (FM) and has shown efficacy for improving pain, patient global status, functioning, and fatigue in clinical trials. This analysis compares the key baseline demographic and disease characteristics of FM patients enrolled in 3 US and 1 European (EU) trials.

Method: These studies were randomized, double-blind, placebo-controlled trials of 3- or 6-month duration. Patient demographics, medical history, and baseline efficacy variables were recorded during a 2-week assessment period prior to randomization. Baseline efficacy variables included measures of pain (current and recall [24-hour, weekly], using a patient experience diary [PED]; visual analog scale [VAS] recorded on paper or wireless Tablet); function (Fibromyalgia Impact Questionnaire [FIQ]; Short Form-36 Health Survey [SF-36]); fatigue (Multidimensional Fatigue Inventory [MFI]); and cognition (Multiple Ability Self-Report Questionnaire [MASQ]).

Results: A total of 3985 FM patients were included in these trials. Most of the patients (>90%) were female and white. Mean ages were similar among all studies (range, 48.8 to 50.2 years). Duration of FM symptoms (mean years) was lowest in 1 US study (5.6) compared with the other 2 US (9.7, 10.8) and EU (9.5) studies. Weight and BMI differed markedly between the EU and US trials. Weight (mean lb) was lower in EU patients (158.0) compared with US (range, 180.8 to 183.0). EU patients were overweight (25≤mean BMI<30), whereas US were obese (mean BMI≥30). Although baseline efficacy values varied among the 4 trials, the EU and US populations were generally similar in terms of scores on pain (PED 24-hour recall: EU 65.3, US 63.7 to 68.9; PED weekly recall: EU 66.3, US 66.1 to 70.7); multidimensional functioning (FIQ: EU 56.9, US 57.3 to 64.6); physical functioning (SF-36 Physical Component Summary: EU 33.6, US 32.2 to 32.9); mental and cognitive functioning (SF-36 Mental Component Summary: EU 46.7, US 41.7 to 46.7; MASQ: EU 86.6, US 89.0 to 92.7); and fatigue (MFI: EU 66.6, US 67.5 to 69.1).

Conclusion: Baseline demographic and disease characteristics of FM patients were generally similar among 4 randomized, placebo-controlled trials of milnacipran. With the exception of body weight, there were no remarkable baseline differences between the US and EU study populations.

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1408

Milnacipran 100 Mg/Day in the Treatment of Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial. Lesley M. Arnold[1], R. Michael Gendreau[2], Allan Spera[3], Judy Gendreau[2] and Yong Wang[3], [1]University of Cincinnati, Cincinnati, OH, [2]Cypress Bioscience, Inc., San Diego, CA, [3]Forest Research Institute, Jersey City, NJ

Purpose: Milnacipran, a dual norepinephrine and serotonin reuptake inhibitor, is approved in the US for the management of fibromyalgia (FM). Previous clinical trials have demonstrated efficacy of milnacipran in FM with doses up to 200 mg/day. This new Phase 3 trial evaluates the efficacy and tolerability of milnacipran 100 mg/day for the management of FM.

Method: This was a double-blind, placebo-controlled trial of 1025 FM patients randomized to milnacipran 100 mg/day (n=516) or placebo (n=509). Patients underwent 4 to 6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment and a 2-week randomized, double-blind discontinuation phase. Primary outcomes included 2 composite responder analyses. A 2-measure composite responder was defined as an individual achieving ≥30% improvement from baseline in pain (VAS 24-h morning recall, collected on a patient experience diary [PED]) and a rating of "very much improved" or "much improved" on the Patient Global Impression of Change (PGIC) scale. A 3-measure composite responder met the above criteria for improvements in pain and PGIC as well as a ≥6-point improvement from baseline in physical function (SF-36 Physical Component Summary [PCS] score). Additional efficacy measures included change from baseline in fatigue (Multidimensional Fatigue Inventory [MFI]), pain (Brief Pain Inventory [BPI]), and function (Fibromyalgia Impact Questionnaire [FIQ]).

Results: Completion rates at the end of the stable dose period were 69.2% for milnacipran 100 mg/day and 70.5% for placebo. At 3 months, a significantly greater proportion of patients treated with milnacipran 100 mg/day relative to placebo met 2-measure composite responder criteria ($P<.001$, BOCF) and 3-measure composite responder criteria ($P<.001$, BOCF). Milnacipran-treated patients demonstrated significantly greater improvements from baseline vs placebo on a number of additional endpoint scores (LOCF), including PED 24-h recall pain, PGIC, SF-36 physical component summary and mental component summary, BPI average pain severity, FIQ total (all measures, $P<.001$), and MFI total ($P=.036$). Significant improvements in mean pain scores were observed after 1 week of double-blind treatment and were sustained throughout the stable-dose period ($P<.001$ vs placebo, all visits after 1 week). Milnacipran was well tolerated by the majority of patients; nausea was the most common adverse event (20.8%, placebo; 36.6%, milnacipran).

Conclusion: Treatment with milnacipran 100 mg/day improved FM patients' pain, global status, physical and mental functioning, and symptoms of fatigue. The safety profile was consistent with that observed in previous FM trials of milnacipran.

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1409

Milnacipan Improves Physical Function in Patients with Fibromyalgia: Pooled Results From 3 Phase III Trials. Philippe A. Saxe[1], Robert H. Palmer[2], Yong Wang[2] and R. Michael Gendreau[3], [1]Arthritis Associates of S. Florida, Delray Beach, FL, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego, CA

Purpose: Patients with fibromyalgia (FM) suffer from multiple symptoms, including chronic pain, fatigue, sleep disturbances, stiffness, and dyscognition. Health status studies indicate that FM patients have reduced physical, mental, and social functioning compared with the general population and patients with other pain conditions. Milnacipran, which is approved for the management of FM, has been shown in clinical studies to improve the pain and other symptoms of FM for up to 1 year. In this analysis, data from 3 randomized, double-blind, placebo-controlled trials were pooled to further examine the effects of milnacipran on clinically meaningful improvements in physical functioning. Patients in these trials reported their physical function status by using the Medical Outcomes Study Short Form-36 (SF-36), a self-report health status instrument that has been found to be a reliable measure of function in musculoskeletal disorders.

Method: Three-month data were pooled from 3 phase III pivotal studies ranging from 3 to 6 months in duration. Patients were randomized to receive placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=837). Physical function was measured by using the SF-36 Physical Component Summary (PCS) and the 4 individual physical health domains included in the SF-36: physical functioning, role limitation due to physical health, bodily pain, and general health. SF-36 domain responders were defined as patients with clinically meaningful improvements from baseline (≥5 points) in each physical domain. For SF-36 PCS responders, a more stringent definition for clinically meaningful improvement was used (≥6-point improvement from baseline score). Responder analyses were conducted by using a generalized linear mixed model (GLMM) approach.

Results: Compared with placebo, treatment with either dose of milnacipran was associated with a significantly higher proportion of SF-36 responders. At the 3-month endpoint, SF-36 PCS responder rates were 30% (placebo), 44% (100 mg/day, *P*<.0001), and 40% (200 mg/day, *P*=.009). Significantly more patients receiving milnacipran vs placebo were also responders for SF-36 physical functioning (27%, placebo; 35%, 100 mg/day, *P*=.017; 35%, 200 mg/day, *P*=.024), role limitation (40%, placebo; 50%, 100 mg/day, *P*=.006; 49%, 200 mg/day, *P*=.020), bodily pain (35%, placebo; 49%, 100 mg/day, *P*<.0001; 55%, 200 mg/day, *P*<.0001), and general health (21%, placebo; 29%, 100 mg/day, *P*=.006; 28%, 200 mg/day, *P*=.029).

Conclusion: Pooled results from 3 pivotal studies indicate that compared with placebo, treatment with milnacipran 100 mg/day or 200 mg/day resulted in a significantly greater proportion of patients with clinically meaningful improvements in physical functioning domains in patients with FM.

Disclosure: P. A. Saxe, Forest Laboratories, 2 ; **R. H. Palmer**, Forest Research Institute, 1, Forest Research Institute, 3 ; **Y. Wang**, Forest Research Institute, 3 ; **R. M. Gendreau**, Cypress Bioscience, Inc., 3 .

1410

Effect of Sodium Oxybate On Pain, PGIc, & Composite Scores in Fibromyalgia – Results From a Phase 3 Controlled Trial. I. Jon Russell[1], Sarah Alvarez-Horine[2], Yanping Zheng[2], Diane R. Guinta[2], Andrew J. Holman[3] and Todd J. Swick[4], [1]U TX Hlth Sci Ctr, San Antonio, TX, [2]Jazz Pharmaceuticals, Inc., Palo Alto, CA, [3]Pacific Rheumatology Assoc, Renton, WA, [4]Houston Sleep Center, UT Houston School of Medicine, Houston, TX

Background/Purpose: Fibromyalgia (FM) is characterized by widespread pain, but is often complicated by unrefreshing sleep, chronic fatigue, and psychologic distress. Small studies have demonstrated that sodium oxybate (SXB), a treatment with a novel mechanism of action, has potential for benefit in FM. This 14-week, double-blind, placebo-controlled trial is the largest study to date examining the treatment effects of SXB in FM.

Methods: 548 subjects with FM (per American College of Rheumatology criteria) were randomized to parallel therapy with SXB 4.5g/night (SXB4.5g), 6g/night (SXB6g), or placebo (PBO) in a 1:1:1 ratio. Treatments were administered in equal, divided doses at bedtime and 2.5-4h later. The primary outcome measure was the percent of patients reporting clinically relevant, >=30% reduction in Pain Visual Analog Scale (PVAS). Other measures included the percent of patients reporting >=50% reduction in PVAS, clinically relevant pain responders defined by >=30% reduction in PVAS *plus* “much better” or “very much better” on the patient global impression of change (PGIc), and FM syndrome composite responders defined by pain responders *plus* >=30% reduction in FM Impact Questionnaire (FIQ). Analysis: LOCF.

Results: Treatment with SXB4.5g and SXB6g resulted in significantly more patients reporting clinically relevant >=30% improvement in PVAS versus PBO (54.2% and 58.5%, respectively, vs 35.2%; both p<0.001). This was also true for >=50% improvement in PVAS (44.7% and 43.3%, respectively, vs 22.7%; both p<0.001). Significant reductions in mean PVAS scores were noted in SXB 4.5g and SXB6g compared with PBO at all weekly time points starting as early as week 1 (p<=0.002 for all). Both SXB4.5g and SXB6g resulted in a higher proportion of pain composite responders (42.9% and 49.6% vs 27.6%; p=0.008 and p<0.001, respectively) and FM syndrome composite responders (40.1% and 48.9% vs 26.1%; p=0.013 and p<0.001, respectively). Both SXB4.5g and SXB6g, vs PBO, showed significant improvement for each of 3 individual FM composite endpoints (PVAS, FIQ, PGIc; p-values all <0.01). Strong Pearson correlations for changes in pain were seen with PGIc and FIQ (0.70 and 0.79, respectively, p<0.001). The most common adverse events (AEs) on SXB treatment with incidences greater than 5% and twice the placebo rate were headache, nausea, dizziness, vomiting, diarrhea, anxiety, and sinusitis. The most commonly reported AE was headache (23.1%, SXB 6g).

Conclusion: This Phase 3 trial confirms earlier work (Russell IJ et al, *Arthr Rheum* 2009; 60:299-309) and demonstrated that sodium oxybate was well tolerated and improved pain in FM patients as early as one week after initiation of treatment. In addition, clinically meaningful improvements were noted in composite measures of pain and FM syndrome.

Disclosure: I. J. Russell, UCB, 6, Allergan, 2, Jazz Pharma, 2, Pfizer Inc, 2, Eli Lilly and Company, 2, Jazz Pharma, 5, Pfizer Inc, 5, Pfizer Inc, 8, UCB, 5, Eli Lilly and Company, 8 ; **S. Alvarez-Horine**, Jazz Pharmaceuticals, Inc., 3, Jazz Pharmaceuticals, Inc., 1 ; **Y. Zheng**, Jazz Pharmaceuticals, 3 ; **D. R. Guinta**, Jazz Pharmaceuticals, Inc., 3, Jazz Pharmaceuticals, Inc., 1 ; **A. J. Holman**, Jazz Pharmaceuticals, 2 ; **T. J. Swick**, Jazz Pharamacuticals, 5, Jazz Pharmacuticals, 2, Jazz Pharmacuticals, 8 .

1411

Patterns of Pain-Related Pharmacotherapy and Healthcare Resource Use Among Elderly Patients with Fibromyalgia Prescribed Pregabalin. Mugdha Gore[1], Alesia Sadosky[2], Gergana Zlateva[2] and Daniel Clauw[3], [1]Avalon Health Solutions, Inc., Philadelphia, PA, [2]Pfizer Inc., New York, NY, [3]University of Michigan, Ann Arbor, MI

Purpose: To characterize patterns of pain-related pharmacotherapy and use of healthcare resources among elderly patients (≥65 years old) with fibromyalgia (FM) prescribed pregabalin in clinical practice.

Method: Using the PharMetrics® Patient-Centric Database, elderly patients with FM (ICD-9-CM diagnosis code 729.1X) who were newly prescribed pregabalin (n=98; mean age 72.4±6.4 years; 82% female) on or after July 1, 2007 were identified. Patterns of pain-related pharmacotherapy and healthcare resource use and costs (pharmacy, outpatient, inpatient and total) were examined in these patients during the 6-month periods preceding (pre-treatment) and following (follow-up) the date of the first pregabalin prescription.

Results: On average patients received 3.3 (±2.3) pregabalin prescriptions; the average days of therapy were 121 (±88.9) days. Although patients had a high medication burden in both the pre-treatment and follow-up periods, except for the use of SSRIs which decreased significantly from pre-treatment to follow-up (24.5% vs. 19.4%, p=0.0253), there were no statistically significant changes in use of any of the other medications including NSAIDs (36.7% vs. 32.7%), opioids (54.1% vs. 59.2%), tramadol (17.4% vs. 24.5%), muscle relaxants (18.4% vs. 21.4%), tricyclic antidepressants (21.4% vs. 18.4%), SNRIs (10.2% vs. 12.2%), and anticonvulsants (17.4% vs. 21.4%). There were decreases in the number of physician office visits and total outpatient visits (both p-values <0.01) and in the proportions of patients with visits to physical therapists (21.4% vs. 12.2%, p=0.0201); however there were no changes in healthcare costs (pharmacy, outpatient, inpatient or total) from the pre-treatment to the follow-up period.

Conclusion: Elderly patients with FM in this study were characterized by a high medication burden. Although it is not possible to establish cause-effect relationships in claims database studies, it is interesting to note the decreases in outpatient resource use after initiation of treatment with pregabalin and also that the addition of pregabalin was cost-neutral.

Disclosure: M. Gore, Pfizer Inc, 5 ; **A. Sadosky**, Pfizer Inc, 3 ; **G. Zlateva**, Pfizer Inc, 3 ; **D. Clauw**, Cypress Biosciences, Inc., 9, Pfizer Inc, 9, Forest Laboratories, 9, Lilly, 9, UCB, 9, Pierre Fabre, 9 .

1412

Sodium Oxybate Improves Fatigue, Sleep Disturbance, and PGIc in Fibromyalgia – Results From a Phase 3, 14-Week, Controlled Trial. Philip J. Mease[1], Todd J. Swick[2], Sarah Alvarez-Horine[3], Neil Inhaber[3], Diane R. Guinta[3], Andrew J. Holman[4] and Ij Russell[5], [1]Seattle Rheumatology, Seattle, WA, [2]Houston Sleep Center, UT Houston School of Medicine, Houston, TX, [3]Jazz Pharmaceuticals Inc, Palo Alto, CA, [4]Pacific Rheumatology Assoc, Renton, WA, [5]U TX Hlth Sci Ctr, San Antonio, TX

Purpose: In addition to the hallmark symptom of widespread pain, fatigue and disturbed, unrefreshing sleep are frequent complaints in patients with fibromyalgia (FM) and can lead to significant impairment in daytime function. This Phase III, 14-week, double-blind, placebo-controlled trial examined the effects of sodium oxybate (SXB) on FM symptoms, including fatigue, sleep disturbance, and global status as measured by patient global impression of change (PGIc).

Method: Subjects with FM (548 meeting American College of Rheumatology criteria) were randomized to parallel therapy with SXB 4.5g/night (SXB4.5g), SXB 6g/night (SXB6g), and placebo (PBO) in a 1:1:1 ratio. Treatments were administered as two equal, divided doses at bedtime and 2.5-4 h later. The primary outcome measure was the percent of subjects reporting a clinically relevant, ≥30% reduction on the Pain Visual Analog Scale (VAS) from baseline to week 14. Secondary measures included Fatigue VAS, Jenkins Sleep Scale (JSS; a 4-item, self-report questionnaire for sleep disturbance, range 5-20), and PGIc at week 14. Analysis: LOCF.

Results: Significant reductions in mean Fatigue VAS scores were seen in SXB4.5g and SXB6g vs PBO at week 14 (-27.94 and -30.02, respectively, vs -17.57; both p<0.001) and at all weekly time points as early as week 1 (p<0.01 for all). These improvements paralleled improvements in pain ≥30% reduction in Pain VAS at week 14 (both active doses vs PBO, p<0.001). Compared with PBO, treatment with SXB4.5g and SXB6g resulted in significantly greater reductions in mean JSS scores at week 14 (-6.1 and -6.2, respectively, vs -2.9; both p<0.001) and at all other time points beginning at the first measurement, week 4 (p<0.001 for all). In addition, a significantly greater percentage of subjects receiving SXB4.5g or SXB6g reported clinically meaningful improvement in global status, evidenced by PGIc scores of "much better" or "very much better" vs PBO (48.3% and 45.4%, respectively, vs 27.2%; both p<0.001). Strong Pearson correlations for

changes in pain were seen with Fatigue VAS and JSS (0.89 and 0.51, respectively, p<0.001). The most common adverse events (AEs) on SXB treatment with incidences greater than 5% and twice the placebo rate were headache, nausea, dizziness, vomiting, diarrhea, anxiety, and sinusitis. The most commonly reported AE was headache (23.1%, SXB6g).

Conclusion: In addition to its effect on the hallmark symptom of pain, SXB resulted in clinically meaningful improvement in patient global status as well as measures of fatigue and sleep disturbance, two important symptoms commonly seen in FM. Sodium oxybate was well tolerated, safe, and efficacious in this Phase III trial.

Disclosure: P. J. Mease, Jazz, 9, Allergan, 9, Boehringer Ingelheim, 9, Fralex, 9, Wyeth Pharmaceuticals, 9, Eli Lilly, 9, Forest Laboratories, 9, Cypress Biosciences, Inc., 9, Pfizer Inc, 9 ; **T. J. Swick**, Jazz Pharamacuticals, 5, Jazz Pharmacuticals, 2, Jazz Pharmacuticals, 8 ; **S. Alvarez-Horine**, Jazz Pharmaceuticals, Inc., 3, Jazz Pharmaceuticals, Inc., 1 ; **N. Inhaber**, Jazz Pharmaceuticals, 1, Jazz Pharmaceuticals, 3 ; **D. R. Guinta**, Jazz Pharmceuticals, Inc., 3, JazzPharmaceuticals, Inc., 1 ; **A. J. Holman**, Jazz Pharmaceuticals, 2 ; **I. Russell**, UCB, 6, Allergan, 2, Jazz Pharma, 2, Pfizer Inc, 2, Eli Lilly and Company, 2, Jazz Pharma, 5, Pfizer Inc, 5, Pfizer Inc, 8, UCB, 5, Eli Lilly and Company, 8 .

1413

The Effects of Milnacipran On Self-Reported Complaints of Decreased Cognitive Functioning in Fibromyalgia Patients. Alan Manevitz[1], Robert H. Palmer[2], Wei Chen[2] and R. Michael Gendreau[3], [1]Weill Medical College of Cornell University, New York, NY, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego, CA

Purpose: Fibromyalgia (FM) patients report a number of symptoms in addition to chronic widespread pain, including a heterogeneous collection of problems relating to cognitive dysfunction (commonly termed “fibrofog”). Objective measures of cognitive functioning have shown that FM patients show decrements in terms of their attention, susceptibility to distraction, as well as their working and episodic memory (eg, Glass 2008). Irrespective of documented cognitive decrements, many FM patients report experiencing problems with fibrofog. These analyses evaluate the effect of milnacipran on self-reported problems with cognition in patients with FM.

Method: This study was a pooled analysis of data from 3 phase III pivotal studies in FM patients randomized to receive placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=837). All 3 studies had similar design: following a dose escalation phase, patients underwent 12 weeks of stable dose treatment that included 4 study visits (Visits 1 to 4). Data from 12 weeks of the stable dose phases were pooled and analyzed by visit. Self-reported problems with cognition were measured by using the 38-item Multiple Ability Self-report Questionnaire (MASQ) total and subscale scores. Mean changes from baseline at individual study visits and the 3-month endpoint were analyzed by using a mixed model repeated measures (MMRM) approach.

Results: Patients treated with milnacipran 200 mg/day demonstrated significantly greater improvement than placebo-treated patients at all visits in MASQ total scores (P<.01). Improvements from baseline in MASQ Verbal Memory and Attention subscale scores were significantly greater in patients treated with milnacipran 200 mg/day than placebo at all visits (Verbal Memory, P=.02; Attention, P=.002). Significant improvements were observed with milnacipran 100 mg/day over placebo on the MASQ total score from Visit 1 to Visit 3 (P<.05).

Conclusion: Milnacipran 200 mg/day resulted in significant improvements in self-reported measures of cognitive complaints in patients with FM.

Disclosure: A. Manevitz, Forest Laboratories, Inc., 5 ; **R. H. Palmer**, Forest Research Institute, 1, Forest Research Institute, 3 ; **W. Chen**, Forest Research Institute, 3 ; **R. M. Gendreau**, Cypress Bioscience, Inc., 3 .

1414

Long Term Therapeutic Response to Milnacipran Treatment for Fibromyalgia. A European 1-Year Extension Study Following a 3-Month Study. Jaime C. Branco[1], Patrick Cherin[2], Michael Späth[3] and Yves Mainguy[4], [1]Hospital Egas Moniz, Lisbon, Portugal, [2]Hopital Pitié Salpêtrière, Paris, France, [3]Facharzt für Innere Medizin, Grafelfing, Germany, [4]Institut de Recherche Pierre Fabre, Labège, France

Purpose: A dose-blinded, 1-year extension study of milnacipran in the treatment of fibromyalgia (FM) was performed in completers of a 3-month European lead-in phase III study of milnacipran 200 mg/day versus placebo.The objectives were to assess the long-term efficacy and safety of milnacipran 100, 150, and 200 mg/day (BID regimen) used for treating FM.

Methods: 468 FM patients completing the lead-in study were enrolled 1 week later, in the extension study. 198 patients were maintained on milnacipran 200 mg/day and patients receiving placebo in the lead-in study were re-randomised to milnacipran 100 (n=91), 150 (n=92) or 200 mg/day (n=87) for an additional 12 months (including a 4-week dose-escalation period). The efficacy endpoint was a 2-measure composite responder rate (using the lead-in study baseline) requiring a reduction by 30% of the weekly-recall pain score on a paper 100-mm visual analogue scale (VAS) and a much or very much improved scoring of Patient Global Impression of Change (PGIC) .The loss of therapeutic response after 3 months was established if seen at 2 further consecutive visits. Other efficacy assessments consisted of pain, quality of life (QoL), fatigue and sleep scores.

Results: All milnacipran doses showed a long-term beneficial effect with endpoint composite responder rates of 27.5%, 31.5% and 32.2% respectively in the 100 mg/day, 150 mg/day and 200 mg/day groups of re-randomised patients, and 35.9% in the milnacipran 200 mg/day throughout group. The greatest increase in the composite responder rate from extension study baseline occurred with milnacipran 200 mg/day, regardless of the lead-in study treatment. The durability of composite response was also the highest in the 200 mg/day groups with 44.1% (throughout group) and 45.2% (re-randomised group) of early responders maintaining their response throughout the treatment period compared with the lower dose groups: 39% (150 mg/day) and 35.3% (100 mg/day). At endpoint, an improvement from lead-in or extension study baseline was shown in all groups on all measures of pain, QoL-physical, fatigue and sleep measures. These improvements were similar in all groups, except a greater effect with 150 and 200 mg/day on mean changes from lead-in study baseline in weekly-recall pain VAS score (-26.5 to -27.9 mm versus

-20.9 mm with 100 mg/day) and in all fatigue and sleep scores.

Over 1 year, all doses of milnacipran were as well tolerated as in the previous 3-month study. The most common drug-related adverse events were hyperhidrosis (22%) and nausea (20%).

Conclusion: Over 1 year, milnacipran 100, 150 and 200 mg/day exhibited sustained efficacy on the multidimensional symptoms of FM, with a safety profile similar to the lead-in study

Disclosure: J. C. Branco, Pierre Fabre Médicament, 5 ; **P. Cherin**, Pierre Fabre Médicament, 5 ; **M. Späth**, Pierre Fabre Médicament, 5 ; **Y. Mainguy**, Institut de Recherche Pierre Fabre, 3 .

1415

Treatment Response to Pregabalin in Fibromyalgia: Effect of Patient Baseline Characteristics. T. Kevin Murphy[1], Danielle Lauren Petersel[1], Ed Whalen[1], Birol Emir[1] and Alison Gagnon[2], [1]Pfizer Global Research and Development, New York, NY, [2]UBC Scientific Solutions, Southport, CT

Purpose: Pregabalin has been shown to reduce pain associated with fibromyalgia. The objective of this study was to evaluate the effect of age, depression and anxiety symptoms, duration of disease, and pain at baseline on the magnitude of treatment response to pregabalin in patients with fibromyalgia.

Methods: Data from 4 randomized, multicenter, placebo-controlled clinical studies of pregabalin in patients with fibromyalgia were used for the analysis. Approved doses (300 and 450 mg/d) were pooled to enhance the sensitivity of the interaction tests. Pain was assessed on an 11-point numeric rating scale (0 [no pain]; 10 [worst possible pain]). Treatment response was evaluated using pain change at last observation carried forward. A centered covariate interaction model was used to assess the treatment effects, but a non-centered model was used for estimated mean pain changes and least square means across different levels of baseline covariates. The interaction was considered significant if $P<0.10$. The covariates of mean pain score at baseline, Hamilton Anxiety Scale (HADS-A), and Hamilton Depression Scale (HADS-D), age in years, and duration of fibromyalgia in months were used for analysis.

Results: Among fibromyalgia patients at baseline, the median pain score was 7.0 (range, 1–10; n=2060), median HADS-A total score was 9.0 (range, 0–21; n=2048), median HADS-D total score was 8.0 (range, 0–21; n=2048), median age was 49 years (range, 18–82 y; n=2061), and median duration of fibromyalgia was 83 months (range, 2–656 mo; n=2060). A significant effect on pain was observed for pregabalin versus placebo in patients with fibromyalgia ($P<0.0001$). No significant interaction was observed between treatment and anxiety (HADS-A;

interaction test, *P*=0.654), depression (HADS-D; interaction test, *P*=0.689), or duration of fibromyalgia symptoms (interaction test, *P*=0.100). Significant treatment by baseline mean pain (interaction test, *P*=0.037) and treatment by age (interaction test, *P*=0.051) interactions were observed. For these combined studies, the pregabalin versus placebo differences in pain changes were –0.91 (baseline pain=9) and –0.33 (baseline pain=5). For age, the differences were –0.45 for age=40 and –0.94 for age=70. As a sensitivity analysis, we excluded a European study and found the interaction effects greatly diminished.

Conclusion: In patients with fibromyalgia, the treatment response to pregabalin may not depend on anxiety and depression symptoms or duration of fibromyalgia at baseline. The magnitude of response to pregabalin in terms of changes in pain may depend on age and pain levels at baseline in patients with fibromyalgia. The magnitude of these effects can be substantial; however, results are sensitive to which studies are included in the analyses.

Disclosure: T. K. Murphy, Pfizer Inc., 3 ; **D. L. Petersel**, Pfizer Inc, 3 ; **E. Whalen**, Pfizer Inc, 3, Pfizer Inc, 1 ; **B. Emir**, Pfizer Inc, 3 ; **A. Gagnon**, UBC Scientific Solutions, 3 .

1416

Women Are More Susceptible to Increased Symptoms of Pain, Fatigue, Negative Mood, and Cognitive Dysfunction After Exercise and Sleep Restriction. Jennifer M. Glass[1], Jacob N. Ablin[2], Angela K. Lyden[1], Kirsten Ambrose[3], David A. Williams[1], Daniel Clauw[4] and Cathryn Byrne-Dugan[1], [1]U. Michigan, Ann Arbor, MI, [2]Rheumatology Institute, Tel Aviv, Tel Aviv, Israel, [3]Algynomics, Inc, Chapel Hill, NC, [4]University of Michigan, Ann Arbor, MI

Purpose: Chronic pain disorders such as fibromyalgia sometimes follow a stressful event that disrupts normal sleep and exercise, and nearly all chronic pain disorders are more common in women. We hypothesize that good sleep and routine exercise are necessary to avoid somatic symptoms such as pain, fatigue, and cognitive problems, as well as depressed mood, and that different subsets of healthy individuals have variable effects of lack of sleep and exercise. Previously, we reported such increases after sleep and exercise restriction. Here we present our findings on sex differences in the expression of these symptoms.

Method: Eighty-seven (45 male) healthy adults ages 18-41 years were included who ran at least five times per week and slept 7-9 hours per night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. We assessed symptom development in 5 domains: pain (McGill VAS), mood (CES-D, POMS, STPI-anxiety), fatigue (Multiple Fatigue Index), somatic symptoms (Modified Somatic Perceptions Questionnaire) and cognition (Multiple Ability Self-Report Questionnaire) at baseline and between days 7-8 of the deprivation period. For initial analyses, a Total Symptom change variable was calculated. Effects of sex, sleep, and exercise were entered into examined via ANOVA. Subsequently, similar analyses were carried out for each symptom domain.

Results: Significant effects of sleep restriction ($p = .001$) and sex ($p = .007$) were found for the Total Symptom variable. Sleep restriction resulted in more symptoms, and women were more likely to report increased symptoms. Exercise restriction did not affect Total Symptoms. Examining individual symptom domains, sleep restriction significantly increased all symptom domains ($p = .008$). Exercise deprivation significantly increased symptoms of fatigue ($p = .021$). Women reported more symptoms of negative mood ($p = .016$), cognition ($p = .031$), and somatic complaints ($p = .052$). Women reported increased fatigue after either exercise or sleep restriction; men reported increases only in the combined group ($p = .044$). A similar, but marginally significant pattern was observed for negative mood ($p = .090$).

Conclusion: Significant increases in somatic symptoms and mood were observed after a period of relatively mild sleep restriction. Exercise deprivation was not as potent a stressor in this study. There was a high correlation between symptom domains, suggesting that when symptoms increased in one domain, they increased in all domains. Strikingly, women appear much more susceptible than men to experience these increased symptoms, particularly in the domains of mood, cognition and somatic symptoms.

Disclosure: J. M. Glass, Pfizer Inc, 2, Forest Laboratories, 2 ; **J. N. Ablin**, None; **A. K. Lyden**, None; **K. Ambrose**, None; **D. A. Williams**, None; **D. Clauw**, Pfizer Inc, 5, Lilley, 5, Forest Laboratories, 5, Cypress Biosciences, Inc, 5, Wyeth Pharmaceuticals, 5 ; **C. Byrne-Dugan**, None.

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Cognitive Dysfunction in Fibromyalgia Assessed by the Multiple Abilities Self-Report Questionnaire. David A. Williams[1], Jennifer M. Glass[1], Paloma Barjola[2], Lynn Zwinck[1] and Daniel Clauw[3], [1]U. Michigan, Ann Arbor, MI, [2]Rey Juan Carlos University, Madrid, Spain, [3]University of Michigan, Ann Arbor, MI

Purpose: Individuals with fibromyalgia (FM) often report cognitive difficulties (a.k.a., "fibro-fog"). Studying fibro-fog has been difficult due to several factors: (a) incongruence between objective (i.e., neuropsychological) assessment and self-report, and (b) the inconsistent manifestation of cognitive difficulties across individuals with FM. The current study sought to (a) assess multiple cognitive difficulties within individuals, (b) compare cognitive difficulties in FM with healthy controls (HC)'s, and (c) identify clinical correlates for the various types of cognitive problems. To date, fibro-fog has been hypothesized to be associated with a wide variety of clinical problems (e.g. pain, sleep loss, fatigue, mood etc.).

Method: 101 individuals meeting American College of Rheumatology criteria for FM were compared to 63 HC's. All participants completed the Multiple Abilities Self-report Questionnaire (MASQ), a measure of perceived cognitive difficulties with language, Visual-perception, verbal memory, visual-spatial memory, and attention/concentration. Multiple Analysis Of Variance (MANOVA) was used to compare the MASQ scales between FM and HC. The following clinical correlates of fibro-fog were assessed: age, pain severity (Brief Pain Inventory, (BPI)), fatigue (physical and mental scales of the Multidimensional Fatigue Inventory, (MFI)), sleep problems (MOS sleep index 1), stress (Perceived Stress Scale, (PSS)), trait anxiety and depression (State-Trait Personality Inventory, (STPI). For individuals with FM, correlations were obtained for the MASQ scales and each clinical variable. Clinical variables having significant first order correlations with the MASQ scales were then used in stepwise regression models so as to identify significant and unique clinical contributors to each of the MASQ scales.

Results: MANOVA revealed significant differences between FM and HC on all MASQ scales (Wilk's Lambda=.070, $p<.0001$.). Language problems were significantly associated with physical and mental fatigue, stress, and trait depression. The strongest predictor of language problems was mental fatigue accounting for 16% of the variance. Problems with visual perception were only significantly correlated with stress accounting for 8% of the variance. Verbal memory difficulties were associated with mental fatigue, stress, and trait anxiety. Together, mental fatigue and stress accounted for 45% of the variance. Visual-spatial memory was associated with age, trait depression, and stress. Stress accounted for greatest amount of variance (12%). Attention/concentration was associated with physical and mental fatigue and trait depression; all three made unique and significant contributions accounting for 24% of the variance.

Conclusion: The MASQ is an assessment tool that can capture multiple dimensions of fibrofog which appear to be related to differing constellations of underlying clinical factors.

Disclosure: D. A. Williams, NIAMS-NIH, 2, Pfizer Inc, 5, Eli Lilly and Company, 5, Forest Laboratories, 5, Cypress Biosciences, Inc., 5 ; **J. M. Glass**, Pfizer Inc, 2, Forest Laboratories, 2 ; **P. Barjola**, None; **L. Zwinck**, None; **D. Clauw**, Forest Laboratories , 2, Pfizer Inc, 2, Cypress Biosciences Inc, 5, Lilly , 5, Pfizer Inc, 5, Forest Laboratories, 5, UCB, 5, Astra-Zeneca, 5, Pierre-Fabre, 5 .

1418

Improving Internal Locus of Pain Control in Fibromyalgia. David A. Williams[1], Kirsten Ambrose[2], Linda Skalski[3], Jordana Muroff[4], Lynn Zwinck[1] and Daniel Clauw[5], [1]U. Michigan, Ann Arbor, MI, [2]Algynomics, Inc., Chapel Hill, NC, [3]Duke University, Durham, NC, [4]Boston University, Boston, MA, [5]University of Michigan, Ann Arbor, MI

Purpose: Interventions for pain typically target sensory (e.g. nociceptive) or affective aspects of pain with little to no emphasis on altering cognitive aspects of pain. One cognitive factor, "a perceived ability to control pain" holds clinical relevance across many pain conditions. An internal locus of pain control (I-loc) refers to a belief in pain being an experience that can be modified through personal effort. Actual life experiences may support such beliefs (e.g., success in using behavioral coping skills for pain). An external locus of control such as believing that powerful doctors (PD-loc) or chance events (C-loc) control the experience of pain are more common among individuals with pain. For many diseases including chronic pain, possession of a strong (I-loc) is associated with better outcomes. This study sought to improve (I-loc) in a sample of individuals with FM.

Method: 72 females satisfying ACR criteria for FM (mean age=45.5, (SD=9.9)) were randomly assigned to one of three treatment arms: Exercise (exc), Relaxation (rlx), or standard care (std). Manualized exercise or relaxation sessions consisted of 1 face-to-face session with a therapist who followed patients by scheduled telephone contact over 8 weeks. Baseline and 12-week endpoint evaluations included the following: the Beliefs in Pain Control Questionnaire (BPCQ), the Brief Pain Inventory, and the SF-36. Within subject and between group

comparisons were made using ANCOVA with the baseline value of the dependent variable serving as the covariate. Responders to treatment were defined as individuals demonstrating a minimal clinically important difference on I-loc (i.e., improving >=0.5 SD).

Results: While no differences existed between groups at baseline, ANCOVA revealed significant group differences in (I-loc) at post treatment $F_{(2,68)}$=3.14, p<.05. I-loc was significantly more improved for the exercise arm than for std care but not different from the relaxation arm. Responders were identified in each arm at differing rates: std: 17%; exc: 42%; rlx: 33%. In comparisons of responders with non-responders from any treatment, ANCOVAs revealed that even though pain severity was not different, I-loc responders had significant reductions in the number of painful body regions ($F_{(1,69)}$=4.53, p<.05) at post treatment.. Responders also demonstrated significant improvements in physical functional status as assessed by the SF-36 PCS score ($F_{(1,69)}$=6.55, p<.01). Improvement in I-loc was not associated with change on any of the indices of affect.

Conclusion: I-loc, a belief in personal pain control, is modifiable through brief non-pharmacological approaches such as exercise and relaxation. Bolstering the belief in I-loc appears to influence pain by influencing perceptions of illness impact rather than symptom severity in individuals with FM.

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Neurobiological Correlates of Spontaneous Chronic Pain Variability. Richard Harris[1], Daniel Clauw[2], Eric Ichesco[1], Michael Geisser[1] and David A. Williams[1], [1]U. Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI

Purpose: Spontaneous large fluctuations in pain intensity are commonly seen in some individuals with fibromyalgia (FM), whereas others have more stable pain over time (Harris et al. Arthritis and Rheumatism 2005). Variability in chronic pain intensity has features of a trait in that it is fairly stable over long periods. However little is known about either the psychological correlates or the underling neuronal mechanisms of this characteristic. Here we couple functional magnetic resonance imaging (fMRI) and "real-time" assessment of chronic pain in individuals with FM to examine neurobiological factors associated with pain variability.

Methods: 20 individuals with FM who were receiving standard medical care participated in the study. Pain intensity levels were captured in real-time over 60 days by participants using electronic Palm-based diaries. Variability in pain was determined as being the standard deviation of pain entries over time (Pain Variability Index:PVI). Participants also underwent a single fMRI session wherein multiple pressures were applied to the thumbnail bed in pseudo-random order. Images were pre-processed with SPM2 and resulting contrast images ($2kg/cm^2$ pressure vs. no touch) were analyzed. Catastrophising and beliefs in personal pain control were also incorporated as predictors of PVI in a regression model using SPSS v.17.

Results: After controlling for age and pain severity, greater PVI was associated with more catastrophising (beta: 2.28, p=0.04) and lower internal locus of control (beta: -0.41, p=0.057). Higher PVI was also associated with reduced pain activation within the periaqeductal grey (PAG: r=-0.53, p=0.01), amygdala (r=-0.56, p=0.005), dorsal anterior cingulate (r=-0.51, p=0.01), and the primary somatosensory cortex (r=-0.61, p=0.002). Within the PAG region, greater pain evoked neural activity was associated with greater internal locus of control (r=0.34, p=0.03) and lower external locus of control (chance: r=-0.36, p=0.02; powerful doctors: r=-0.39; p=0.01).

Conclusion: These data suggest that individuals with FM who have highly variable pain differ from those who do not in that they have: 1) higher levels of catastrophising and lower internal locus of pain control, and 2) different neuronal activation patterns on fMRI, especially in regions such as the PAG which modulate descending analgesic pathways. Future studies are needed to replicate these findings.

Disclosure: R. Harris, None; **D. Clauw**, Cypress Biosciences, Inc, 5, Forest Laboratories, 5, Lilley, 5, Pfizer Inc, 5, Wyeth Pharmaceuticals, 5 ; **E. Ichesco**, None; **M. Geisser**, None; **D. A. Williams**, NIAMS-NIH, 2 .

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A Randomized, Double-Blind, Placebo-Controlled Trial of Dolasetron, a 5-HT(3) Receptor Antagonist, in Patients with Fibromyalgia. Pascale Vergne-Salle[1], Philippe Bertin[1], Carine Dufauret-Lombard[1], Christine Bonnet[1] and Richard Treves[2], [1]University Hospital, Limoges, France, [2]Chu Dupuytren, Limoges Cedex, France

Purpose: the purpose of the study was to evaluate the efficacy and safety of dolasetron for symptomatic relief of pain associated with fibromyalgia (FM) meeting the American College of Rheumatology criteria.

Method: This prospective, double-blind, placebo-controlled trial randomly assigned 60 patients with FM to receive placebo (n=31) or dolasetron (n=29) at the dose of 12.5 mg/d to intravenous route for 4 days in a intermittent way at month 0 (M0), one month (M1), two months (M2) and three months (M3) with a follow-up until 12 months. The primary outcome variable was the reduction of pain intensity measured by visual analog scale (VAS) between M0 and M3. The secondary outcome variables were reduction of pain intensity between M0 and the follow-up visits at M4, M6 and M12, the patient global impression of change (PGIC), the fibromyalgia impact questionnaire, assessments of quality of life (SF-36), the hospital anxiety and depression scale, the manual tender point count and the functional symptoms associated with FM.

Results: reduction in pain intensity at M3 was significantly greater in dolasetron-treated patients (p=0.04, -21.3 on a 0-100 scale) compared with placebo-treated patients (-5.9). More patients in the dolasetron group had ≥30% and ≥50% improvement in pain (42.5% and 28% respectively in the dolasetron group versus 25% and 16% in the placebo group). The pain intensity measured by VAS more decreased in the follow-up visits M4, M6 and M12 in the dolasetron group compared with placebo. The PGIC was significantly greater in the dolasetron group at M3 (p=0.02). The other secondary outcomes failed to reach statistical significance. The most common adverse events were constipation, nausea, dizziness and headache without difference between the two groups.

Conclusion: dolasetron to intermittent intravenous route was safe and efficacious for the treatment of pain associated with FM at three months with persistence of beneficial effects after treatment.

Disclosure: P. Vergne-Salle, None; **P. Bertin**, None; **C. Dufauret-Lombard**, None; **C. Bonnet**, None; **R. Treves**, None.

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A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Milnacipran 100 Mg/Day for the Management of Fibromyalgia: Results From a 2-Week Discontinuation Phase. Philippe A. Saxe[1], Lesley M. Arnold[2], R. Michael Gendreau[3], Allan Spera[4], Judy Gendreau[3] and Yong Wang[4], [1]Arthritis Associates of S. Florida, Delray Beach, FL, [2]University of Cincinnati, Cincinnati, OH, [3]Cypress Bioscience, Inc., San Diego, CA, [4]Forest Research Institute, Jersey City, NJ

Purpose: A randomized controlled trial in fibromyalgia (FM) patients demonstrated significant improvements with milnacipran (MLN) 100 mg/d vs placebo (PBO) in measures of pain, global status, and physical function. Patients completing 12 weeks of stable-dose treatment were rerandomized to a 2-week, double-blind, placebo-controlled discontinuation phase to assess durability of efficacy and possible withdrawal effects of MLN 100 mg/d.

Method: Patients completing the stable-dose phase were assigned to a discontinuation phase where patients initially assigned to PBO remained on PBO (n=359) and patients treated with MLN 100 mg/d were rerandomized and switched to PBO (n=178) or maintained on MLN 100 mg/d (n=178). Efficacy assessments included changes during the discontinuation phase in 24-h recall pain (e-diary), Patient Global Impression of Change (PGIC), SF-36 Physical Component Summary (PCS), Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Multidimensional Fatigue Inventory (MFI), and Multiple Ability Self-Report Questionnaire (MASQ).

Results: 715 patients entered the discontinuation phase; 5 patients discontinued before the final study visit (2 PBO; 2 MLN rerandomized to PBO; 1 continuing on MLN). Two weeks after removal of active drug, the proportion of 3-measure composite responders (≥30% improvement in 24-h recall pain; PGIC ≤2; and ≥6-point improvement in SF-36 PCS) was significantly reduced in patients rerandomized from MLN to PBO compared with patients maintained on MLN ($P<.05$). Patients rerandomized from MLN to PBO had an 11.4% increase in 24-h recall pain scores during the discontinuation phase compared with 5.2% and 3.2% increases for patients remaining on MLN or PBO, respectively. Patients rerandomized to PBO also had at least a 2-fold worse change in BPI average pain, PGIC, FIQ, SF-36 PCS, MFI, and MASQ scores than patients remaining on PBO or MLN. In patients discontinuing MLN and rerandomized to PBO, supine systolic blood pressure returned to prestudy baseline values, diastolic blood pressure returned to within 1 mm Hg, and pulse returned to within 4 bpm; values for patients continuing with MLN treatment remained unchanged. Incidences of newly-emergent adverse events (NEAE) were lower in patients discontinuing MLN (16.3%) than in patients remaining on MLN (18.0%) or PBO (19.2%). On abrupt discontinuation of MLN, no NEAE occurred in ≥2% of patients.

Conclusion: Patients discontinuing milnacipran experienced a loss of therapeutic effect in multiple efficacy parameters, including the proportion of 3-measure composite responders compared with patients maintained on milnacipran. Abrupt withdrawal of milnacipran did not appear to result in new safety concerns in this study.

Disclosure: P. A. Saxe, Forest Laboratories, 2 ; **L. M. Arnold**, Eli Lilly and Company, 2, Pfizer, Inc, 2, Cypress Biosciences, 2, Wyeth Pharmaceuticals, 2, Sanofi-aventis, 2, Boehringer Ingelheim, 2, Allergan, 2, Forest, 2, Eli Lilly and Company, 5, Pfizer, Inc, 5, Cypress Biosciences, 5, Wyeth Pharmaceuticals, 5, Sanofi-aventis, 5, Boehringer Ingelheim, 5, Sepracor, 5, Forest, 5, Allergan, 5, Vivus Inc, 5, Organon, 5, Takeda, 5, UCB, 5, Theravance, 5, Eli Lilly and Company, 8, Pfizer, Inc, 8, Forest, 8 ; **R. M. Gendreau**, Cypress Bioscience, Inc., 3 ; **A. Spera**, Forest Research Institute, 3 ; **J. Gendreau**, Cypress Bioscience, Inc., 3 ; **Y. Wang**, Forest Research Institute, 3 .

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Milnacipran's Effect On Body Weight by Baseline BMI: Results Across 3 Randomized, Double-Blind, Placebo-Controlled Fibromyalgia Trials. Lesley M. Arnold[1], Robert H. Palmer[2], Michael R. Hufford[3] and Wei Chen[2], [1]University of Cincinnati, Cincinnati, OH, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego

Purpose: Fibromyalgia (FM) is a chronic disorder characterized by widespread pain and other symptoms which impair physical function and adversely impact quality of life. Obesity is a common comorbid condition in FM. Weight gain in overweight or obese patient populations can exacerbate negative health effects and adversely affect patients' willingness to continue therapy. Using data from 3 randomized, double-blind, placebo (PBO)-controlled trials, this analysis evaluated the effects of milnacipran (MLN), an FDA-approved medication, on body weight in FM patients stratified by baseline body mass index (BMI).

Method: Baseline BMI and between-group comparisons of 3-month weight change data were analyzed individually from 3 FM studies (Study 1, N=888; Study 2, N=1196; Study 3, N=1025). In Studies 1 and 2, patients were randomized to PBO, MLN 100 mg/d, or MLN 200 mg/d; in Study 3, patients were randomized to PBO or MLN 100 mg/d. Least squares (LS) mean changes in weight (observed cases) were analyzed over 3 months. LS mean weight change at 3 months was also analyzed after pooling the 3 studies and stratifying weight change by baseline BMI subpopulations (ie, underweight to normal weight [BMI<25], overweight [25≤BMI<30], and obese [BMI≥30]).

Results: In all 3 studies, FM patients' mean baseline BMI exceeded the threshold for obesity (baseline BMI: 30.5, Study 1; 30.6, Study 2; 30.9, Study 3). MLN treatment was associated with statistically significant LS mean weight loss relative to PBO at 3 months in all 3 studies (Study 1: +0.9 lb, PBO; -2.4 lb, MLN 100; -2.2 lb, MLN 200; both doses vs PBO, $P<.001$; Study 2: -0.6 lb, PBO; -2.3 lb, MLN 100; -1.8 lb, MLN 200; both doses vs PBO, $P<.05$; Study 3: -0.5 lb, PBO; -2.3 lb, MLN 100; $P<.001$ vs PBO). In each study, nausea rates were consistently lower in MLN-treated patients who lost weight compared with those who did not lose weight, although differences were not significant (all studies, $P>.09$). In the pooled analysis at 3 months, MLN-treated patients who were in the overweight or obese BMI categories at baseline lost statistically significant amounts of weight compared with PBO (Overweight: -0.1 lb, PBO; -2.5 lb, MLN 100; -1.8 lb, MLN 200; both doses, $P<.05$ vs PBO; Obese: -0.5 lb, PBO; -3.0 lb, MLN 100; -2.4 lb, MLN 200; both doses, $P<.01$ vs PBO). MLN-treated patients who were in the underweight to normal BMI categories did not lose a statistically significant amount of weight compared with PBO (0.0 lb, PBO; -0.8 lb, MLN 100; -1.0 lb, MLN 200; both doses, $P>.12$ vs PBO).

Conclusion: Baseline BMI exceeded the threshold for obesity in each of the 3 studies. MLN treatment for 3 months resulted in weight loss across all 3 studies, with MLN-treated patients who were overweight or obese at baseline showing modest, but statistically significant amounts of weight loss compared with patients on PBO.

Disclosure: L. M. Arnold, Eli Lilly and Company, 2, Pfizer, Inc, 2, Cypress Biosciences, 2, Wyeth Pharmaceuticals, 2, Sanofi-aventis, 2, Boehringer Ingelheim, 2, Allergan, 2, Forest, 2, Eli Lilly and Company, 5, Pfizer, Inc, 5, Cypress Biosciences, 5, Wyeth Pharmaceuticals, 5, Sanofi-aventis, 5, Boehringer Ingelheim, 5, Sepracor, 5, Forest, 5, Allergan, 5, Vivus Inc, 5, Organon, 5, Takeda, 5, UCB, 5, Theravance, 5, Eli Lilly and Company, 8, Pfizer, Inc, 8, Forest, 8 ; **R. H. Palmer**, Forest Research Institute, 1, Forest Research Institute, 3 ; **M. R. Hufford**, Cypress Bioscience, Inc., 3 ; **W. Chen**, Forest Research Institute, 3 .

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Milnacipran Improves Fatigue in Fibromyalgia: Pooled Analyses From 3 Randomized, Placebo-Controlled Clinical Trials. Philip Mease[1], Robert H. Palmer[2], Yong Wang[2] and R. Michael Gendreau[3], [1]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego, CA

Purpose: Fibromyalgia (FM) is a chronic disorder that includes symptoms beyond widespread musculoskeletal pain. Fatigue is one of the most common complaints in FM patients. Milnacipran, a dual reuptake inhibitor of serotonin and norepinephrine, is approved by the US FDA for the management of FM. This current analysis further evaluates the effect of milnacipran on fatigue in patients with FM.

Method: Fatigue data were pooled from 3 phase III pivotal studies (3 to 6 months) in FM patients randomized to receive placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=837). All studies had similar design: following a dose escalation phase, patients underwent 12 weeks of stable dose treatment that included 4 study visits (Visits 1 to 4). Data from 12 weeks of the stable dose phases were pooled and analyzed by visit. Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI) total score and subscale scores (general fatigue, mental fatigue, physical fatigue, reduced activity, reduced motivation) and the Fibromyalgia Impact Questionnaire (FIQ) fatigue items (6 and 7). Mean changes from baseline were analyzed by using a mixed model repeated measures (MMRM) approach.

Results: Patients treated with milnacipran 100 and 200 mg/day demonstrated significant improvements at all visits in MFI total score compared with placebo ($P<.01$). Additionally, all MFI subscale scores were significantly improved at endpoint (Visit 4) in patients treated with milnacipran 200 mg/day compared with placebo (general fatigue, $P=.005$; mental fatigue, $P<.001$; physical fatigue, $P=.001$; reduced activity, $P=.03$; reduced motivation, $P<.001$). Milnacipran 100 mg/day was associated with significant improvements vs placebo in general fatigue ($P=.04$), physical fatigue ($P=.002$), and reduced motivation ($P=.002$) scores. FIQ fatigue scores (items 6 and 7) were significantly improved at all visits in patients treated with milnacipran 100 mg/day compared with placebo ($P<.01$); milnacipran 200 mg/day significantly improved FIQ fatigue over placebo (item 6) at Visit 2 and Visit 4 ($P<.01$), and FIQ fatigue (item 7) from Visit 2 through Visit 4 ($P<.01$).

Conclusion: Among patients with FM, 3 months of milnacipran treatment resulted in significant improvements relative to placebo in multiple dimensions of their fatigue. Milnacipran may be effective in treating symptoms of fibromyalgia beyond pain, including fatigue.

Disclosure: P. Mease, Cypress Bioscience, Inc., 5, Forest Laboratories, Inc., 8, Forest Laboratories, Inc., 5, Abbott Laboratories, 5, Abbott Laboratories, 2, Abbott Laboratories, 8 ; **R. H. Palmer**, Forest Research Institute, 1, Forest Research Institute, 3 ; **Y. Wang**, Forest Research Institute, 3 ; **R. M. Gendreau**, Cypress Bioscience, Inc., 3 .

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Towards Development of Fibromyalgia Responder Index: Identifying Responders Using Patients Global Assessment. Lesley M. Arnold[1], Gergana Zlateva[2], Alesia Sadosky[2], Birol Emir[2], Ed Whalen[2] and Gayle Scott[3], [1]University of Cincinnati, Cincinnati, OH, [2]Pfizer Inc, New York, NY, [3]UBC Scientific Solutions, Southport, CT

Purpose: The Fibromyalgia (FM) Working Group of OMERACT is developing an FM responder index. Towards that objective, we conducted an analysis of pooled data from pregabalin fibromyalgia trials to determine what FM domains drive patients' perception of improvement.

Method: Data from 3 double-blind, placebo-controlled trials of pregabalin monotherapy (13-14 weeks) in FM conducted in North and South America, Europe, and Asia were pooled for this analysis. We analyzed changes in independent variables, including the Short-Form 36 (SF-36) health survey scale, Medical Outcomes Study (MOS) sleep scale, sleep quality score from the daily sleep diary, pain score from the daily pain diary, Fibromyalgia Impact Questionnaire (FIQ), and Multidimensional Assessment of Fatigue (MAF) as predictors of outcome on the dependent variable PGIC. Correlation analysis was used to assess the strength and direction of relationship between the independent variables and PGIC. Cluster analysis was conducted using Hoeffding's D similarity measure to identify dependencies or clustering among variables. Finally, a LASSO (least absolute shrinkage and selection operator) technique was used to derive rank order among the independent variables most highly related to changes in PGIC.

Results: 1664 patients were included in the intention-to-treat population of these pooled analyses. More than 90% were white women, and mean age was 49 years. In each of the treatment groups (pregabalin 300 mg/day, 450 mg/day, and placebo), improvement in PGIC at endpoint showed highest correlation with improvement in pain, fatigue, sleep, and work and physical function ($0.4< r <0.6$). Mood, emotional and social functioning generally had smaller correlation with PGIC ($0.3 < r <0.4$). When pooled, the combined treatment groups showed similarly moderate correlation between PGIC and pain, fatigue, sleep, and function. Cluster analysis identified 5 main clusters of symptoms in FM patients at endpoint: emotion, function, tiredness, pain, and sleep. LASSO analysis ranked 3 pain variables (pain diary score, FIQ Pain, and SF-36 Bodily Pain) as the most important variables explaining variability in PGIC, followed by MAF Global Fatigue

Index, MOS Sleep Disturbance, FIQ Feel Good, SF-36 Vitality and FIQ Rested domains. LASSO results were similar by dose and across the pooled analysis.

Conclusion: Patients' response to FM treatment was driven by improvement of multiple domains. Pain, fatigue and sleep associate most strongly with improvement in PGIC. Physical and work-related function also correlate with patients overall assessment of improvement. These domains and their respective outcome measures can be used in the development of a responder index.

Disclosure: L. M. Arnold, Cypress Biosciences, 2, Wyeth Pharmaceuticals, 2, Allergan, 5, Forest, 5, Sepracor, 5, Boehringer Ingelheim, 5, Sanofi-aventis, 5, Wyeth Pharmaceuticals, 5, Cypress Biosciences, 5, Pfizer, Inc, 5, Eli Lilly and Company, 5, Forest, 2, Allergan, 2, Boehringer Ingelheim, 2, Sanofi-aventis, 2, Pfizer, Inc, 2, Eli Lilly and Company, 2, Vivus Inc, 5, Organon, 5, Takeda, 5, UCB, 5, Theravance, 5, Eli Lilly and Company, 8, Pfizer, Inc, 8, Forest, 8 ; **G. Zlateva**, Pfizer Inc, 3 ; **A. Sadosky**, Pfizer Inc, 3 ; **B. Emir**, Pfizer Inc, 3 ; **E. Whalen**, Pfizer Inc, 3 ; **G. Scott**, UBC Scientific Solutions, 3 .

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Assessment of Pregabalin Utilization in Patients with Fibromyalgia at a University-Based Rheumatology Clinic. William Lai[1], Sean Barnes[1], Yingxue Zhang[1], Kevin V. Hackshaw[1] and Thomas Wolfe[2], [1]The Ohio State University Medical Center, Columbus, OH, [2]Pfizer US Medical Affairs and The Ohio State University College of Pharmacy, OH

Purpose: To describe the utilization of Pregabalin in the management of FMS and whether the use of FMS approved medications improves patient care as assessed by changes in concomitant medications, opiate use, and fibromyalgia impact scores.

Method: A retrospective cohort study of adult patients with a diagnosis of FMS on one or more encounters and treated with Pregabalin. Changes in concomitant medications over time were assessed from the Pregabalin Index Date to present or to the discontinuation of Pregabalin. Changes in concomitant medications were assessed for patients with more than 1 office visit (89).

Results: A total of 185 patient records (89% female) were reviewed. Most patients had diagnosis of FMS for more than one year (78%). Pregabalin mean daily dose increased from baseline to follow-up, 82.3 ± 61.3 vs. 197 ± 141 ($p<0.001$), with 68% of patients experiencing a dose increase. A majority of patients were taking multiple medications (74%). Utilization of concomitant therapies increased from baseline to follow-up (0.94 ± 0.97 vs 1.64 ± 1.04, respectively, $p<0.001$). Current therapy in all patients consisted of 2.4 ± 1.2 (0-5) medications per patient. Concomitant medication changes occurred in 95 patients (51.4%). Of the patients currently on Pregabalin, fewer patients had discontinuation of concomitant medications vs. initiation of new medications (48 vs. 76, respectively). SNRI and muscle relaxants were the most common medications added. Concomitant opiate use was more common in patients on high dose (≥ 300 mg/day) Pregabalin compared to low dose (47.8% vs. 21.2%, $p=0.014$). The number of concomitant medications was numerically higher in the high dose Pregabalin group (1.96 vs. 1.53, $p=0.093$). Patients initiated on Pregabalin at the Rheumatology clinic were more likely to be on low dose compared to patients on Pregabalin prior to clinic visit (72.9% vs. 41.7%, $p=0.003$). The number of concomitant medications (1.66 vs 1.92, $p=0.267$) and concomitant opiate use (27.1% vs 25%, $p=0.833$) was not different between those initiated on Pregabalin at the Rheumatology clinic compared to those on prior. Ninety-seven patients (83%) had documentation of symptom relief with Pregabalin. FIQ information was available in 85 patients (physical function score 1.29 ± 0.76 (0-3)). For patients with multiple FIQ scores, mean scores were not statistically different between time periods (68 ± 15.6 vs. 64.6 ± 10.6 $p=0.198$).

Conclusion: Concomitant medication use was common with increased utilization overall from baseline despite taking pregabalin. Discontinuation of concomitant medication is not common. The total number of concomitant medications was not significantly different regardless of where pregabalin was initiated. Relatively low doses of Pregabalin were used. Concomitant use of SNRI and muscle relaxants appeared to increase the most. Patients not on pregabalin when they visited Rheumatology clinic were likely to be on an opiate already.

Disclosure: W. Lai, None; **S. Barnes**, None; **Y. Zhang**, None; **K. V. Hackshaw**, Lilly, 8, Forest Laboratories, 8, Pfizer Inc, 8, Novartis Pharmaceutical Corporation, 8 ; **T. Wolfe**, Pfizer Inc, 3, Pfizer Inc, 1 .

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Pregabalin-Long-Term Follow-up in Treatment of Fibromyalgia Syndrome (FMS). Micha Abeles[1] and Aryeh M. Abeles[2], [1]University Connecticut Health Ctr, Farmington, CT, [2]University of Connecticut Health Center, Farmington, CT

Purpose: Long-term studies regarding the usefulness of pharmacological therapy in FMS are lacking. We compared pregabalin to conventional treatment in fibromyalgia patients and found that although response rate was somewhat better with pregabalin, when accounting for patient dropout due to side effects, there appeared to be no advantage to pregabalin over a 12 week period. The purpose of this study was to monitor the responders to treatment in the original study over an extended period of time to evaluate for persistence of response.

Method: Randomization in the original cohort was done by placing every other patient who presented with FMS on pregabalin or routine therapy (defined as medication chosen by treating physician preference). Evaluation was done utilizing the Fibromyalgia Impact Questionnaire (FIQ), Hospital Anxiety and Depression Scale, and visual analogue scale (VAS). The primary endpoint was a comparison of the FIQ global score and the VAS. In the long- term follow-up, the FIQ global score and VAS were the primary endpoints. Response was considered to be clinically meaningful if there was a 30% or greater improvement from baseline. This was a prospective non-blinded and unfunded study.

Results: 18 of the original 68 pregabalin responders patients and 16 of 66 of the original comparator responders patients entered the long term observational phase of the study. All patients were female. Other characteristics of the subgroup included average age of 53 in the pregabalin and 51 in the comparator groups, average fibromyalgia duration of 6 and 7.2 years duration respectively and predominance of white (80%) and the remainder Hispanic (20%). Therapy in the comparator group included duloxetene (3), gabapentin (2), tricyclics (nortriptyline or amitriptyline), (5) tramadol (5), and hydrocodone (2). At the end of one year, 16 of 18 pregabalin but only 6 of 16 comparator patients were still on the same medication.

Conclusion: Although pregabalin appeared to be equivalent to standard of care therapy in a short-term observational study, when responders are followed for a prolonged period of greater than one year, pregabalin's efficacy appears to persist whereas there is loss of efficacy in standard treatment therapy. Despite this is being an observational uncontrolled and unblinded study, our observations suggest that pregabalin may offer an advantage over standard therapy when prolonged use is indicated; further study comparing the long-term efficacy of individual drugs (or combinations of drugs) in a blinded fashion is warranted.

Disclosure: M. Abeles, None; **A. M. Abeles**, None.

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Inadequately Managed Depression in Fibromyalgia Drives Referral to Specialists. MA Fitzcharles[1], Marta Ceko[2], Ann Gamsa[2], Mark A. Ware[2] and Yoram Shir[2], [1]MGH, Montreal, QC, [2]McGill University, Montreal, QC

Purpose: Although the cornerstone for diagnosis of FM is pain, mood disorders are reported to occur frequently in these patients. Recognition and appropriate management of mood may impact on suffering and quality of life in FM patients, and may be a factor contributing to poor response to standard treatments. We have evaluated the frequency of depression and treatments thereof, in FM patients newly referred to a tertiary care centre.

Method: Demographic, disease related variables and measurements for functional status (fibromyalgia impact questionnaire, FIQ), mood (arthritis impact measurement scale, AIMS), and pain catastrophizing (pain catastrophizing scale, PCS) were recorded for FM patients newly referred. Depression was defined on the AIMS depression scale as 4 or greater. Using this cut-off, comparisons were made between depressed (D) and non-depressed (ND) subjects with respect to selected variables. Univariate comparisons of continuous variables were made using Student's t-tests, and for categorical variables using chi-squared tests. Logistic regression was used to model the association between age, gender, pain duration, catastrophizing, disability and pain intensity.

Results: 137 consecutively attending FM patients referred to a multidisciplinary clinic were evaluated. Depression (D) vs. no depression (ND) was present in 110 (80%) vs 27 (20%). No differences between groups (D vs ND) were noted for age (48 vs. 46 yrs), employment status (32 vs.42%), disability status (35 vs 37%) or pain intensity VAS (6.6 vs 6.0). D vs ND had longer disease duration, 12.2 vs 7.3 years (P=0.03), scored higher for pain catastrophizing, 30 vs. 21.5% (P=0.002), anxiety 6.6. vs 5.5% (P=0.05), and total FIQ 65 vs. 57% (P=0.048). After adjusting for other covariates, duration of pain was the only factor associated with depression in multivariate analysis, adjusted OR 1.11, 95% CI 1.03, 1.19). Use of any antidepressant for D vs ND was 48% vs. 63% (p=0.2), with tricyclic antidepressant (TCA) use in 19 vs 44% (P=0.006) and non-TCA use in 39% vs. 22% (P=0.024).

Conclusion: Important depression was identified in 80% of FM patients. Of greater concern was the lack of any treatment to address depression in more than 50% of depressed patients, with the remainder treated for depression but mostly with inadequate effect. TCA use in the ND reflects treatment patterns for FM pain and sleep, rather than use for mood effect. Prolonged pain duration was independently associated with depression. Poorly controlled depression may be an important factor driving referral of FM patients for specialist consultation.

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Sex Differences in Predictors of Increased Symptoms After Exercise and Sleep Restriction. Jennifer M. Glass[1], Jacob N. Ablin[2], Angela Lyden[1], Kirsten Ambrose[3], David A. Williams[1], Richard Gracely[4] and Daniel Clauw[5], [1]U. Michigan, Ann Arbor, MI, [2]Rheumatology Institute, Tel Aviv, Tel Aviv, Israel, [3]Algynomics, Inc, Chapel Hill, NC, [4]U. North Carolina, Chapel Hill, NC, [5]University of Michigan, Ann Arbor, MI

Purpose: Chronic pain disorders such as fibromyalgia are often precipitated by an event that prevents normal sleep and exercise. We hypothesize that sleep restriction and exercise deprivation can act as stressors, and that neurobiological factors can predict if an otherwise healthy individuals will respond to such stress with an acute increase in symptoms of pain, fatigue, cognitive problems and negative mood. Previously, we reported preliminary results where heart rate variability (HRV) measures were significantly correlated with symptoms after sleep and exercise restriction. Here, we report our findings on sex differences in the relationship between HRV and increased symptoms.

Method: Eighty-seven (45 male) healthy adults ages 18-41 years were included who ran at least five times per week and slept 7-9 hours per night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. At baseline, HRV was measured via 24 hour holter readings. We assessed symptom development in 5 domains: pain (McGill VAS), mood (CES-D, POMS, STPI-anxiety), fatigue (Multiple Fatigue Index), somatic symptoms (Modified Somatic Perceptions Questionnaire) and cognition (Multiple Ability Self-Report Questionnaire) at baseline and between days 7-8 of the deprivation period. For initial analyses, a Total Symptom change variable was calculated. Pearson product moment correlations were calculated to assess the association between baseline HRV and changes in symptoms.

Results: Sleep restriction led to increased symptoms across domains (reported separately). However, not all subjects reported increased symptoms. Total Symptom change ranged from -12 to +11. Women were more likely (65%) to report increased symptoms than men (40%). Among men, strong negative correlations were observed between Total Symptom Change and 24-hr total power (TP; $r = -.579$) as well as 24-hr ultra low frequency (ULF; $r = -.628$). Among women, there were no significant correlations between Total Symptom Change and any HRV measure (r values $< -.180$). Among men, all 5 individual symptom domains were significantly correlated with both TP and ULF (r values between -.388 and -.599).

Conclusion: We have shown that sleep restriction leads to increased symptoms of pain, fatigue, mood, cognition, and somatic complaints, especially among women. Somewhat paradoxically, neurobiological measures of autonomic nervous system function were only correlated with increased symptoms in men. However, our results are consistent with previous research on heart rate reactivity and variability to painful stimuli that suggest dramatically different sympathetic regulation of pain in men and women.

Disclosure: J. M. Glass, Pfizer Inc, 2, Forest Laboratories, 2 ; **J. N. Ablin**, None; **A. Lyden**, None; **K. Ambrose**, None; **D. A. Williams**, Cypress Biosciences, Inc., 5, Pfizer Inc, 5, Forest Laboratories, 5, Eli Lilly and Company, 5 ; **R. Gracely**, None; **D. Clauw**, Cypress Bioscience, 5, Forest Laboratories, 5, Lilly, 5, Pfizer, Inc., 5, Wyeth Pharmaceuticals, 5 .

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The Effects of Nabilone On Insomnia in Fibromyalgia: Results of a Randomized Controlled Trial. MA Fitzcharles[1], Yoram Shir[2], Lawrence Joseph[3] and Mark A. Ware[2], [1]MGH, Montreal, QC, [2]McGill University, Montreal, QC, [3]MUHC, Montreal, QC

Purpose: Fibromyalgia (FM) is a chronic pain syndrome with generalized tender points. Insomnia affects over 75% of patients with FM, and tricyclic antidepressants are the mainstay of treatment. Cannabis has been used by patients with FM to help sleep. We evaluated nabilone, a synthetic cannabinoid, for insomnia in FM.

Method: We conducted a randomized double-blind active control equivalency crossover trial to compare nabilone (0.5-1.0mg qHS) to amitriptyline (10-20mg qHS) in FM patients with chronic insomnia. Subjects received each drug for two weeks with a two-week washout. The primary outcome was sleep quality using the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ); secondary outcomes included pain, mood, quality of life and adverse events (AEs).

Results: Thirty-one subjects were enrolled and 29 completed the trial (26 female, mean age 49.5y). While sleep was improved by both nabilone and amitriptyline, nabilone was superior to amitriptyline (ISI difference=3.2, 95%CI 1.2-5.3). Nabilone was marginally better on the restfulness LSEQ sleep quality scale (difference=0.5 (0.0-1.0) but not on wakefulness (difference=0.3 (-0.2, 0.8)). Adverse events were all mild-moderate and were more frequent with nabilone (102) than amitriptyline (53). Most common AEs for nabilone were dizziness (10), nausea (9) and dry mouth (7).

Conclusion: Nabilone is effective in improving sleep in patients with FM and is well tolerated. Low dose nabilone given once daily at night may be considered as an alternative to amitriptyline. Longer trials are needed to determine the duration of effect and to characterize long-term safety.

Disclosure: M. Fitzcharles, Pfizer Inc, 8, Boehringer Ingelheim, 8, Valeant, 8 ; **Y. Shir**, None; **L. Joseph**, None; **M. A. Ware**, Pfizer Inc, 8, Valeant, 8 .

1430

Pregabalin Efficacy in Treatment of Refractory Pain in Fibromyalgia. Brett R. Stacey[1], T. Kevin Murphy[2], Birol Emir[2], Suzanne Giordano[2] and Vardit Dror[3], [1]Oregon Health & Science University, Portland, OR, [2]Pfizer Global Research and Development, New York, NY, [3]UBC Scientific Solutions, Southport, CT

Purpose: Fibromyalgia (FM) is a chronic musculoskeletal pain disorder. Pain associated with FM can be intractable and may not respond to commonly-used treatments, such as tricyclic antidepressants (TCAs) and opioids. This is an analysis of a long-term, open-label study evaluating pregabalin response in the subset of patients with FM whose pain had been judged refractory to other treatments.

Method: Patients had previously participated in a double-blind, placebo-controlled, randomized trial of pregabalin[1] and had moderate to severe pain despite treatment with gabapentin, a TCA, and a third medication (e.g., other anticonvulsants, opioid, SSRI, tramadol). Patients were allowed to take other pain medications during the study. Flexible-dose pregabalin 150-600 mg/day was added for 3-month treatment cycles, each followed by 3- to 28-day pregabalin "drug holiday" that lasted until a relapse occurred. Once the patient completed 4 relapse visits, no additional drug holidays were required. Pain intensity was measured using the visual analogue scale of the Short-Form McGill Pain Questionnaire (SF-MPQ pain VAS) completed at baseline, the end of each 3-month treatment period and at the relapse visit.

Results: In total, 25 patients (76% female; mean age, 64 y; mean duration of FMS, 11 y) were included in this analysis. At baseline, 88% were receiving ≥1 pain medication (24% TCAs, 28% gabapentin, 72% others) other than pregabalin. Pregabalin 150-600 mg/day was associated with clinically meaningful and sustained pain reduction during each treatment cycle. Mean SF-MPQ pain VAS level decreased from 73.6 mm at baseline to 51.7 mm across the treatment cycles (P<0.005). All patients met relapse criteria during each of the drug holidays. The median duration (range from 2-4 days) and mean pain scores (71-79 mm) across the 4 pregabalin drug holidays indicated pain quickly returned to baseline levels, but was reduced again when pregabalin was reinstated. At baseline, 71% of patients experienced severe pain ≥70 mm on SF-MPQ pain VAS compared to only 38% of patients after 15 months of treatment.

Conclusion: These results suggest that pregabalin may be beneficial in patients with fibromyalgia who have had an unsatisfactory response to treatment with other medications.

References:

1. Crofford LJ et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005 Apr;52(4):1264-73.

Disclosure: B. R. Stacey, Pfizer Inc, 2 ; **T. K. Murphy**, Pfizer Inc, 3 ; **B. Emir**, Pfizer Inc, 3 ; **S. Giordano**, Pfizer Inc, 3 ; **V. Dror**, UBC Scientific Solutions, 3 .

ACR/ARHP Poster Session C

Genetics, Etiology, and Pathogenesis of Spondyloarthritis

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1431

DKK-1 Levels Are Decreased in Patients with Ankylosing Spondylitis and not Influenced by Anti-TNF Therapy. Seong-Ryul Kwon[1], Won Park[1], Mie-Jin Lim[1], Chang-Hee Suh[2], Hyoun-Ah Kim[2], Yeon-Sik Hong[3] and Bo-Young Yoon[4], [1]IN-HA University Hospital, Choong-Gu Incheon, South Korea, [2]Ajou University School of Med, Suwon, South Korea, [3]Incheon St. Mary's Hospital, Incheon, South Korea, [4]Inje Iniversity Ilsan Paik Hospital, Goyang, South Korea

Background: Signaling through the Wnt pathway leads to new bone formation, whilst DKK-1 is a Wnt antagonist. Preliminary data in patients with ankylosing spondylitis (AS) shows that levels of DKK-1 are low in patients with AS than in healthy controls suggesting that this might account for the propensity to new bone formation in AS.

Purpose: 1. To compare DKK-1 levels and other bone biomarkers in patients with AS compared to controls. 2. To examine the effects of anti-tumor necrosis factor (TNF) therapy for 3 months on DKK-1 levels and other bone biomarkers in AS.

Method: We studied 56 patients with AS (47 males, age 35.1 ± 9.6 years, disease duration 6.9 ± 4.8 years, BASDAI 7.7 ± 1.9, CRP 1.7 ± 2.0 mg/dl, mean ± SD), and 40 controls (31 male, age 43.5 ± 8.6 years). We also assessed DKK-1 in 49 AS patients and 39 healthy controls at baseline and 3 months after initiating anti-TNF therapy in AS patients (etanercept = 6, infliximab = 22, adalimumab = 21). DKK-1 was assayed by ELISA. We evaluated biomarkers of bone formation (osteocalcin, osteoprotegerin) and resorption (C-terminal telopeptide of type I collagen, CTX-1) by ELISA.

Results: Serum DKK-1 (12320.6 ± 6136.8 pg/ml) levels were significantly lower in AS than in controls (20811.1 ± 6136.8 pg/ml) ($p<0.0001$). Serum osteocalcin (14.5 ± 5.6 ng/ml), osteoprotegerin (3.5 ± 1.1 pmol/L) levels were significantly higher in AS than in controls (osteocalcin 8.9 ± 3.4 ng/ml, osteoprotegerin 2.03 ± 1.04 pmol/L, $p<0.0001$ respectively). Mean serum CTX-1 levels were not significantly different between AS and controls. Serum DKK-1 and CTX-1 levels were not changed 3 months after treatment with anti-TNF. But, serum osteocalcin levels increased significantly after treatment with anti-TNF for 3 months (14.5 ± 5.6 to 17.6 ± 4.5 ng/ml, $p<0.0001$). Serum osteoprotegerin levels decreased significantly 3 months after treatment with anti-TNF (3.5 ± 1.1 to 3.1 ± 1.2 pmol/L, $p=0.025$).

Conclusion: In accordance with a previous report, we show decreased DKK-1 in AS than healthy controls. DKK-1 levels are not influenced by anti-TNF therapy for 3 months. Our data does support a role for DKK-1 and Wnt interaction in the pathogenesis of new bone formation in AS.

Disclosure: S. R. Kwon, None; **W. Park**, None; **M. J. Lim**, None; **C. H. Suh**, None; **H. A. Kim**, None; **Y. S. Hong**, None; **B. Y. Yoon**, None.

1432

Heightened HLA Molecules Upregulation and Decreased CD4+ T Cells Stimulation in Monocytes-Derived Dendritic Cells (DCs) From Ankylosing Spondylitis (AS) Patients. Nelly Bonilla[1], Maxime Breban[2] and Gilles Chiocchia[1], [1]Institut Cochin, INSERM U567, Paris, France, [2]Ambroise Paré Hospital, Boulogne-Billancourt, France

Purpose: In lines of rats transgenic for HLA-B27 and human β2-microglobulin, the spontaneous development of an inflammatory disease resembling human AS correlates with high levels of B27 expression. Furthermore, DCs from B27 transgenic rats have a diminished ability to interact with CD4+ T cells and to stimulate a proliferative response, as compared to control DCs. Such results raised the hypothesis that an altered interaction between antigen-presenting cells and CD4+ T lymphocytes might be critical in AS pathogenesis. Thus, it is of first importance to analyse the expression of HLA molecules and to evaluate the function of DCs in AS patients.

Objectives: To study HLA and accessory molecules expression in PBMC and in monocytes-derived DCs, and to examine the functional capacity of monocytes-derived DCs from AS patients and normal controls.

Method: Twenty two AS patients (21 HLA-B27+; mean age 44±12 years; BASDAI = 38±22; BASFI = 19±21) and 17 healthy controls were studied. We used multi-colours FACS analysis of PBMC and *in vitro* monocyte-derived DCs to compare the expression levels of HLA-DR, pan-class I, B27, and a full set of cell markers: CD4, CD8, CD11c, CD14, CD40, CD80, CD83, CD86, and CD123. *In vitro* derived DCs were obtained from purified CD14+ cells cultured for 7 days in the presence of IL-4 and GM-CSF. The cells were activated with LPS and FACS analysis was performed. The capacity of the DCs to stimulate proliferative responses of highly purified CD4+ T cells was evaluated.

Results: Expression levels of total HLA class I molecules were significantly higher on circulating lymphocytes and monocytes in patients than in controls ($p=0.01$, and $p=0.0004$, respectively). The levels of HLA-DR molecules were also significantly increased on lymphocytes from AS patients ($p<0.03$). None of the other markers showed a differential level of expression on PBMCs. The expression level of HLA-DR molecules was higher in AS patients than in controls on monocyte-derived DCs obtained after 7 days of culture. LPS-activation of DCs induced both class I and DR molecules up-regulation and exacerbated the differential level of DR expression between patients and controls ($p=0.009$). Finally, monocytes-derived DCs from AS patients exhibited a weaker stimulatory efficiency of CD4+ T cells than DCs from controls both on autologous and heterologous conditions.

Conclusion: Our findings reveal consistent differences in HLA molecules expression on PBMCs and DCs from AS patients, as compared to healthy controls. We bring evidence that DC from SpA patients have a lower ability to stimulate CD4+ T cell proliferation, as compared to control DC. We propose that this hypostimulatory ability of DCs could play an important role in initiating/maintaining the systemic inflammatory response in AS.

Disclosure: N. Bonilla, None; **M. Breban**, None; **G. Chiocchia**, None.

1433

High-Resolution Association Mapping in the MHC Region Identifies Multiple Independent Loci for Psoriatic Arthritis. Proton Rahman[1], Nicole M. Roslin[2], Fawnda Pellett[3], Andrew Paterson[2], Joseph Beyene[4], Mathieu Lemire[5], Lynette Peddle[1], Angela Pope[1], Mohammed Uddin[1], Celia Greenwood[2] and Dafna D. Gladman[3], [1]Memorial University of Newfoundland, St Johns, NF, [2]The Hospital for Sick Children Research Institute, The Center for Applied Genomics, Toronto, ON, [3]Toronto Western Hospital, Toronto, ON, [4]The Hospital for Sick Children Resarch Institute, Child Health Evaluative Sciences, Toronto, ON, [5]Ontario Institute for Cancer Research, Toronto, ON

Purpose: The greatest genetic effect in PsA resides within the MHC region with various HLA alleles demonstrating consistent association. However, HLA alleles by themselves cannot account for the entire genetic contribution of this region. Thus we set out to identify SNPs independent of known HLA alleles within the MHC region that are associated with PsA using a high density SNP map.

Method: In total, 422 PsA cases and 487 controls were analyzed. PsA patients and controls were from two well established PsA cohorts (Toronto and Newfoundland). All PsA patients satisfied the CASPAR criteria. The MHC region was genotyped with 2269 SNPs in a 5 Mb region on chromosome 6 using Illumina's MHC Panel Set. HLA-B, HLA-Cw, and HLA-DRB1 were genotyped to two digit accuracy using sequence -specific oligonucleotide probes (SSOP) or PCR sequence-specific primers (PCR-SSP). A stratified case/control analysis was conducted on each SNP separately to test for allelic association with PsA. Due to extensive LD across the MHC region, a conditioning analysis approach was performed. This approach tests whether a SNP is associated with PsA conditional on known HLA risk alleles: B13, B27, B38, B39, B57, Cw6, and DR7. This analysis was performed using the program UNPHASED 3.1.3.

Results: The high density SNP analysis revealed 17 SNPs from 13 regions that were associated with PsA (p-values $< 10^{-5}$). Conditional tests were performed to find additional risk factors which are not confounded by the background HLA haplotypes. Five SNPs were significant at $< 10^{-4}$, with SNP rs1150735 demonstrating the strongest association. Haplotype analysis was then performed. OR of haplotypes that included SNP rs1150735 and any non-risk allele at all three HLA loci was 2.19, 95% CI: 1.43-3.36, $p=0.00052$. SNP rs1150735 resides 1.5 kb upstream from ring finger protein 39 (RNF39). In humans, SNPs in RFN39 have been associated with disease progression in GWAS in AIDS defined by CD4+ T cell depletion (Fellay J et al. Science, Aug 2007).

Conclusion: Fine mapping of the MHC identified SNP rs 1150735 which resides 1.5 kb upstream RFN39. This SNP association is independent of known HLA alleles.

Disclosure: P. Rahman, None; **N. M. Roslin**, None; **F. Pellett**, None; **A. Paterson**, None; **J. Beyene**, None; **M. Lemire**, None; **L. Peddle**, None; **A. Pope**, None; **M. Uddin**, None; **C. Greenwood**, None; **D. D. Gladman**, None.

1434

The Voltage-Gated Potassium Channel Kv1.3 in Psoriasis and Psoriatic Arthritis: A Therapeutic Target for T Cell-Mediated Autoimmune Diseases. Siba P. Raychaudhuri[1], Smriti K. Raychaudhuri[2] and Heike Wulff[3], [1]UC Davis/ VA Sacramento, Davis, CA, [2]VA Sacramento Medical Center, Davis, CA, [3]University of California, Davis, Davis, CA

Purpose: Engagement of the T cell receptor triggers a Ca^{2+}-influx through voltage-independent Ca^{2+} channels, which results in the increase in cytosolic Ca^{2+} concentration necessary for the translocation of NFAT to the nucleus and the initiation of new transcription ultimately resulting in cytokine secretion and T cell proliferation. However, this crucial Ca^{2+}-influx is only possible if the T cell can keep its membrane potential negative by a counterbalancing K^+ efflux through Kv1.3 and/or KCa3.1. Both channels are therefore regarded as attractive new targets for immunotherapy: KCa3.1 for acute immune reactions mediated by naïve T cells and Kv1.3 for chronic immune reactions carried by memory T cells. Here we investigated the functional significance of Kv1.3 in psoriatic disease and rheumatoid arthritis.

Method: Using a combination of immunohistochemistry, flow cytometry and electrophysiology we have studied skin tissue, synovial tissue, lymphomononuclear cells (LMNC) from blood and synovial fluid from patients with psoriasis, psoriatic arthritis and rheumatoid arthritis. In these autoimmune conditions we have identified $Kv1.3^{high}$ T cells and determined their phenotypic and functional features in.

Results: We have found that psoriasis plaques (n=12) and psoriatic arthritis synovial tissues (n=6) are enriched with $Kv1.3^+$ T cells and that $Kv1.3^+$ T cells are retained in the psoriasis SCID mouse model. The numbers of $Kv1.3^+$ T cells in per square millimeter were significantly increased in psoriatic dermis (92 ±18) compared to the non-lesional psoriatic skin (6±4) ($P<0.01$). $Kv1.3^+$ infiltrating T cells in per square millimeter were also significantly higher in psoriatic arthritis synovial tissue (86 ±24) compared to synovial tissues of OA (4 ±2) patients. We have observed a significant enrichment of $Kv1.3^+$ T cells within the synovial fluid of psoriatic arthritis and rheumatoid arthritis as compared to the peripheral blood of PsA/RA patients and synovial fluid of OA patients. We have further seen that the majority of these $Kv1.3^+$ T cells were $CCR7^-$ effector memory T cells.

Conclusion: These results suggest that effector T lymphocytes at the site of inflammation in autoimmune inflammatory diseases like in psoriasis, PsA and RA are of activated memory phenotype and have marked expression of Kv1.3. To demonstrate the functional dependence of "psoriasis" T cells on Kv1.3 and to develop a novel therapeutic approach for T cell-mediated autoimmune diseases we are investigating the therapeutic efficacy of a selective Kv1.3 blocker (PAP-1) in the SCID mouse model of psoriasis. The availability of highly specific Kv1.3 inhibitors and the critical patho-physiologic role of the channel in effector memory T cells make Kv1.3 an important therapeutic target in autoimmune diseases.

Disclosure: S. P. Raychaudhuri, None; **S. K. Raychaudhuri**, None; **H. Wulff**, None.

1435

Nerve Growth Factor in Psoriatic Arthritis: A New Dimension in the Pathogenesis and a Novel Target Molecule for Therapy. Siba P. Raychaudhuri[1] and Smriti K. Raychaudhuri[2], [1]UC Davis/ VA Sacramento, Davis, CA, [2]VA Sacramento Medical Center, Davis, CA

Purpose: The effect of NGF/ NGF-R in inflammatory and rheumatologic diseases is a novel and an active research field. Major evidences for a role of NGF and its receptor system [NGF-R] in inflammatory disease have come from studies on psoriasis. Here we are reporting the role of NGF and its receptor system in inflammatory arthritis such as in psoriatic and rheumatoid arthritis

Method: We examined, blood, synovial fluid (SF) and synovial tissues from psoriatic arthritis (PsA, n=12), Rheumatoid (RA, n=15). Osteiarthritis (OA=10) was used as control. We have identified levels of NGF in SF and determined the functional significance of NGF/NGF-R on proliferation of fibroblast like synovial cells (FLS) and activation of T cells.

Results: Total NGF level was highest in the PsA group (365.5 pg/ml ±85.2 [mean±SD]). In RA group level of NGF was 120 pg/ml ± 35, whereas in OA patients level of NGF was 35 pg/ml ± 6. PsA derived FLS expressed significantly higher levels of TrkA and produced increased amount of NGF compared to FLS from healthy subjects, RA and OA. Effect of NGF (100ng/ml) on proliferation was determined in FLS derived from PsA (n=4), OA (n=4) and RA (n=4) synovial tissues. Third passage FLS (5000 cells/200ul DMEM complete medium)

in 96 well plates were cultured for 5 days. NGF demonstrated marked mitogenic effect on FLS derived from PsA compared to RA and OA. We have observed that synovial fluid of PsA has significantly higher percentage of activated CD3+T cells expressing TrkA (18±6.2). In RA synovial fluid TrkA+CD3+ T cells were also high (4.5±1.3) whereas OA synovial fluid did not show any detectable TrkA+CD3+ T cells. Further we have demonstrated that NGF activates T lymphocytes and influences the expressions of Th-1 type cytokines/chemokines. This is a plaussible mechanism of the neuroimmunologic interactions of NGF in inflammatory responses

Conclusion: These observations indicate Nerve Growth Factor (NGF) and its receptor system play a critical role in the pathogenesis of psoriatic arthritis by regulating the local pathologic events such as proliferation of target tissues (FLS) and activation of T lymphocytes. A new discipline is emerging in clinical pharmacology focusing on the development of drugs targeting the neuropeptides, NGF, and TrkA. Regulatory role of NGF in inflammatory and proliferative cascades of psoriatic arthritis opens new vistas to develop NGF/NGF-R targeted therapies.

Disclosure: S. P. Raychaudhuri, None; **S. K. Raychaudhuri**, None.

1436

HLA-B27 Expression Affects RANKL and TNF-α Induced Osteoclast Development in Transgenic Rats. Gerlinde Layh-Schmitt[1], Shuzhen Bai[2] and Robert A. Colbert[1], [1]NIAMS, NIH, Bethesda, MD, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Purpose: Susceptibility to spondyloarthritides is strongly linked to HLA-B27. The pathogenesis of these diseases involves inflammation mediated in part by TNF-α, as well as an imbalance in bone formation. The discovery that HLA-B27 misfolding can generate ER stress and activate the unfolded protein response (UPR), suggests that it may have additional immunobiologic effects in cells not principally involved in antigen presentation. Therefore, we examined whether HLA-B27 expression has an effect on osteoclast differentiation in a rat model of spondyloarthritis.

Methods: Bone marrow cells were isolated from HLA-B27 transgenic (B27 Tg) (prior to the development of inflammatory disease) and wild type (WT) rats and cultured with M-CSF (20 ng/ml) for 2 days to obtain CD11b+ myeloid cells/osteoclast precursors. Adherent and non-adherent cells (> 90% CD11b+) were then separated and treated with M-CSF and either RANKL (100 ng/ml) or TNF-α (30 ng/ml) for 5 days to promote osteoclast differentiation. Osteoclast formation was quantified by counting multi-nucleated (>3 nuclei) cells and measuring TRAP (tartrate resistant acid phosphatase) activity. HLA-B27 expression was visualized by immunoblotting.

Results: In the population derived from the non-adherent cells, HLA-B27 expression results in a 2-3-fold inhibition of osteoclast formation as measured by cell number or TRAP staining, with either RANKL or TNF-α stimulation ($p<0.05$). However, in the adherent cell population, HLA-B27 expression leads to a slight (~1.5-fold) increase in osteoclast numbers and TRAP activity when treated with RANKL or TNF-α ($p<0.05$). In fact, only HLA-B27 expressing populations formed mature osteoclasts (>3 nuclei) in response to TNF-α. HLA-B27 upregulation and accumulation of misfolded heavy chains was documented in mature osteoclasts.

Conclusion: Our results indicate that HLA-B27 expression in transgenic rats can lead to differences in osteoclast formation in response to RANKL and TNF-α, with the effect dependent upon the precursor cell population. These results are of interest given that bone loss and bone formation occur simultaneously in spondyloarthritis. The mechanisms involved in differential osteoclast development, and whether HLA-B27 misfolding plays a role, are currently being investigated.

Disclosure: G. Layh-Schmitt, None; **S. Bai**, None; **R. A. Colbert**, None.

1437

Association of BEND2 with Ankylosing Spondylitis. Mohammed Uddin[1], Proton Rahman[1], Walter P. Maksymowych[2], Dafna Gladman[3], Angela Pope[1] and Robert D. Inman[4], [1]Memorial University of Newfoundland, St Johns, NF, [2]University of Alberta, Edmonton, AB, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]Toronto Western Hospital, Toronto, ON

Purpose: Ankylosing Spondylitis (AS) is a complex rheumatic disease with a clear genetic predisposition. Pleiotropic genes have been associated with AS including IL-23R and IL-1. As a result we examined the genetic association of 13 nonsynonymous SNPs (nsSNPS) in AS that were identified after a pooled analysis from GWAS of related autoimmune diseases.

Method: In order to generate candidate markers, 1,428 nsSNPs that were common to 5 autoimmune diseases (ankylosing spondylitis, rheumatoid arthritis, type 1 diabetes, autoimmune thyroid disease, and multiple sclerosis) that underwent GWAS by the Welcome Trust Case Control Consortium (WTCCC) were selected. The genotypes were retrieved from the European Genome-Phenome Archive. A pooled analysis involving 6812 UK patients with autoimmune disease and 2952 UK controls was performed. 26 nsSNPs showed a significance of $p < 10^{-3}$, of which 13 nsSNPs were prioritized for genotyping a cohort of Canadian AS patients. 889 AS cases of Caucasian European ancestry from Canada and 987 controls were genotyped. The patients came from 2 well established AS cohorts: 510 AS cases 502 controls from Alberta and 379 cases and 485 controls from Toronto. The genotyping was done using the Sequenom platform. The Cochran-Amirtage test for trend was performed using the program PLINK.

Results: All samples satisfied the Hardy-Weinberg equilibrium and all SNPs had at least a 92% call rate. In the combined analysis of the Canadian samples nsSNP rs17274127 located on exon 4 of BEN containing domain 2 (BEND2) gene on chromosome Xp22.13 and rs1063588 is located on exon 3 of GCS1 gene at chromosome 2p13.1 achieved statistical significance. For nsSNP rs17274127 of the BEND2 gene the minor allele frequency for the combined population in the cases was 0.170 and in controls was 0.118 (OR 1.56 (1.14-2.04, p=0.0038). BEND2 is a novel domain in chromatin and DNA viral proteins and mediates protein-DNA and protein-protein interactions during chromatin organization and transcription. For nsSNP rs1063588 of GCS1 gene, the MAF for allele A was 0.183 in the AS cases and 0.153 in the controls (OR 1.24 (1.04-1.48, p=0.016). GCS1 encodes a GTPase activating protein (GAP) for ADP ribosylation factors that regulate the formation of coated vesicles in intracellular trafficking.

Population	Gene	rsSNP	Minor Allele	MAF Case	MAF Control	p-value
Combined	BEND2	17274127	C	0.170	0.118	0.0038
Toronto	BEND2	17274127	C	0.200	0.122	0.0077
Alberta	BEND2	17274127	C	0.152	0.115	0.1168

Conclusion: A nsSNP within gene BEND2 appears to be associated with AS in the Canadian cohort. Further replication studies are warranted to replicate these findings.

Disclosure: M. Uddin, None; **P. Rahman**, None; **W. P. Maksymowych**, None; **D. Gladman**, None; **A. Pope**, None; **R. D. Inman**, None.

1438

Microarray Analyses of Peripheral Blood Cells Identifies Gene Expression Profile That Differentiates Psoriatic Arthritis (PsA) Form Psoriasis and Controls. D. Gladman, Remy Pollock, Carl Virtanen, Fawnda Pellett, Sutharshini Shanmugarajah, Cheryl Rosen and Vinod Chandran, University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Peripheral blood gene expression profiles may help distinguish PsA from psoriasis alone. Our purpose was to identify genes that are differentially expressed in the peripheral blood cells of patients with PsA by comparing the expression profiles of patients with PsA, patients with psoriasis alone, and healthy controls.

Methods: 20 patients with PsA and 20 patients with psoriasis without arthritis were recruited for the study from university hospital-based PsA and psoriasis clinics, respectively. 20 healthy controls were recruited from hospital personnel. Psoriasis in all patients was confirmed by a dermatologist. All patients with PsA satisfied CASPAR classification criteria. Patients with psoriasis alone were evaluated by a rheumatologist and PsA was excluded. All subject groups were matched for age and sex. Patients with PsA and psoriasis were matched for psoriasis duration. None were treated with biologic agents. Peripheral blood was collected at the time of assessment in PAXgene tubes for RNA extraction and stored at -80°C. Total RNA was extracted using PAXgene Blood RNA Kit and RNA quantified. cDNA/cRNA synthesis and labeling were performed and cRNA was hybridized to a 2-colour Agilent 44K Whole Human Genome Oligo Microarray. Appropriate quality control measures were undertaken. Gene expression values (intensities) for each gene were obtained. The expression values of the

differentially expressed genes were log transformed, and compared between groups (Psoriatic disease vs. controls, PsA vs. psoriasis and PsA vs. psoriasis vs. controls using t-test or one-way ANOVA) and genes with >1 fold change and $p<0.05$ corrected for multiple testing (false discovery rate) were used in unsupervised hierarchical clustering to generate heat maps for each comparison. Gene ontologies were examined to determine type of genes over or under represented.

Results: Patients with PsA (10 male, mean age 48.1 years, disease duration 15.5 years, psoriasis duration, 23.2 years) had an actively inflamed joint count of 10.8, swollen joint count of 5.4 and PASI score 5. Patients with psoriasis (mean age 44 years, psoriasis duration 19.8 years) had PASI score of 5.4, and controls had a mean age of 43.5 years. Between the 3 groups there were 1547 differentially expressed genes. 112 genes were differentially expressed between psoriatic disease and controls, and 711 between PsA and psoriasis alone. Between Psoriatic disease and controls, 35 (31%) genes were downregulated, and 77 (69%) were upregulated. Genes downregulated included MPL, MYST3, CREBBP, EP300 and NRLP2; CROP was upregulated. Between PsA and psoriasis 495 genes (70%) were downregulated and 216 (30%) were upregulated. Genes upregulated included CLEC4d, CLEC2b, CSTA, LY96 and P2RY5.

Conclusion: Results indicate that genes of inflammation pathways, innate immunity and epidermal development are differentially expressed in the peripheral blood cells of patients with psoriasis and PsA.

Disclosure: D. Gladman, None; **R. Pollock**, None; **C. Virtanen**, None; **F. Pellett**, None; **S. Shanmugarajah**, None; **C. Rosen**, None; **V. Chandran**, None.

1439

Interferon-γ Production Is Impaired in Patients with Ankylosing Spondylitis. Dorothea Zauner, Eva-Maria Kober, Winfried Graninger and Josef Hermann, Medizinische Universitätsklinik, Graz, Austria

Purpose: In patients with ankylosing spondylitis (AS) impaired IFNγ production has been reported in stimulated peripheral blood mononuclear cells (PBMCs) using flow cytometry and ELISA techniques. We used ELISpot assays to detect cytokines produced spontaneously ex vivo in AS patients. This highly sensitive method allows for the assessment of the number of cytokine producing cells and the amount of cytokine produced per cell.

Method: Blood samples were obtained from 16 patients with AS according to the modified New York criteria (12 male, 4 female; median age 41 years (range 30-66)), median disease duration 9.5 years (range 2-41) and 24 healthy controls (10 male, 14 female; median age 38.5 (range 23-75)). Median BASDAI was 3.2 (range 0.1-7.1), median CRP was 3.6 mg/l (range 1.0-14.8)) and median ESR was 14 mm/h (range 4-63). None of the patients were on corticosteroid or TNF-blocker therapy. PBMCs were isolated from freshly drawn blood samples immediately after acquisition, plated on 96-well microtiter plates pre-coated with IL-17- or IFNγ-antibodies, and incubated overnight at 37°C without prior antigen stimulation. Detection antibodies were added and spot colour reactions developed according to the manufacturer's protocol (ELISpot Kits by R&D Systems, Minneapolis). Microtiter plates were scanned and spots were analyzed for the production of IL-17 and IFNγ using the ImmunoSpot® Image Analyzer (Cellular Technology, Cleveland OH) and ImmunoSpot® Software. Spot sizes were compared between groups using Student's t-test and spot numbers were compared using the non-parametric Wilcoxon rank sum test.

Results: Unstimulated PBMCs of patients with AS produced significantly smaller IFNγ spots compared to healthy controls (mean(SD) spot sizes 6.8(0.5) μm^2 vs. 8.8(0.4) μm^2; $p=0.003$), whereas IFNγ spot numbers did not differ significantly between groups (mean(SD) 76.5(54.2) spots per 10^6 cells vs. 65.2(55.1) spots per 10^6 cells). In addition, we found no significant differences between patients and healthy controls concerning IL-17 spot numbers (mean (SD) 24.7(23.6) spots per 10^6 cells vs. 26.5(26.6) spots per 10^6 cells, respectively) and IL-17 spot sizes (mean(SD) 12.5(3.3) μm^2 vs. 12.3(3.0) μm^2, respectively). IL-17 and IFNγ spot numbers and sizes did not correlate with disease activity measured either by the BASDAI or by serum CRP/ESR levels.

Conclusion: Our data suggest that in patients with AS in vivo IFNγ production of peripheral blood mononuclear cells might be decreased, whereas IL-17 production and frequencies of IL-17 producing T-cells seem to be unaltered.

Disclosure: D. Zauner, None; **E. M. Kober**, None; **W. Graninger**, None; **J. Hermann**, None.

1440

Is Bone Formation Observed in Patients with Ankylosing Spondylitis Related to Clinical Signs and Symptoms? A Subanalysis of ATLAS. Désirée M.F.M. van der Heijde[1], Paul Emery[2], Kaushik Patra[3], Jesse Hall[3] and Frederic Lavie[4], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Leeds Teaching Hospital, Leeds, United Kingdom, [3]Abbott Laboratories, Abbott Park, IL, [4]Abbott Laboratories, Rungis, France

Purpose: In all clinical trials conducted with TNF antagonists in patients with ankylosing spondylitis (AS), patients experienced radiographic progression characterized by bone formation as assessed by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at a similar rate and frequency as patients from a historical cohort of AS patients without treatment with TNF antagonists.[1–3] We determined whether there is a link between the level of signs and symptoms in the patients during follow-up visits and the radiographic outcome.

Methods: ATLAS was a Phase III, randomized, placebo-controlled trial of adalimumab in patients with AS. After the 24-week double-blind period, placebo-treated patients switched to adalimumab and enter an open-label extension phase and receive up to 4 years of follow up. Patients were categorized by the degree of radiographic progression (□mSASSS >2 over 2 years). Patients were also evaluated by clinical response measures between baseline and Week 208, including the ASAS20, 40, 5/6, and 70 responses, ASAS partial remission (ASAS PR), BASDAI, ASDAS, ASQOL, and CRP concentrations. All data are observed, and the baseline value for each measure was the last observation before the first dose of adalimumab.

Results: Of the 307 patients analyzed from the ATLAS trial, 257 had no progression in mSASSS (no progression, NP) at 2 years, and 50 had a □mSASSS >2 at 2 years (progression, P). Clinical responses and disease activity levels were similar between the 2 groups at baseline and at each time point for all assessed criteria. ASAS20, ASAS PR, BASDAI, ASQOL, and CRP concentrations observed from baseline to Week 208 are presented in the table.

Clinical Responses and Disease Activity During Up to 4 Years of Adalimumab Treatment

	ASAS20, % Responders		**ASAS PR, % Yes**		**BASDAI, Mean (SD)**		**ASQOL, Mean (SD)**		**CRP, Mean mg/dL (SD)**	
Week	**NP**	**P**	**NP**	**P**	**NP**	**P**	**NP**	**P**	**NP**	**P**
0	NA	NA	NA	NA	5.9 (2.0)	5.9 (1.9)	9.8 (4.4)	10.7 (4.9)	1.8 (2.3)	2.7 (3.6)
12	60.7	58.0	24.1	24.0	3.3 (2.5)	3.5 (2.5)	6.5 (5.1)	7.6 (5.6)	0.5 (1.1)	0.5 (1.0)
24	71.2	78.0	31.1	20.0	2.8 (2.3)	2.8 (2.3)	5.3 (5.0)	5.7 (5.2)	0.5 (1.1)	0.5 (0.8)
52	75.5	76.0	37.7	34.0	2.6 (2.3)	2.5 (2.2)	5.0 (4.7)	5.8 (5.1)	0.6 (1.5)	0.4 (0.6)
76	75.9	78.0	40.9	38.0	2.4 (2.2)	2.3 (2.1)	4.8 (4.8)	5.4 (4.9)	0.5 (1.0)	0.3 (0.6)
104	75.7	81.6	43.1	34.7	2.3 (2.2)	2.2 (2.1)	4.7 (4.6)	5.3 (5.2)	0.4 (0.7)	0.5 (1.1)
128	78.8	73.3	42.5	37.8	2.3 (2.2)	2.5 (2.4)	4.5 (4.8)	5.1 (5.6)	0.3 (0.6)	0.8 (2.4)
156	75.4	77.3	41.9	43.2	2.4 (3.3)	2.2 (2.2)	4.4 (4.5)	5.4 (5.2)	0.4 (1.0)	0.4 (0.6)
180	79.4	81.8	41.7	38.6	2.1 (1.9)	2.3 (1.9)	4.2 (4.6)	4.8 (4.6)	0.4 (0.7)	0.3 (0.4)
208	81.6	82.1	43.4	43.6	2.1 (2.0)	2.3 (2.2)	4.2 (4.2)	5.5 (5.5)	0.4 (1.2)	0.5 (1.3)

NA=not applicable; NP=no progression; P=progression.

Conclusion: These results reinforce the hypothesis that mSASSS progression is not related to the level of clinical signs and symptoms. Different mechanisms of action that may explain bone formation in patients with AS should be further explored.

Reference: [1]van der Heijde, et al. *Arthritis Rheum*. 2006;54:2136–46.

Disclosure: D. M. F. M. van der Heijde, Abbott Laboratories, 5, Amgen, 5, Aventis Pharmaceuticals, 5, Bristol Meyers Squibb, 5, Centocor, Inc., 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCB, 5, Wyeth Pharmaceuticals, 5 ; **P. Emery**, Abbott Laboratories, 5, Centocor, Inc., 5, Amgen, 5, Wyeth, 5 ; **K. Patra**, Abbott Laboratories, 3 ; **J. Hall**, Abbott Laboratories, 3 ; **F. Lavie**, Abbott Laboratories, 3 .

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Disturbance in Differentiation Status of B Lymphocytes in Ankylosing Spondylitis. MO Ying-qian, Dai Lie, Zheng Dong-hui, LI Ting and Zhang Bai-yu, 2nd Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Purpose: Disturbance in humoral immunoregulation was found in patients with ankylosing spondylitis (AS), and B lymphocytes could be detected in synovium from inflamed jonits of AS patients. We aimed to detect the differentiation status of B lymphocytes in peripheral blood and synovium from AS patients.

Method: (1) Peripheral blood mononuclear cells from 52 AS patients were measured by flow cytometry with 4-color fluorescence-activated cell sorting analysis, which distinguished three different CD19+ B lymphocyte subpopulations including naïve (CD19+ CD27- CD38- CD69-), activated (CD19+ CD69+) and memory cells (CD19+ CD27+), and CD19- CD38+ plasmocytes. 62 patients with rheumatoid arthritis (RA) and 30 healthy volunteers were chosen as control. (2) Synovium from inflamed knees of 8 AS patients were collected by closed needle synovial biopsies and serial sections were analyzed by HE staining and immunostaining for CD20 (mature B lymphocytes), CD38 (plasmocytes) and CD 79a (all B lymphocytes and plasmocytes)

Results: (1) Ratio of B lymphocytes to total lymphocytes in AS patients was higher than that in healthy volunteers (17.0% vs 11.8%, P=0.007), but there was no significant differences between AS and RA patients. (2) Among CD19+ B lymphocytes, percentage of naïve or activated B cells in AS patients was higher than that in healthy volunteers (naïve B cells: 80.1% vs 72.8%, P=0.01; activated B cells: 18.4% vs 0.62%, P<0.001), and percentage of memory cells in AS was lower than that in RA (19.5% vs 25.4%, P=0.032) and in healthy volunteers (19.5% vs 27.6%, P=0.003). (3) Percentage and count of activated B cells in AS patients with peripheral arthritis were higher than in those without peripheral arthritis (P<0.001). (4)Percentage and count of naïve or activated B cells in AS patients with extra-articular involvement like iritis were higher than in those without extra-articular involvement (P=0.045, 0.031, P<0.001, P<0.001). (5) The counts of CD20+, CD38+ and CD79a+ cells in AS synovium were lower than that in RA synovium (seen in Table 1).

Conclusion: Our results show disturbance in differentiation status of B lymphocytes in AS patients with elevation of activated and naïve cells and reduction of memory cells, especially in patients with peripheral arthritis or extra-articular involvement. Less synovial B lymphocytes in AS might indicate different pathogenesis of B lymphocytes from RA.

Table 1 B lymphocytes and plasmocytes in synovium from AS, RA and orthopedic arthropathies ($\chi \pm s$, /mm^2)

Group	N	CD20	CD38	CD79a
AS	8	148.8±39.2 #	96.6±27.67 #	280±41.0 #
RA	48	420.5±76.1	415.5±96.8	975.3±131.0
orthopedic arthropathies	15	133.5±42.6	84.54±11.8	242.1±68.3

#: Compared with RA, P<0.001

Disclosure: M. Ying-qian, None; **D. Lie**, None; **Z. Dong-hui**, None; **L. Ting**, None; **Z. Bai-yu**, None.

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ZSTK474, a Phosphatidylinositol 3-Kinase Inhibitor, Ameliorates Ankylosing Enthesitis in DBA/1 Mice. Shigeyuki Mori[1], Fumitaka Kamachi[1], Asako Sasaki[1], Kazuhiko Haruta[1] and Shigeto Kobayashi[2], [1]Central Research Laboratory of Zenyaku Kogyo Co., Ltd., Tokyo, Japan, [2]Juntendo University Koshigaya Hospital, Saitama, Japan

Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disorder that affects the axial skeleton, sacroiliac joints, entheses and peripheral joints, resulting in new bone formation and fusion of the joints. Nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) are often used to treat AS, but there remain unsolved problems such as adverse events or limited effects on the symptoms of AS. However, it was demonstrated that PI3-kinase signaling cascade was crucial for bone formation by osteoblasts. Moreover, we previously reported that ZSTK474, an orally active PI3K inhibitor suppressed the proliferation and activation of lymphocytes. These reports led us to hypothesize that ZSTK474 might have a therapeutic potential for AS. In this study, we attempted to evaluate the efficacy of ZSTK474 on spontaneous ankylosing enthesitis in DBA/1 mice, a model of AS.

Method: First, 26 week-old male DBA/1 mice were divided into two groups according to the presence (semi-therapeutic group) or absence (prophylactic group) of arthritis. Then the animals were orally administered ZSTK474 (50 or 100 mg/kg/day) once a day for 4-5 weeks. Each hind paw was scored every day for clinical signs of arthritis as follow: 0, no symptom; 0.5, instep swelling; 1, redness and swelling in one toe; 2, redness and swelling in more than one toe; 3, toe stiffness; 4, deformity or ankle involvement. After the dosing period, bone formation markers (osteocalcin, alkaline phosphatase) in serum were assessed. Histologically, frozen sections of calcaneus bones in the hind paws were stained with toluidine blue.

Results: Prophylactic treatment with ZSTK474 significantly reduced the mean clinical score and incidence (% score ≥2) of arthritis compared with those in vehicle-treated controls on Day 34 (50 mg/kg [$p<0.05$] and 100 mg/kg [$p<0.01$]). Semi-therapeutic treatment with ZSTK474 also inhibited the mean clinical score and incidence on Day 27 (50 mg/kg [$p<0.001$] and 100 mg/kg [$p<0.001$]). Histological examination revealed that increased bone formation, which was observed in the calcaneal epiphysis from vehicle-treated mice, was decreased in ZSTK474-treated mice (50 mg/kg and 100 mg/kg). Furthermore, ZSTK474 reduced the levels of osteocalcin and alkaline phosphatase in serum.

Conclusion: ZSTK474 ameliorates ankylosing enthesitis in DBA/1 mice by suppressing osteogenesis, suggesting that ZSTK474 is promising candidates for treatment of AS.

Disclosure: S. Mori, Zenyaku Kogyo Co., Ltd, 3 ; **F. Kamachi**, Zenyaku Kogyo Co., Ltd, 3 ; **A. Sasaki**, Zenyaku Kogyo Co., Ltd, 3 ; **K. Haruta**, Zenyaku Kogyo Co., Ltd, 3 ; **S. Kobayashi**, None.

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Peripheral and Axial New Bone Formation Is Different According to Gender in Ankylosing Spondylitis. Sibel Zehra Aydin, Gokhan Keser, Vedat Inal, Veli Yazisiz, Omer Karadag, Merih Birlik, Pamir Atagunduz, Eren Erken, Haner Direskeneli and Salih Pay, Turkish Ultrasonography Study Group, Istanbul, Turkey

Purpose: To investigate the prevalence of Achilles enthesophytes in ankylosing spondylitis (AS) patients according to gender and to explore the relationship between new bone formation of the spine and presence or severity of peripheral enthesophytes, using US and conventional radiographics.

Method: We conducted a multicenter, case control, prospective study of 170 consecutive AS patients and 86 age and body mass index (BMI) matched healthy controls (HC) in six rheumatology units. All patients were assessed for disease characteristics, activity and enthesitis. Radiographics of the spine were evaluated for mSASSS, presence and number of syndesmophytes. For US data, the same US machine ((E-Saote MyLab70, Genoa, Italy) and US probe (6-18 MHz, lineer) were used in each center. Three images were stored for each Achilles tendon. A semi-quantitative scoring, between 0-3 was performed at the end of the study by one investigator, by mixing all the US images anonymously. The inadequate US images were excluded. The relationship between axial findings and peripheral US findings were compared by separating the data according to genders.

Results: US images and axial imaging was found eligible in 153 AS patients and 84 HC. Male AS patients had significantly higher enthesophyte scores than HC (2.3±1.6 vs 1.3±1.5; p<0.001), whereas differences in females were not significant (2.3±1.5 vs 1.9±1.7; p=0.2). The number of syndesmophytes (r=0.29; p=0.003), mSASSS (r=0.28; p=0.005) and the presence of syndesmophytes (r=0.37; p<0.001) were observed to correlate significantly with peripheral enthesophytes in males. For females, none of the axial findings correlated with US

findings. In multiple regression analysis of a model including age, BMI and enthesophyte scores, the presence of a syndesmophyte was related to age ($p<0.001$) and BMI ($p=0.003$) in males and only to age ($p<0.001$) in females, but not to US scores in both groups.

Conclusion: Age seems to be an independent factor for developing enthesophytes and syndesmophytes in AS patients. Male AS patients have more severe enthesophytes associated with syndesmophyte presence suggesting a gender-associated difference of peripheral and axial new bone formation.

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The TH17 Related Cytokines IL-21 and IL-23 in Patients with Spondylarthropathy. Thomas Andersen[1], Tue A. K. Rasmussen[1], Malene Hvid[1], Karen Berenth Madsen[2], AG Jurik[2], Berit Schiøttz-Christensen[3] and Bent Deleuran[1], [1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Aarhus Clinic for Rheumatic Diseases, Aarhus, Denmark

Background: The TH17 subprofile of CD4+ T cells has been strongly associated with the pathogenesis of spondyloarthropathy (SpA).

Purpose: The purpose of this study was to investigate the role of the TH17 associated cytokines IL-21 and IL-23 in SpA by analyzing the levels of these cytokines in plasma. Furthermore we investigated, whether levels of these cytokines correlated to clinical findings and MRI-score.

Method: Patients with SpA (n = 80) were clinically examined and characterized in regard to BASMI 0 (0 – 0), BASFI 1.1 (0.2 – 2.8), BASDAI 2.1 (0.9 – 4.4), Global VAS 24 (8 – 51), as well as CRP 20 nmol/l (12 nmol/l – 37 nmol/l). Plasma samples were collected and MRI of the spine and sacroiliac joints was performed using T1-weighted sequence with regard to erosion and fatty marrow degeneration to define chronic changes and STIR to detect activity. Plasma samples from normal healthy volunteers (NHV) (n=37) were used as controls. Plasma levels of IL-21 and IL-23 were measured by ELISA.

Results: IL-21 plasma levels above the detection limit (16 pg/ml) were observed in 46 of the 80 (58%) SpA patients and in 22 of the 37 (58%) NHV. IL-21 was significantly increased in SpA plasma compared to the NHV ($p < 0.05$). Similarly IL-23 levels above the detection limit (2,5 pg/ml) were observed in 25 of the 80 (31%) SpA patients and in 3 of the 37 (8%) NHV. A statistically significant increase of IL-23 was seen in the SpA patients compared to the NHV ($p < 0.001$). When comparing the different subgroups of SpA patients (Psoriatic Arthritis, Ankylosing Spondylitis, Reactive Arthritis, Enteropathic Arthritis and Unspecified Arthritis) regarding IL-21 and IL-23 levels, no difference was observed. However, a significant correlation was observed between individual levels of IL-21 and IL-23 ($r = 0.7$ $p < 0.001$). In contrast, the levels of IL-21 and IL-23 was not correlated to the MRI changes nor to any of the examined clinical parameters, including CRP.

Conclusion: The TH17 related cytokines IL-21 and IL-23 are increased in SpA patients, reflecting the increased T cell and dendritic activity in SpA, but without correlation to MRI or clinical parameters.

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ERAP1 R528 Variants Influence the Radiological Progression in Ankylosing Spondylitis. Nigil Haroon[1], Finbar (Barry) D. O'Shea[1], Proton Rahman[2], F.W.L. Tsui[1] and R.D. Inman[1], [1]Toronto Western Research Institute, Toronto, ON, [2]Memorial University of Newfoundland, St Johns, NF

Purpose: The pathogenesis of ankylosing spondylitis (AS) is not well understood. Polymorphisms in the endoplasmic reticulum aminopeptidase 1 (ERAP1) gene are associated with AS. The possible explanations for this association are the involvement of ERAP1 in cytokine receptor shedding or peptide processing. There is no evidence so far that ERAP1 influences radiological progression in AS.

Method: Caucasian AS patients (modified New York criteria) were recruited from the spondylitis clinic and followed prospectively. At the baseline visit the BASDAI, BASFI and BASMI were noted and cervical and lumbar x-rays taken. The x-rays were repeated every 2 years while the clinical data was updated annually. DNA was isolated from peripheral blood and genotyped for the *rs30187, rs27044* and *rs10050860* SNP of ERAP1 gene by allelic discrimination. X-rays were read independently by two readers and mSASSS scores were calculated. The change in mSASSS scores were noted between the first and last visit and divided by the duration between the x-rays to get the rate of change in mSASSS scores per year. The rate of change in mSASSS scores were compared between the different genotypic groups using the Kruskal-Wallis test. Logistic regression was used for identifying baseline predictors of mSASSS progression.

Results: Radiographs were available in 52 patients (7 female) on at least 2 occasions with mean (±SD) gap of 2.6 ± 1.01 years between them. The mean age of the patients was 35.1 ± 13.1 years and had mean disease duration of 14.3 ± 8.7 years. The mean BASDAI, BASFI and BASMI scores were 4.7 ± 2.7, 4.1 ± 2.9 and 2.3 ± 1.9 respectively at baseline visit and 3.6 ± 2.4, 3.3 ± 2.7 and 2.5 ± 2.2 respectively at the last visit. Thirty four patients were on anti-TNF medications for a mean duration of 15.7 ± 2.2 months. The mean baseline and follow up mSASSS scores were 16.0 ± 22.1 and 17.9 ± 22.5 respectively with a mean change of 1.9 ±2.8 units ($p<0.0001$, paired T test) and mean rate of change of 0.9 ± 1.7 units per year. The frequency of ERAP1 genotypes were 13/27/9 (*rs30187*), 19/28/4 (*rs27044)* and 40/10/1 (*rs10050860*) respectively. The age, disease duration, baseline mSASSS scores and the patients as well as the mean duration of anti-TNF intake were comparable between the genotypic groups. There was significant difference in the rate of change in mSASSS between the genotypic groups of the *rs30187* SNP of ERAP1 ($H=8.8$, $df=2$; $p=0.01$). The median (interquartile range) change in mSASS scores were 1.0 (0.4, 1.8), 0 (0, 2) and 0 (0, 1) respectively for the CC/TC and TT genotypes of *rs30187*. There was no significant difference in the rate of change in mSASSS with the *rs27044* and *rs10050860* SNP. Logistic regression showed that the rs30187 genotype predicted patients who had any degree of radiological progression.

Conclusion: This is the first report to suggest a phenotypic influence of ERAP1 polymorphisms in patients with AS. Our novel finding suggests that the K528R ERAP1 polymorphisms can affect the radiological severity in AS.

Disclosure: N. Haroon, None; **F. (. D. O'Shea**, None; **P. Rahman**, None; **F. W. L. Tsui**, None; **R. D. Inman**, None.

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Interleukin 23 Expression in Inflammatory Arthritis. Axel J. Hueber, Darren L. Asquith, Neal L. Millar, Roger D. Sturrock and Iain B. McInnes, University of Glasgow, Glasgow, United Kingdom

Purpose: A novel subset of IL-17 producing T cells (Th17 cells) has been suggested to be crucial in the pathogenesis of arthritis and psoriasis. The necessity of IL-23 for the polarisation of Th17 cells has been demonstrated using mice deficient for the IL-23 receptor (IL-23R) which exhibit impaired expansion and function of Th17 cell population. Furthermore, deletion of IL-23(p19) in a murine model of arthritis ameliorated disease suggesting a pro-inflammatory effect of IL-23 in inflammation and antibodies against IL-23p40 have yielded beneficial effects in psoriasis. Additionally, psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are strongly associated with IL-23R polymorphisms. These studies support a pathological role of IL-23, potentially by positively regulating the expansion of Th17 cells.

Method: RNA extracted from peripheral blood mononuclear cells (PBMCs) from rheumatoid arthritis (RA, n=48), psoriatic arthritis (PsA, n=22) and ankylosing spondylitis (AS, n=19) patients relative to healthy controls (HC, n=38) was analysed for IL-23 transcripts. For detection of IL-23 in synovial fluid ELISA was performed. IL-23 was stained by immunohistochemistry in synovial tissue (RA n=5, PsA n=3 and OA n=4). Utilising an *in vitro* model of synovitis healthy human $CD3^+$ T cells were activated in the presence of IL-2, IL-6 and TNF-α for 6 days and were added in co-culture to syngeneic MCSF matured $CD14^+$ macrophages. Supernatants were measured by ELISA.

Results: The level of IL-23 transcript was significantly increased in PBMCs from PsA patients ($P = 0.0244$), but was not altered in RA patients and was only detectable in 4 out of 19 AS patients. In synovial fluid, bioactive IL-23 was only detectable in 3 out of 15 patients with PsA and was not detectable in the RA (in contradiction to previous reports) and OA group. Study of IL-23 expression within synovitis revealed cytoplasmic staining for IL-23 in both RA and PsA synovial tissue. However, staining for IL-23 was absent under non-inflammatory conditions in synovial tissue from OA patients suggesting that IL-23 is only expressed under inflammatory conditions within the synovium. To address a potential mechanism by which IL-23 is secreted we sought to determine which cytokines were secreted upon the interactions of T cells and macrophages. Co-culture experiments resulted in the secretion of IL-1β, IL-6 and IL-23 suggesting that macrophage/ T cell interactions within the synovium may provide an environment that would favour Th17 polarisation and expansion.

Conclusion: In summary, we demonstrate an increase in the expression of IL-23 in PsA and by utilising an *in vitro* model of synovitis we demonstrate that the secretion of the cytokines IL-23, IL-1β and IL-6, which support the polarisation and expansion of Th17 cells, is mediated through the interactions of cytokine activated T cells and macrophages.

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Identification of Specific Phenotypic Markers for HUMAN Polarized Macrophages. Carmen A. Ambarus[1], Sarah Krausz[1], Marco van Eijk[1], Jorg Hamann[1], Paul P. Tak[2] and D. Baeten[3], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [3]AMC, University of Amsterdam, Amsterdam, Netherlands

Purpose: The concept of macrophage polarization describes the heterogeneity of activated macrophages under specific microenvironmental conditions. Based on their pro- or anti-inflammatory functions in mice, two major types of macrophages (M1 and M2) have been described. According to this paradigm, we aim to assess type 2 inflammation in spondyloarthritis (SpA) versus type 1 inflammation in rheumatoid arthritis (RA). Here, we investigated the expression of cell surface molecules on in vitro differentiated human macrophages in order to identify reliable markers for characterization of polarized human macrophages in vivo.

Method: Monocytes were isolated from peripheral blood of healthy donors and differentiated in vitro for 4 days in the presence of GM-CSF, IFN-γ, LPS, TNF-α, M-CSF, IL-4, or IL-10. Expression of CD14, CD16, CD32, CD64, CD80, CD86, TLR2, TLR4, CD 163, CD200R and CD206 was analyzed by flow cytometry.

Results: M1 macrophages are prototypically induced by IFN-γ (M1a) or by TNF-α or bacterial components like LPS (M1b). In our analysis, IFN-γ induced selective up-regulation of CD64 and CD80,, while LPS strongly up-regulated CD14. M2 cells develop in the presence of IL-4 or IL-13 (M2a), immune complexes (M2b), or IL-10, TGF-β, or glucocorticoids (M2c). IL-4 up-regulated CD200R expression whereas IL-10 strongly up-regulated the expression of CD163 and, to a lesser extent, CD16. In contrast to mouse macrophages, CD206 was not a specific marker for IL-4 polarized macrophages in humans. Additionally, CD86 was not only up-regulated by IFN-γ but also by Il-4. TLR2 and TLR4 did not display a specific expression profile. The expression of specific phenotypic markers by polarized cells was similar for monocytes in healthy controls, RA, and SpA. However, the phenotype defined here upon polarization of fresh peripheral blood monocytes only partially holds through when polarizing already matured macrophages. Especially LPS induced up-regulation of different M1 and M2 markers.

Conclusion: Our data indicate that CD64 and CD80 are specific surface markers for in vitro-polarized M1a macrophages and CD14 for the M1b phenotype. CD200R specifically characterizes the M2a and CD163 and CD16 the M2c macrophages. These phenotypic markers now allow to classify polarized human macrophages in inflamed tissue and to assess the function and signalling pathways of specific macrophage subsets.

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ERAP1 Q730E Variants Affect the HLA B27 Free Chain Expression On Monocytes of Patients with Ankylosing Spondylitis. Nigil Haroon[1], F.W.L. Tsui[2], Basil Chiu[1], H.W. Tsui[3], Finbar (Barry) D. O'Shea[1] and R.D. Inman[1], [1]Toronto Western Hospital, Toronto, ON, [2]Toronto Western Research Institute. University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON

Purpose: Polymorphisms in the Endoplasmic Reticulum Aminopeptidase 1 (ERAP1) gene were recently reported to be associated with ankylosing spondylitis (AS). ERAP1 is known to be involved in peptide processing for MHC-I presentation. The surface MHC-I expression level is a surrogate marker for endogenous peptide processing within the ER. To date there is no definite evidence of an interaction between ERAP1 and HLA B27 in the pathogenesis of AS. We studied the surface expression of HLA B27 and free heavy chains on PBMC of patients with AS in the context of their ERAP1 genotype.

Methods: Caucasian HLAB27 positive patients satisfying the modified New York criteria for AS and not on any biologic treatment were recruited from the spondylitis clinic. The BASDAI, BASFI, BASMI, CBC, ESR and CRP were noted. DNA was isolated from peripheral blood and genotyped for the *rs30187* and *rs27044* SNPs of the ERAP1 gene by allelic discrimination. PBMC were isolated by Ficoll

layering and stained with ME1 (Native HLA B27), HC10 (free class I heavy chains), APC tagged anti-CD14 (monocytes) and PE tagged anti-C19 (B cells) antibodies to identify their respective surface molecules. 1 x 10^4 PBMCs were acquired by FACSCalibur and the mean fluorescence intensities (MFI) of ME1 and HC10 on whole PBMC, monocytes and B cells were analyzed using FlowJo. The MFI were compared between the genotypic groups using the dominant and recessive models with relevant statistical tests.

Results: Twenty nine patients (5 females) with a median (interquartile range –IQR) age of 37 (24, 47) years and median (IQR) disease duration of 15.3 (9.5, 24) years, were included in the study. The median (IQR) values for BASDAI, BASFI and BASMI were 3.5 (2.8, 6), 2.3 (1.3, 4.5) and 1.5 (1, 4) respectively. The frequency of patients with the different genotypes of *rs30187* was 3, 13, 13 (TT, CT, CC) and for *rs27044* was 4, 13, 12 (CC, CG, GG). There was no significant difference in the age, disease duration, BASDAI, BASFI, BASMI, ESR or CRP between the genotypic groups. The MFI for HC10 staining was significantly different across the genotypic groups by Kruskal-Wallis test (H=6.28, df=2; p=0.04). In the dominant model, there was significantly higher HC10 staining (Z=-2.4, p=0.01) as well as a lower ME1 to HC10 ratio on the monocytes of patients who had the *rs27044* minor allele G compared to those with only the major allele C. There was no significant difference in the ME1 staining in any cell population nor the HC10 staining in the whole PBMC or B cells in both models.

Conclusion: This is the first study to show a functional consequence of the ERAP1 Q730E variant and to implicate ERAP1 in the pathogenesis of AS, . This is further support for the free chain theory HLA B27 involvement in the pathogenesis of AS.

Disclosure: N. Haroon, None; **F. W. L. Tsui**, None; **B. Chiu**, None; **H. W. Tsui**, None; **F. (. D. O'Shea**, None; **R. D. Inman**, None.

1449

Analysis of HLA B27 Effect On Macrophage Function Using Transgenic Mice. R. D. Inman and F. Zhu, University of Toronto, Toronto, ON

Purpose: The association of HLA-B27 with spondyloarthritis remains the strongest genetic association in rheumatic diseases, but the mechanistic role of B27 in disease pathogenesis remains unresolved. Hypotheses of B27 mechanisms have implicated distinct features of cell physiology (such as an unfolded protein response) which would predict distinct functional features. The present study addressed this question in mice transgenic for class I MHC alleles.

Method: Mice transgenic for HLA alleles B27, B7, and A2 were crossed with MHC class I-deficient mice (double knock-out, or DKO) so that the human HLA allele was the only class I MHC molecule expressed on the cell surface of the respective mice. Peritoneal macrophages were harvested after thioglycollate injection, and were coincubated with Salmonella typhimurium (1:10 cells/bacteria), IFN-γ (100 units/ml), or LPS (10 mg/ml). Readouts included (i) phagocytosis of bacteria (ii) intracellular killing of bacteria (iii) nitrite generation (iv) TNF-α production (v) IL-10 production.

Results: There was no significant difference in phagocytosis of S. typhimurium by macrophages of the respective mice at 1hr and 4hr time points. Intracellular killing of S. typhimurium was also comparable across the groups. There was no difference between the respective cells in nitrite generation after coincubation with S. typhimurium. In contrast, following exposure to S. typhimurium, B27+ macrophages produced less TNF-α (420.6- pg/ml +/- 16.6) than B7+ macrophages (630.4 pg/ml +/- 5.3) (p=0.002) but more than A2+ macrophages (302.5 pg/ml. +/- 20.5) (p=0.001). These B27-specific differences in TNF-α production were still observed when exogenous IFN-γ was added to the cells concurrent with the bacteria. There was no HLA-related difference in TNF-α production after incubation with LPS. After incubation with Salmonella, B27+ macrophages produced more IL-10 (199.4 pg/ml +/- 7.1) than B7+ macrophages (123.6 pg/ml +/- 7.4) (p=0.003) or A2+ macrophages (98.4 pg/ml +/- 7.1) (p=0.002).

Conclusion: Murine macrophages expressing HLA-B27 generate less TNF-α and more IL-10 than HLA-B7-positive macrophages after *in vitro* exposure to an arthritogenic pathogen. Diminished TNF-α production has previously been associated with defective host clearance of pathogens *in vivo*, suggesting that B27-related alterations in cytokine production may play a role in disease pathogenesis.

Disclosure: R. D. Inman, None; **F. Zhu**, None.

ACR/ARHP Poster Session C

Imaging - Ultrasound

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Inter-and Intra-Reliability of Ultrasonographic Joint Scoring in RA Patients with US Atlas as a Reference. Hilde Berner Hammer[1], Pernille Bolton-King[1], Vivi Bakkeheim[2], Torill Helene Berg[1], Elisabeth Sundt[1] and Espen A. Haavardsholm[1], [1]Department of Rheumatology, Oslo, Norway, [2]Department of Rheumatology, Trondheim, Norway

Ultrasonography (US) detects synovitis (BM) and vascularization (power Doppler,PD). Reliable measurements are necessary to assess disease activity. The OMERACT US group has described a scoring system for BM and PD; 0 = Normal, 1= Minor, 2=Moderate, 3=Major. A local US atlas was made using this scoring system, including several examples of each joint for each of the scorings in 32 joints.

Purpose: By use of the US atlas as background to assess the intra-and inter-rater reliability of US scoring (BM and PD) in 32 joints from RA patients.

Method: Five rheumatologists (with 3-8 years of US experience) examined 10 patients with RA (median (range) 63 (34-75) years old, disease duration 13 (3-24) years), with a printed US atlas available. An agreement had been made in advance on the scoring system. Each patient was in a room with a table for hand examination, a bench and an US machine with a fixed settings of BM and PD (Siemens Antares Acuson or Sonoline). Each sonographer was given maximum 20 min for scoring BM and PD of 32 joints (bilateral MCP 1-5, wrist (radiocarpal, intercarpal, radioulnar), elbow, knee, talocrural and MTP 1-5). The patients were assessed in a random order, with as long as possible interval before reassessing the same patient. A study nurse (with six years of experience with joint counting) performed the assessment of tender and swollen joints. CRP and ESR were analyzed. The intra-reliability of the US examinations was assessed by use of kappa values and percentage exact and close agreement, and the inter-reliability was analyzed by use of intraclass correlation coefficients (ICC).

Results: The patients had median (range) 3 (0-19) tender joints and 6 (1-17) swollen joints (of 28), CRP 15 (1-96) mg/l, ESR 27 (10-107) mm/h and DAS28 4.4 (2.9-8.2). Pathological BM (score ≥1) was found in 169 of 320 examined joints. The US examinations were performed on median (range) 16 (9-20) minutes. The intra-reliability results are shown in table 1, and the ICCs for BM and PD are shown in table 2 and 3.

Table 1

	Rater 1	**Rater 2**	**Rater 3**	**Rater 4**	**Rater 5**	**Average**
B-mode Kappa	0.72	0.66	0.61	0.60	0.56	0.63
B-mode PEA	80.1	80.6	71.9	73.1	70.3	75.2
B-mode PCA	99.4	98.1	99.7	96.2	96.8	98.0
PowerDoppler Kappa	0.69	0.73	0.71	0.65	0.58	0.67
PowerDoppler PEA	83.7	87.6	85.4	82.9	76.7	83.3
PowerDoppler PCA	98.4	98.0	98.0	98.1	96.8	97.9

PEA=Percentage exact agreement, PCA=Percentage close agreement

Table 2

	Rater 1	**Rater 2**	**Rater 3**	**Rater 4**	**Rater 5**
Rater 1	**0.98**	0.92	0.95	0.93	0.92

Rater 2	0.97	**0.95**	0.92	0.86	0.89
Rater 3	0.97	0.96	**0.99**	0.97	0.93
Rater 4	0.96	0.95	0.97	**0.94**	0.95
Rater 5	0.98	0.96	0.94	0.93	**0.93**

Intra- and inter-rater reliability BM score (ICCs for sum scores)

Table 3

	Rater 1	**Rater 2**	**Rater 3**	**Rater 4**	**Rater 5**
Rater 1	**0.96**	0.95	0.96	0.95	0.97
Rater 2	0.97	**0.99**	0.99	1.00	0.96
Rater 3	0.96	0.99	**0.97**	0.99	0.96
Rater 4	0.99	0.97	0.97	**0.95**	0.96
Rater 5	0.97	0.96	0.94	0.95	**0.98**

Intra and inter-rater reliability PD score (ICCs for sum scores)

Conclusion: High intra-and inter-rater reliability were found for BM and PD scoring of 32 RA joints in spite of a short examination time. The rheumatologists performing the US examinations had in advance agreed on a scoring system based on the US atlas, and use of an atlas may be important if US scoring should be used in longitudinal follow-up studies.

Disclosure: H. B. Hammer, Abbott Immunology Pharmaceuticals, 2 ; **P. Bolton-King**, None; **V. Bakkeheim**, None; **T. H. Berg**, None; **E. Sundt**, None; **E. A. Haavardsholm**, None.

1451

Utility of Ultrasonographic Measures of Synovitis in Early Phase Clinical Trial Design. M. Seymour[1], F. Pétavy[2], F. Chiesa[2], H. Pocock[2], P. Lukey[3], M. Binks[3], C. McClinton[1], K. Dolan[1] and P. Taylor[1], [1]Imperial College London, London, United Kingdom, [2]GlaxoSmithKline, Middlesex, United Kingdom, [3]GlaxoSmithKline, Stevenage, United Kingdom

Purpose: Current practice in developing new therapeutics for rheumatoid arthritis (RA) involves clinical assessment of response by means of endpoints that include composite measures of disease activity, such as the Disease Activity Score (DAS28). However, many of the component measurements are subjective, imprecise and insensitive to change therefore necessitating lengthy clinical trials using large cohorts of patients. In this study we test the sensitivity of ultrasonographic endpoints to change in the context of an early phase clinical trial in patients with active RA.

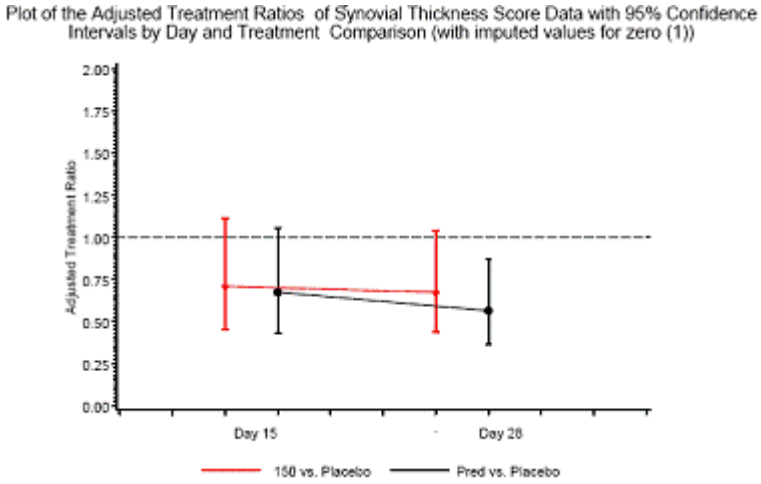
Method: The study was a double-blind, placebo and comparator controlled, two-centre study to investigate the effect on synovial thickness and vascularity of 28 days repeat daily oral dosing of 60 mg of the oral iNOS inhibitor GW274150 or 7.5 mg prednisolone in RA subjects. All patients had disease activity defined as DAS28≥4.0 and at least one metacarpophalangeal joint (MCPJ) with either detectable vascularity or synovial thickening. 50 subjects were randomized into 3 treatment arms of 17, 19 and 14 (on placebo, GW274150 and prednisolone respectively). Synovial thickness and vascularity of all 10 MCPJs were assessed at 3 time points (pre-dose on Day 1, Day 15 and Day 28) using the Esaote Technos Plus with a 13MHz transducer. Images were ranked by semi-quantitative scale. Vascularity was also measured by quantitative determination of the power Doppler area (PDA).

Results: At Day 28 GW274150 showed a trend towards reduction in synovial thickness compared with placebo, with an adjusted mean decrease of 33% (p=0.072). Prednisolone 7.5 mg showed a statistically significant decrease of 44% (p=0.011) [Fig.1A]. GW274150 decreased synovial vascularity by 42% compared with placebo but the reduction was not statistically significant (p=0.075). However, prednisolone 7.5 mg resulted in a statistically significant decrease of 55% (p=0.012) [Fig.1B]. There was a 55% decrease in PDA for

GW274150, compared with placebo although the result was not statistically significant (p=0.375). Prednisolone 7.5 mg resulted in a highly statistically significant decrease of 95% (p=0.003) [Fig.1C]. There was a 0.42 decrease in the DAS28 score in the GW274150 group compared with placebo, however this was not statistically significant (p=0.290). Prednisolone showed a statistically significant adjusted mean decrease of 0.98 (p=0.018).

Conclusion: This study confirms the utility of ultrasonographic measures of metacarpophalangeal joint synovitis as a primary endpoint in early phase studies assessing the therapeutic potential of new compounds in small patient cohorts over a 28 day test period.

A



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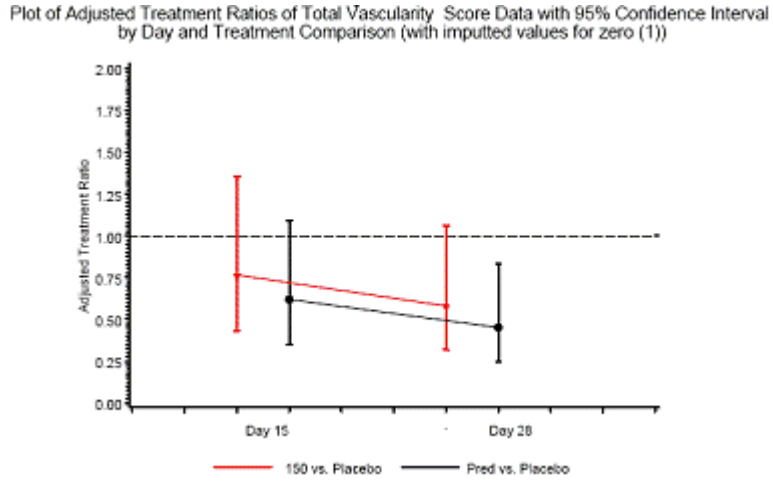

C

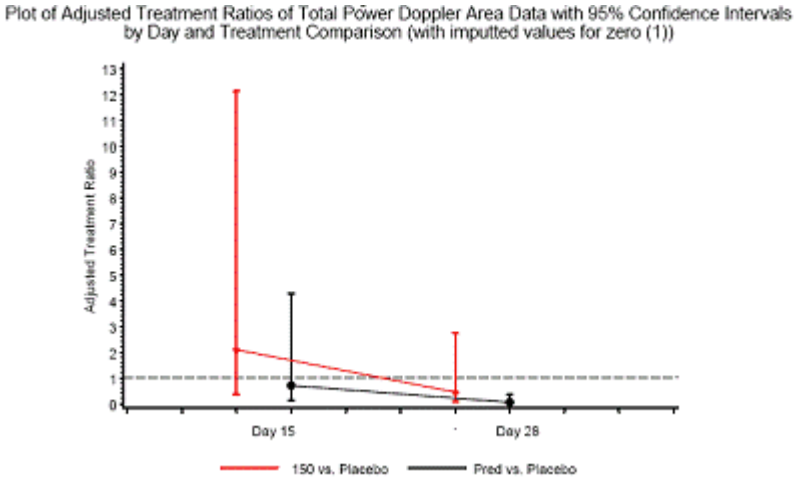

Figure 1.

Disclosure: M. Seymour, None; **F. Pétavy**, GlaxoSmithKline, 3 ; **F. Chiesa**, GlaxoSmithKline, 3 ; **H. Pocock**, GlaxoSmithKline, 3 ; **P. Lukey**, GlaxoSmithKline, 3 ; **M. Binks**, GlaxoSmithKline, 3 ; **C. McClinton**, None; **K. Dolan**, None; **P. Taylor**, GlaxoSmithKline, 2 .

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Ultrasound Quantification of Tendon and Hypodermal Abnormalities in Patients with Systemic Sclerosis. Paul R. Sweeney, R. Simms, Elliot Sternthal, Michael R. York, Hyon K. Choi and Eugene Y. Kissin, Boston University School of Medicine, Boston, MA

Purpose: Systemic sclerosis (SSc) can cause disabling hand contractures, and tendon friction rubs associated with disease severity. Abnormal dermal thickness in SSc has been quantified, but there has been no quantification of tendon involvement. Ultrasound has been used to shown tendon sheath enlargement in diabetic cheirarthropathy (DMc). We aim to define tendon, hypodermal, and skin alteration in SSc with ultrasound by comparing these structures in patients with SSc to those in patients with fibromyalgia (FM), and with DMc.

Methods: Consecutive patients on routine clinic visits with the established diagnosis of FM, DMc, or SSc were recruited. GE Logiq e Ultrasound System with 8-12 MHz linear array transducer, and electronic calipers was used to measure cross sectional areas of the 2nd flexor tendon at the MCP joint and the abductor pollicus longus at the distal radius. The skin and hypodermal thickness were measured at the midpoint of the dorsal forearm, at the interface of the common extensors and extensor carpi radialis. Hand function was assessed by Hand Mobility in Scleroderma (HAMIS) testing.

Results: 10 FM, 10 DMc , 17 limited SSc (lSSc), 14 diffuse SSc (dSSc) patients consented. There was no relationship between BMI, age, or height with any recorded measurements (demographics in Table). Student's T-Test was used to compare means. Diffuse SSc patients had greater mean forearm skin thickness and smaller cross sectional area of the 2nd flexor tendon than FM controls. Abductor pollicus longus cross sectional area was also smaller in patients with either lSSc or dSSc than in FM controls. Mean flexor tendon sheath thickness was greater in both dSSc and in DMc patients compared to FM controls. HAMIS functional testing showed significant impairment in patients with DMc, lSSc, and dSSc in comparison to FM.

Conclusion: This is the first quantification of chronic tendonopathy (tendon sheath thickening), and connective tissue wasting (tendon and hypodermal thinning) occurring in SSc. These changes are associated with SSc hand dysfunction, and are distinct from the changes that occur in DMc, a condition with a similar clinical appearance in the hand.

Soft tissue quantification by ultrasound

	Fibromyalgia	**DM Cheirarthropathy**	**Limited Systemic Sclerosis**	**Diffuse Systemic Scleros**
	N=10	**N=10**	**N=17**	**N=14**

	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	45.3 ± 10.2	64.6 ± 10.0	49.1 ± 12.3	45.3 ± 10.2
Gender (% female)	30	50	27	27
BMI	27.6 ± 7.2	29.2± 5.9	25.0 ± 5.7	25.2 ± 5.7
2nd flexor tendon area (cm^2)	0.18 ± 0.02	0.20 ± 0.04 (p=0.18)	0.16 ± 0.03 (p=0.13)	***0.14 ± 0.03 (p=0.01)**
APL tendon area (cm^2)	0.15 ± 0.06	0.13 ± 0.06 (p=0.52)	***0.09 ± 0.03 (p=0.02)**	***0.08 ± 0.06 (p=0.01)**
Flexor tendon sheath (cm)	0.05 ± 0.02	***0.09 ± 0.02 (p<.001)**	0.05 ± 0.02 (p=0.32)	***0.07 ± 0.04 (p=.05)**
Dermal thickness (cm)	0.14 ± 0.04	0.14 ± 0.03 (p=0.43)	0.14 ± 0.05 (p=0.50)	***0.18 ± 0 .06 (p=0.03)**
Hypodermal thickness (cm)	0.61 ± 0.18	***0.35 ± 0.13 (p=0.02)**	0.52 ± 0.31 (p=0.30)	***0.49 ± 0.26 (p=0.01)**
HAMIS score	0.5 ± 0.7	***4 ± 1.8 (p<.001)**	***5.5 ± 4.0 (p<.001)**	***12.8 ± 6.6 (p<.001)**

P values are for comparisons with fibromyalgia controls. * significance with p<0.05

Disclosure: P. R. Sweeney, None; **R. Simms**, None; **E. Sternthal**, None; **M. R. York**, None; **H. K. Choi**, TAP Pharmaceuticals Inc., 9, Takeda, 9, Savient, 9, Centocor, Inc., 9 ; **E. Y. Kissin**, GE Healthcare, 2, Stryker, 5, Amgen, 5, SonoSite, 5 .

1453

Ultrasonography Shows Persistent Hyperemia of Synovial Tissues in Rheumatoid Arthritis Despite Apparent Serological Remission.

Ralf G. Thiele, Allen P. Anandarajah and Darren Tabechian, University of Rochester, Rochester, NY

Purpose: The goal of treatment in rheumatoid arthritis is remission. The cardinal features of rheumatoid arthritis are synovitis and tenosynovitis, which subsequently lead to erosive disease and joint deformity. Synovitis can be assessed directly through biopsies, MRI assessment or ultrasound assessment. Often, only indirect measures are used to assess synovitis, including history and physical examination (assessment of painful and swollen joints). More indirectly yet, ESR and CRP are used as a measure of disease activity. However, despite widespread use, such clinical scores correlate only modestly with biopsy results and direct visualizion of inflamed tissues. This study aims at assessing the proportion of patients with active inflammation seen sonographically in patients whose ESR or CRP readings have remained within normal limits.

Method: Patient characteristics: All patients ("all comers") followed for rheumatoid arthritis (fulfilling ACR criteria and had a positive RF and/or CCP antibody) whose acute phase reactants (ESR and CRP) had remained within normal limits within a time frame from 5 days before to 5 days after the visit were included in this analysis to avoid selection bias (n = 233). Patient were seen and examined sonographically by one provider (R.T.) within a period of 3 months. Half of these patients (n=112) underwent an ultrasound examination of MCP joints 2-5, radiocarpal and midcarpal joints. Synovial tissue was defined as hypoechoic, poorly compressible and non-displaceable tissue within the hyperechoic joint capsule. Color and power Doppler examination were performed in all sonographically examined patients. Hyperemia of synovial tissue was defined as a color or power Doppler signal seen within the hyperechoic joint capsule, projecting over synovial tissue and displaying pulsation synchronous with the patient's pulse. Studies were performed on a Toshiba Xario XG machine using a 18 mHz linear probe or on a SonoSite M-Turbo using a 14 mHz linear transducer. At the time of the examination, patients were on no therapy or NSAIDs alone (n=23); on prednisone alone (n=11); on conventional DMARDs alone (n=89) or on biologic agents with or without additional DMARDs (n=111).

Results: Of all comers with RA and normal ESR and CRP, 19.3 % (45/233) were found to have active inflammation by Doppler ultrasound criteria. Of all patients that were examined sonographically, 40.1 % (45/112) had active inflammation. A higher percentage of patients in apparent remission treated with conventional DMARDs showed sonographic inflammation (21/89 or 23.5% of all comers; 21/45 or 46.6% of sonographically examined patients on DMARDs) than patients treated with biologics (9/111 or 8.1 % of all comers; 9/55 or 16% of all sonographically examined patients).

Conclusion: Ultrasound finds active inflammation in a substantial proportion of patients who are in apparent remission based on ESR and CRP normalization. In RA patients with normal CRP and ESR, hyperemic, proliferative synovial tissue is found more often in patients treated with conventional DMARDs than in patients treated with biologics.

Disclosure: R. G. Thiele, None; **A. P. Anandarajah**, None; **D. Tabechian**, None.

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Standardized Ultrasound Examination of the Hand in Patients with Rheumatoid Arthritis-a Multicentre Learning Experience: Education in Ultrasound of Rheumatoid Arthritis-EURA. K. Ellegaard[1], S. Torp-Pedersen[2], R. Christensen[3], M. Stoltenberg[4], Annette Hansen[5], T. Lorenzen[6], D. Jensen[7], Hanne Lindegaard[8], L. Juul[9], H. Røgind[10], P. Bülow[11], S. Chrysidis[12], M. Kowalski[13], Bente Danneskiold-Samsoe[14] and H. Bliddal[15], [1]KE, Copenhagen, Denmark, [2]STP, Copenhagen, Denmark, [3]RC, Copenhagen, Denmark, [4]MS, Køge, Denmark, [5]Gentofte, Gentofte, [6]TL, Denmark, [7]DVJ, Hørsholm, Denmark, [8]Odense University Hospital, Odense, Denmark, [9]LJ, Openhagen, Denmark, [10]HR, Openhagen, Denmark, [11]PB, Copenhagen, Denmark, [12]SC, Esbjerg, Denmark, [13]MK, Aalborg, Denmark, [14]Copenhagen, Denmark, [15]Parker Institute, Frederiksberg, Denmark

Purpose: There is a lack of standardized US examination procedures in the rheumatological area and such standardized procedures are needed. Standardized examination procedures are important in order to improve the validity of the US measurements and to make it possible to compare US studies from different institutions.

The purpose of this study was to investigate the learning progress for rheumatologists trained in a standardized US examination of the hand in patients with rheumatoid arthritis (RA).

Method: Ten rheumatologists from Denmark having varying experience in US were trained for two days in a standardized US examination of the wrist and MCP joints in pateints with RA . The examination contained both grey-scale and Doppler assessment. The tutors were two persons with intensive experience in US. After training, the rheumatologists performed the examination in their own clinics. All examinations were sent to the tutors for quality evaluation. The tutors evaluated the examinations according to a scoring sheet containing 16 positions (four in the wrist and 12 in MCP II-V). In each position nine items were scored.

Both the general examination technique and the Doppler examination technique were assessed. A high quality of the Doppler images is essential to obtain a valid measure of hyperaemia. Thus the general examination was accepted if >80% of the scores were correct, but the Doppler part was only accepted if >90% were correct.

Results: Ninety-six patients were scanned in a total of 378 examinations. High level of scores was obtained very fast, however some persisting mistakes were made throughout the study despite the intensive evaluation and feed-back. 97% of the examinations scored >80% in the general examination and 47% scored > 90% in the Doppler examination. No correlation was seen between earlier US experience and scores obtained. Some participants had decreasing scores in the study period, which might be due to carelessness.

Conclusion: Skills in a standardized US examination can be achieved relatively fast making US suitable for clinical practice and both single and multi centre trials. However, to ensure high validity, the investigators must continue performing systematic US examination. This is of particular importance in the Doppler examination.

Disclosure: K. Ellegaard, None; **S. Torp-Pedersen**, None; **R. Christensen**, None; **M. Stoltenberg**, None; **A. Hansen**, None; **T. Lorenzen**, None; **D. Jensen**, None; **H. Lindegaard**, Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Roche Pharmaceuticals, 5, Schering-Plough, 5 ; **L. Juul**, None; **H. Røgind**, None; **P. Bülow**, None; **S. Chrysidis**, None; **M. Kowalski**, None; **B. Danneskiold-Samsoe**, None; **H. Bliddal**, None.

1455

Is Ultrasonography A Useful, Reproducible and Relevant Tool to Assess Erosion Progression in Rheumatoid Arthritis? Ghislaine Gill[1], Isabelle Chary-Valckenaere[1], Jean-Philippe Sommier[1], Anne-Christine Rat[1], Alain Blum[2] and Damien Loeuille[1], [1]Rheumatology, Nancy, France, [2]Radiology, Nancy, France

Purpose: The aim of this study is to evaluate the reproducibility of a new US erosions score in patients with Rheumatoid Arthritis (RA) and to define a threshold of US structural progression.

Method: 35 patients fulfilling ACR revised criteria for RA were included in a one year long prospective study (age: 51.4±13.7, female: 60%, anti-CCP: 78%, RF: 81%, disease duration: 53±46 months, DAS28: 3.88±1.18, DMARD: 91%, biological agents: 26%). X-rays and US were performed at baseline and at 1-year follow-up. US (Philips HD11 and ESAOTE MPX, linear probe: 5-12 MHz) examinations were performed by two experimented rheumatologists. Erosions at MCP2,3,5 and MTP2,3,5 joints were explored on dorsal, ventral and lateral facets (for MCP2,5 and MTP5 joints) and graded from 0 (absence) to 3 (erosion>3 mm or multiples erosions). ScUSSe (Scoring by US Structural erosions: 0-90) is the sum of grades of the 30 facets studied. US intra and inter-examiner reproducibility was assessed on 11 patients and modified van der Heijde Sharp Score (SHS) intra-observer reproducibility on 30 patients. To define a threshold of US structural progression, the Smallest Detectable Difference (SDD) and the Minimal Detectable Change (MDC) by Bland and Altman's formula have been calculated.

Results: Inter-examiner reproducibility of ScUSSe is excellent (ICC= 0.97 [0.92-0.99]). Inter and intra-examiner reproducibility, SDD and MDC for both imaging techniques are reported in the table. According to the SDD of the ScUSSe, 9/35 (26%) patients showed a structural progression (ΔScUSSe≥5). Among them, only 6 showed a structural progression on X-rays. The US progression observed was the occurrence of new erosion in 83% of cases and the worsening of pre-existent erosions in only 17% of cases. In US, the mainly affected joints were MCP2,5 and MTP5 (87%). Only 6/35 (17%) patients increased significantly their X-rays score (ΔSHS≥8). Spearman's correlation between ScUSSe and SHS at baseline is good (R= 0.61 [0.39-0.92]).

Conclusion: In RA, ScUSSe is a reproducible semi-quantitative score to grade erosions on 12 targeted joints. This US score permits to identify structural progression, defined by ΔScUSSe≥5. ScUSSe permits to identify more patients with a structural progression (50%) than X-rays.

	US ScUSSe (0-90)		**X-Ray** SHS (0-448)
Reproducibility study	**INTRA**	**INTER**	**INTRA**
SDD	4.15	4.06	7.29
MDC (%)	4.6	4.5	1.63

Table: Values of SDD and MDC for US intra-examiner, US inter-examiner and X-ray intra-examiner studies

SDD: smallest detectable difference= 1.96 σ ($exam_1$-$exam_2$)

MDC: minimal detectable change= SDD/ (maximal extreme for the score considered).

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1456

Metric Properties of Ultrasound Synovitis in Rheumatoid Arthritis (RA- Systematic Analysis of the Literature. C. Gaujoux-Viala[1], A. Baillet[2], G. Mouterde[3], P. Claudepierre[4], Xavier Le Loët[5], B. Fautrel[1] and Jf Maillefert[6], [1]Rheumatology, Paris VI University, Paris, France, [2]Rheumatology, Grenoble, France, [3]Rheumatology, Montpellier, France, [4]Rheumatology, Créteil Paris XII University, Créteil, France, [5]CHU Rouen, 76031 Rouen Cedex, France, [6]Rheumatology, Dijon, France

Purpose: To assess the metric properties of the ultrasound's synovitis examination in RA.

Method: A systematic review of the literature using PUBMED, EMBASE,Cochrane library and hand searches was performed until March 2009. The outcomes were reproducibility, criterion validity, construct validity, discriminant validity, predictive validity and sensitivity to change.

Results: Of 377 articles, 167 studies with data concerning US synovitis were analyzed.

The intra-observer reliability was evaluated in 19 studies: good (Kappa= 0.59 to 0.90) in 17 (14 with Power doppler assessment) and fair (k= 0.25) in the 2 others (1 with Power doppler). The inter-observer reliability, evaluated in 28 studies, was good in 26 (k= 0.59 to 0.98) (17 with Power doppler) and fair in the 2 others (1 with Power doppler). However half of the studies assessed static images reading rather than real-time acquisition reliability.

The criterion validity was achieved in 7 studies by comparison with histology and in 3 by comparison with macroscopic appearance. The concordance between US and magnetic resonance imaging was evaluated 24 times with a high level of agreement (62 to 100 %, mode B; 52 to 100 %, Power doppler) in 21 studies. The concordance was low in the 3 remaining works, all concerning the shoulder joint. Using MRI as a gold-standard, US was superior to physical examination to detect synovitis (12 studies).

The discriminant validity was excellent in cross-sectional studies evaluating RA patients and healthy controls, but low in the 3 studies comparing RA and other arthritides. The positive predictive value for the diagnosis of RA is unknown. The negative predictive value of US synovitis could be high: 80% if lacking any US synovitis and erosion and 95% in patients with negative antiCCP determination.

The predictive validity for the prediction of further structural progression was evaluated by 6 studies, which suggested that US synovitis is correlated to the 1-year follow-up structural changes (r = 0.59 to 0.78), even in patients clinically considered to be in remission.

The responsiveness was evaluated in 37 studies. 35 demonstrated a reduction in US markers of synovial inflammation following treatment with various agents. This reduction was correlated with similar changes in clinical and laboratory measures of disease activity.

Conclusion: Although further studies are needed to better assess the discriminant and predictive validity, the present results suggest that US examination is a reliable, valid and responsive tool for the assessment of synovitis in RA and more sensitive for assessing signs of disease activity than clinical measures. Further works are needed, particularly therapeutic strategy trials including US synovitis as a surrogate marker for the treatment management.

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Does Sonographic Needle Guidance Affect the Outcome of Intraarticular Injections? Kye S. Park[1], Suzanne Delea[1], Natalia Chavez[1], Randy R. Sibbitt[2], Philip A. Band[3], Wilmer L. Sibbitt Jr.[1] and Arthur D. Bankhurst[4], [1]University of New Mexico, Albuquerque, NM, [2]Helena Pain Center, Helena, MT, [3]New York University Medical Center, New York, NY, New York, NY, [4]University of NM Med Ctr, Albuquerque, NM

Purpose: The present randomized controlled study addressed whether sonographic needle guidance affected clinical outcomes of intraarticular joint injections.

Method: 148 painful joints were randomized (NCT 00651625) to intraarticular triamcinolone acetonide injection by conventional palpation-guided anatomic injection or sonographic image-guided injection enhanced with a one-handed control syringe (the reciprocating procedure device). A one needle, two syringe technique was used where the first syringe was used to introduce the needle, aspirate any effusion, and anesthetize and dilate the intraarticular space. After intraarticular placement and synovial space dilation were confirmed, a syringe exchange was performed, and corticosteroid was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), and changes in pain scores were measured with the 0-10 cm Visual Analogue Pain Scale (VAS).

Results: Relative to conventional palpation-guided methods, sonographic guidance resulted in 43.0% reduction in procedural pain ($p<0.001$), a 58.5% and 22.6% further reduction in absolute pain scores at the 2 week and 6 months outcome respectively ($p<0.01$), a 75% reduction in significant pain (VAS pain score ≥ 5 cm) ($p<0.001$), ($p<0.01$), 62.0% reduction in the non-responder rate (reduction in VAS score < 50% from baseline) ($p <0.01$), and an increase in duration of therapeutic effect by 22.1% ($p <0.01$). Sonography also increased detection of effusion by 200% and volume of aspirated fluid by 337%.

Conclusion: Sonographic needle guidance significantly improves the performance and outcomes of outpatient intraarticular injections in a clinically significant manner.

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Baseline PASI Is Associated with Sonographic Enthesitis in Psoriatic Arthritis. Sibel Zehra Aydin[1], Pamir Atagunduz[1], Dilek Seckin[2], Tulin Ergun[2], Emilio Filippucci[3] and Haner Direskeneli[1], [1]Marmara University Faculty of Medicine, Rheumatology, Istanbul, Turkey, [2]Marmara University Faculty of Medicine, Dermatology, Istanbul, Turkey, [3]Università Politecnica delle Marche, Ancona, Italy

Purpose: Ultrasound (US) has shown to be a sensitive tool for revealing enthesitis, a predominant feature of spondylarthropathies. We aimed to investigate lower limbs entheses with US in patients with psoriasis, to compare US findings according to the presence of psoriatic arthritis (PsA) and to assess their change within time.

Methods: Sixty-six psoriasis patients (M/F: 31/35 mean (SD) age: 46.6(14.4)) and 20 body mass index (BMI)-age matched healthy controls (HC) were investigated. PASI (Psoriasis Area and Severity Index) was determined by a dermatologist and CASPAR criteria for PsA by a rheumatologist. US was performed using a MyLab70 US system (Esaote Biomedica, Genoa – Italy). The entheses of the lower extremities described in Glasgow Ultrasound Enthesitis Scoring System (GUESS) were scanned with power Doppler (PD) assessment. All US pathologic findings were graded semi-quantitatively from 0-2 as previously indicated (1). A grey-scale (GS) score, PD score, damage score (DS) and a total US score (TS) was determined. Twenty-nine (19 with PsA and 10 without PsA) patients were re-evaluated after a mean duration of 9 months.

Results: HC had significantly lower GS and TS compared to psoriasis patients. Fifty-nine percent (39/ 66) of psoriasis patients had PsA. GS, PD scores and DS were found similar in patients with or without PsA (table 1). In multiple regression analysis, GS score of PsAs significantly correlated to age and initial PASI ($r=0.58$, $p=0.001$), whereas the GS score of PsA(-)s only correlated to BMI ($r=0.36$, $p=0.019$) and not to age or baseline PASI. Similarly, DS of PsAs also significantly correlated to baseline PASI ($r=0.29$, $p=0,017$), whereas PsA(-)'s only correlated to BMI ($r=0.51$, $p=0.002$). Follow-up PASI scores were unrelated to US scores. The change in both GS and PD findings of 29 patients were not significant within time, regardless of PsA diagnosis.

Conclusion: US findings of enthesitis in psoriasis seem unrelated to the presence of arthritis. GS scores and DS correlated with the extent of skin involvement in PsA. The correlation between US findings indicating of enthesitis and the initial PASI scores only in patients with PsA suggests that there may be common mechanisms of inflammation at both skin and entheseal level in PsA.

Table 1: Comparison of US findings according to PsA.

	Baseline (n=66)		**Follow-up (n=29)**	
US findings	PsA (+) (n=39)	PsA (-) (n=27)	PsA (+) (n=19)	PsA (-)(n=10)
GS score (range)	7 (0-24)	6.5 (0-28	10 (0-24)	7 (2-11)
PD score (range)	0 (0-5)	0 (0-5	0 (0-6)	0 (0-1)
DS score (range)	6 (0-23)	5.5 (0-21	7 (0-20)	4.5 (0-17)

TS score (range)	13 (0-49)	12.5 (4-50)	19 (2-40)	12 (4-28)

1. Filippucci E, Aydin SZ, Karadag O, Salaffi F, Gutierrez M, Direskeneli H, Grassi W. Reliability of high-resolution ultrasonography in the assessment of Achilles tendon enthesopathy in seronegative spondyloarthropathies. Ann Rheum Dis 2009 (in press).

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Lower, Gender-Specific Cut-off Values for US Measurement of Achilles Enthesis Thickness May Better Identify Enthesitis in Spondyloarthropathies. Sibel Zehra Aydin[1], Emilio Filippucci[2], Sule Yavuz[1], Pamir Atagunduz[1] and Haner Direskeneli[1], [1]Marmara University Faculty of Medicine, Rheumatology, Istanbul, Turkey, [2]Università Politecnica delle Marche, Ancona, Italy

Purpose: To define the best cut-off value for identifying Achilles enthesis thickening using ultrasound (US) in patients with spondyloarthropathies (SpA) and to assess its diagnostic utility in comparison with different cut-off values used in the literature (1-3).

Method: Fifty-five SpA patients and 46 age and BMI-matched healthy controls (HC)) were investigated. US was performed using a MyLab70 US system (Esaote Biomedica, Genoa – Italy) with a linear probe 6-18 MHz. Three images per Achilles enthesis were stored and antero-posterior thickness of the enthesis was measured at the level of the Achilles tendon deeper margin insertion into the calcaneal bone on longitudinal median scan. The best cut-off value for each gender was determined by ROC curve analysis. The other cut-off values were 5.29 mm for both genders, according to *Balint et al* (2), and 5.5 mm for females and 6.2 mm for males, according to *Schmidt et al* (3). The number of measurements exceeding the cut-off values as well as specificity (SP), sensitivity (SE), positive (PPV) and negative (NPV) predictive values were calculated.

Results: A significant difference was found for Achilles enthesis thickness between genders (mean ±SD: 4.6±0.7 mm in males vs 4.0±0.8 mm in females, $p<0.00$) and between SpA patients and HC (mean ±SD: 4.4±0.8 mm in SpA patients vs 4.0±0.8 mm in HC, $p<0.001$). The ROC curve analysis revealed the best cut-off value as 3.9 mm for females and 4.8 mm for males (SE: 46-58%, SP: 71-79%, PPV: 69-74%, NPV: 53-59%) (Table 1). Cut-off values for Balint et al. and Schmidt et al. were found to have high SP (91-98%) but with very low SE (2-11%).

Table 1: Diagnostic value of different cut off levels for entheseal thickness

	Sensitivity	Specificity	PPV	NPV	accuracy
Balint et al	10	96	73	47	54
females	11	98	88	49	57
males	11	91	63	44	49
Schmidt et al	4	99	80	46	48
females	5	98	75	48	50
males	2	97	50	43	44
Current study	53	74	70	57	62
females	58	71	69	59	63
males	46	79	74	53	62

Conclusion: Achilles tendon thickness differs between genders, thus it is crucial to refer to normal values specific for gender (*Aydin et al, ACR Meeting 2008; 804*). High cut-off values, previously suggested, showed very low SE in the current study. When Achilles enthesis

thickening is used for the purpose of screening enthesitis in SpA patients, a lower cut-off value has a higher SE with slightly worse SP, PPV and NPV.
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Balint PVet al. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002; 61:905-10.
Schmidt WA et al. Standard reference values for musculoskeletal ultrasonography. Ann Rheum Dis 2004; 63:988-94.

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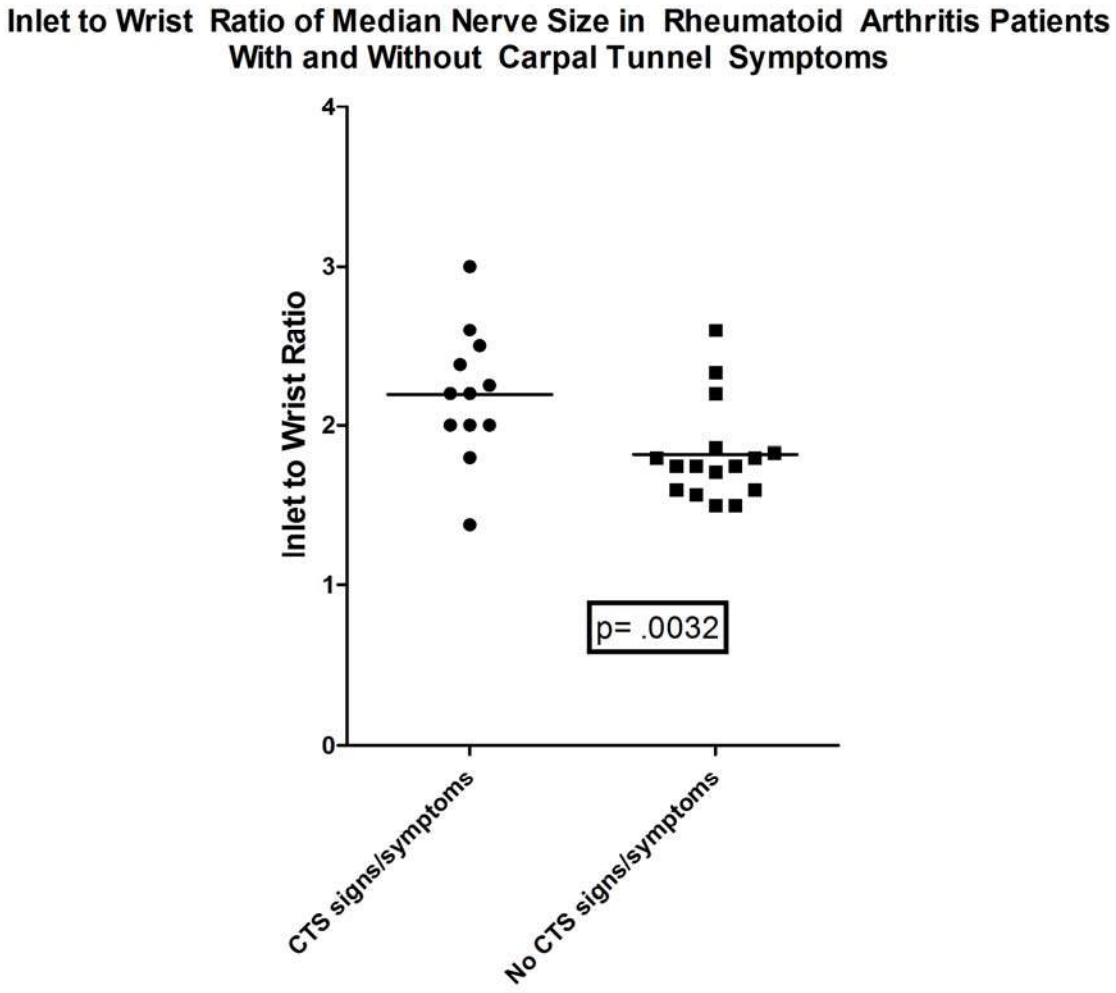
Musculoskeletal Ultrasound Assessment of Carpal Tunnel Syndrome in Rheumatoid Arthritis. Michelle M. Ryan[1] and Jonathan Samuels[2], [1]NYU-HJD, New York, NY, [2]NYU - Hospital for Joint Diseases, New York, NY

Purpose: Wrist pain in rheumatoid arthritis (RA) is often complicated by carpal tunnel syndrome (CTS) secondary to active synovitis. In such cases it can be difficult to determine whether to inject the joint or the carpal tunnel – or treat systemically. Recent literature suggests that musculoskeletal ultrasound can diagnose CTS by identifying a median nerve cross sectional area of >10mm^2 at the inlet, or by using a wrist to forearm ratio of >1.4 (from inlet to 12 cm proximally) to correct for patients with confounding diagnoses that may cause larger nerves at baseline (Hobson-Webb 2008). In this pilot study, we aim to assess how well ultrasound can identify median nerve entrapment noninvasively *specifically in RA patients with active wrist pain*.

Methods: We enrolled 19 consecutive patients with RA and active wrist pain in at least one wrist (total of 28 wrists) and assessed them for CTS by history and physical. Using gray scale ultrasound imaging at 12 MHz, we identified the median nerve at the level of the inlet (volar wrist between the scaphoid and pisiform) and 12 cm proximally to calculate the "wrist-to-forearm" ratio. More than a month after capture, we blindly evaluated median nerve cross-sectional area with a tracing function on the machine and calculated the ratio from wrist to forearm. We averaged the scores from two readings (one each by MMR and JS) for each patient.

Results: In our pilot population of painful RA wrists, irrespective of CTS signs or symptoms, the overall average median nerve size at the inlet was 10.9 (range 5.5 to 26, SD of 3.9), while the overall average wrist-to-forearm ratio was 1.9 (range 1.32 to 2.80, SD of 0.47) Separating those with (n=12) and without (n=16) CTS signs and symptoms, the average median nerve areas at the inlet were 13 mm^2 and 9.42 mm^2 respectively (p=0.0097). The corresponding wrist to forearm ratios for patients with and without CTS signs and symptoms averaged 2.19 and 1.68 (p=.0032). Of the patients with CTS signs and symptoms, 92 % (11of 12) had an inlet nerve size >10 mm^2 and 100 % (all 16) had a wrist-to-forearm ratio greater than the published 1.4 cutoff for CTS. Only 25% (4 of 16) of those without CTS signs and symptoms measured an inlet of >10 mm^2, but 75 % (12 of 16) of these asymptomatic patients had a wrist-to-forearm ratio >1.4.

Conclusion: This pilot data suggests that ultrasound evaluation of the median nerve by assessing cross sectional area at the wrist inlet is a sensitive and specific test in RA patients with active wrist pain, as it is in the general population. Conversely, the wrist-to-forearm ratio, introduced to compensate for size variability in healthy median nerves, may reveal false positive results for carpal tunnel syndrome in patients with RA and wrist pain. Measurements of the median nerve at the inlet can help distinguish RA synovitis of the joint from median nerve compression -- and thus spare patients from painful nerve conduction studies.



Disclosure: M. M. Ryan, None; **J. Samuels**, None.

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US Examination of Wrists and Hands: A Comparison Between Rheumatoid Arthritis and Psoriatic Arthritis. A. Delle Sedie[1], N. Possemato[1], E. Sardano[2], Stefano Bombardieri[3] and L. Riente[1], [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Immunology Unit, University of Pisa, Pisa, Italy, [3]University of Pisa, Pisa, Italy

Purpose: Very little is known about the possible differences in the involvement of joints and periarticular structures in rheumatoid or psoriatic arthritis (PsA). The main pathological features detected by US in rheumatoid arthritis (RA) are synovitis and bone erosion while, in spondyloarthropathies, entheseal inflammation is the common feature. Tendon involvement is particularly frequent and dactylitis is a typical PsA manifestation.

Aim of the study was to investigate the features of wrist and hand involvement in PsA and RA.

Method: Bilateral ultrasound (US) examination of the wrist and hand was performed, by the same physician, in a group of subjects affected by RA (n=25; F:M=20:5; disease duration: 12.5±11 years) and PsA (n=25; F:M=8:17; disease duration: 8.5±7 years), using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe operating at 14 MHz. We examined radiocarpal, intercarpal, metacarpophalangeal, proximal interphalangeal and distal interphalangeal (DIP) joints and flexor and extensor tendons (both in wrist and hand). The patients were recruited on a time-criteria (the last 25 patients for each diagnosis who camed for an outpatient control) from the whole number of subjects referring to the US unit of our Clinic.

Results: US examination showed joint wrist synovitis in 10/25 (40%) and 12/25 (48%) patients (in PsA and RA respectively), hand synovitis in 14/25 (56%) and in 16/25 (64%) RA and PsA patients respectively. We found DIP joint involvement in only 1 PsA patient, as it was for dactylitis (in a different PsA patient). Bone erosions were present in 10/25 (40%) patients, both in RA and PsA group. Tendon involvement was present in the 7/25 (28%) and 5/25 (20%) in the wrist and 7/25 (28%) and 10/25 (40%) in the hand respectively.

Conclusion: We did not observed significant differences in wrist or hand involvement (both in joint and tendon structures) between RA and PsA patients, except for a more frequent involvement of PIP joints and a slightly higher hand's tenosynovitis in PsA group.

Disclosure: A. Delle Sedie, None; **N. Possemato**, None; **E. Sardano**, None; **S. Bombardieri**, None; **L. Riente**, None.

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Assessment of Calcific Tendonitis of Rotator Cuff by Ultrasonography: Comparison Between Symptomatic and Asymptomatic Shoulders. Benoit Le Goff[1], Jean-Marie Berthelot Jr.[2], Pascale Guillot[2], Joelle Glemarec[2] and Yves Maugars[2], [1]University hospital, Nantes, France, [2]University Hospital, Nantes, France

Purpose: Calcific tendonitis of rotator cuff is observed on plain radiographs in 10% of adults, but remains asymptomatic in half these cases. Whereas US is widely used for the diagnosis of rotator cuff tears and tendonitis, few studies evaluated this technique in the management of calcific tendonitis. We looked for differences on ultrasound (US) and power Doppler findings between symptomatic and asymptomatic cases of shoulder calcific tendonitis to search for US features associated with pain.

Method: Sixty-two patients (81 shoulders) with symptomatic (N = 57) or asymptomatic (N = 24) calcific tendonitis were included. From each patient, we recorded: demographic data, onset and duration of symptoms, intensity of the pain and nocturnal pain. Ultrasonography of the shoulders was performed using a multifrequential linear transducer (5 to 12 Mhz). Calcific plaque morphology, power Doppler signaling, and widening of the subacromial-subdeltoid bursa (SSB) were recorded. US-guided steroid injection into the SSB (N = 21) or needle puncture of calcific deposits (N = 29) was performed at the end of US evaluation in 50 of the 57 patients with symptomatic shoulders, and a questionnaire was sent to each patient after 11 +/-6 months. For statistic analysis,Wilcoxon' signed rank test and Fisher's exact test were used. The *p* value less than 0.05 was considered statistically significant.

Results: The distal supraspinatus tendon was the most common site of calcification deposit (89%). The mean longitudinal ($p<0.0001$) and transverse ($p=0.0015$) measurements of the plaques were significantly higher in symptomatic than in asymptomatic shoulders. Fragmented calcifications were also associated with pain ($p=0.01$). A power Doppler signal was identified in 21 of the 57 symptomatic calcification (36%), but in none of the cases of asymptomatic calcification ($p<0.005$). It was associated with the existence of nocturnal pain ($p=0,03$) and the longitudinal size of the calcification ($p=0,03$). A widening of the SSB was found in 17 of the 57 symptomatic calcification (30%) but in none of the asymptomatic calcification ($p<0.005$). At least, Doppler signal or widening of the SSB was present in 31 of the 57 (54%) symptomatic shoulders ($p<0.001$). Long term outcome was favourable for 60% of our patients after steroid injection. However, no correlation was found between the evolution of the pain and the US characteristics at the first evaluation.

Conclusion: We found that ultrasonographic findings associated with symptomatic calcific tendonitis are a larger size and a fragmented aspect of the calcification. Positive power Doppler signal within the calcific deposit and SSB widening are also US features strongly associated with pain with a high specificity. US can help physicians to confirm that calcification is responsible for shoulder pain.

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Baseline Ultrasonographic Shoulder Assessment Can Predict the Functional Status in PMR Patients After Steroid Treatment. Pierluigi Macchioni, Mariagrazia Catanoso, Luigi Boiardi, Irene Modesto and Carlo Salvarani, Arcispedale S.Maria Nuova, Reggio Emilia, Italy

Purpose: To evaluate the relationship between US shoulder examination and the functional status in PMR patients before and after corticosteroid treatment.

Method: 80 PMR (according to Healey criteria) consecutive outpatients were prospectively evaluated in a single secondary center for clinical and laboratory parameters at diagnosis and during CS treatment for a median follow-up of 6 months (range 4-12 m). All the patients had shoulder US examination by standardized method at the same times. The clinical assessments included the core set parameters considered in EULAR response criteria and the Health Assessment Questionnaire (HAQ). Leeb's desease activity score were calculated at each visit. HAQ value of 42 PMR age matched patients during disease remission were used as controls. Chi square test was used to calculate differences between groups.

Results: 79 patients (F60pts/M19pts, mean age 75±7y, mean disease duration15±27wks) completed the study. Pretreatment mean values were : ESR 55±22.5mm/1st h, CRP 4.2±3.25 mg/dl, pain VAS 73±18mm, patient VAS 70±7mm, physician VAS 66±8, HAQ 1.79±0.47, morning stiffness 172±118min, Leeb's DAS 36.5±14.6. Baseline US examination showed bilateral bursal distension in 57% of the pts, bilateral involvement of long head biceps tendon in 71%, bilateral gleno-humeral distension in 15%.

After CS treatment HAQ score and US signs of shoulder inflammation were significantly reduced (p=0.021 and p=0.001 respectively). Patients with HAQ values below the median value of controls (0.25) were considered as HAQ responders. Comparing HAQ responders vs HAQ non-responders we found that female sex (OR 6.65, 95%CI 1.96-22.5), presence of peripheral joint involvement (OR 3.1, 95%CI 1-9.64), US presence at baseline of bilateral bursal and glenohumeral distension (OR 2.76, 95%CI 1.1-6.96 and 4.36, 95%CI 0.97-21.7 respectively) and presence of sopraspinatus tendon lesion (OR 3.46, 95%CI 1-12) were correlated with reduced functionality at 6 month examination. At the time of the second US examination there was a significant correlation between the number inflammed shoulder structure at US and the HAQ value (Spearman=0.419,p<0.001).

Conclusion: US examination is a useful tool to recognize PMR patients with reduced functionality after CS treatment.

Disclosure: P. Macchioni, None; **M. Catanoso**, None; **L. Boiardi**, None; **I. Modesto**, None; **C. Salvarani**, None.

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Predicting Radiographic Progression in Rheumatoid Arthritis with Ultrasound and Biomarkers. G. Cavet[1], Y. Shen[1], S. Abraham[2], D. Chernoff[1], M. Centola[3] and P. Taylor[2], [1]Crescendo Bioscience, Inc., South San Francisco, CA, [2]Imperial College London, London, United Kingdom, [3]OMRF, Oklahoma City, OK

Purpose: The ability to predict progressive joint damage has the potential to improve disease management decisions and outcomes for patients with rheumatoid arthritis (RA). Ultrasonographic B mode imaging (US) can be used to evaluate accumulated joint damage and when used together with power Doppler imaging can also be used for assessment of synovial inflammation and associated vascularity. Studies suggest that expert examination by ultrasound is more sensitive to bone erosions and joint inflammation than X-rays or clinical examination. However, such examination is not available or practical in some clinical settings. Blood-based biomarkers that report on the current rate of joint destructive processes could present a powerful complementary approach to identify patients at risk of accelerated bone and cartilage damage.

Method: We examined samples and data from 24 patients followed in a 2-year blinded study comparing methotrexate+infliximab with methotrexate alone in aggressive early RA. Patients were evaluated with US at 0, 18, 54 and 110 weeks and scored for synovial thickening (ST) and for vascularity by power Doppler area (PDA). Radiographic examination with van der Heijde modified Sharp scores was carried out at 0, 30, 54 and 110 weeks. 93 serum proteins associated with biological processes underlying joint damage were measured in serum samples from 0, 6, 18, 54 and 110 weeks. Associations were examined by Spearman correlation. Multivariate analysis used longitudinal hierarchical linear models, evaluated using leave-one-out cross validation.

Results: Patients all had erosions at baseline and experienced a wide range of changes in total Sharp scores (TSS; median change 6.25, inter-quartile range 4-14.5). Detailed clinical outcomes are reported elsewhere. Ultrasonographic scores from early in the study were predictive of radiographic progression. Predicted rates of change in TSS from 0-110 weeks based on ST or PDA at 18 weeks (with time and treatment)

were correlated to actual changes (r=0.59 and r=0.77 respectively in leave-one-out cross validation). Candidate serum biomarkers were also correlated with change in TSS, with the fewest significant correlations observed in baseline samples and the most in 6 week samples. 34 proteins were correlated with change in TSS using combined biomarker time points (FDR<0.05), representing diverse biological processes including inflammatory regulation, ECM degradation and collagen metabolism. Predicted rates of change in TSS from a multivariate model based on biomarkers at 6 weeks (with time and treatment) correlated strongly with observed changes (r=0.79 in leave-one-out cross validation).

Conclusion: Both ultrasonographic imaging and quantitative serum protein biomarkers can be used to estimate rates of progression and predict joint damage in RA. Serum proteins associated with change in TSS represent multiple biological pathways. Predictive models using US and biomarkers have the potential to improve patient outcomes.

Disclosure: G. Cavet, Crescendo Bioscience, 3, Crescendo Bioscience, 1 ; **Y. Shen**, Crescendo Bioscience, Inc., 3 ; **S. Abraham**, None; **D. Chernoff**, Crescendo Bioscience, Inc., 3 ; **M. Centola**, Crescendo Bioscience, 5 ; **P. Taylor**, Bristol-Myers Squibb, 5 .

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Ultrasonographic and Physical Examination of the Inflamed Knee: Intra and Inter Rater Reliability of the Sonographers and Clinical Examiners. Feride Gogus[1], Gulen Hatemi[2], Koray Tascilar[3], Melike Melikoglu[2], Sebahattin Yurdakul[2], Hasan Kilic[2], Serkan Yalim[2], Mine Batumlu[2] and Hasan Yazici[2], [1]Gazi University, Faculty of Medicine, Ankara, Turkey, [2]Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey, [3]Numune Research and Teaching Hospital, Ankara, Turkey

Background: We had previously shown in a pilot study that there was considerable inter observer variation in physical examination of the knee. The correlation with ultrasonographic (US) examination was also wanting (1).

Purpose: i) To test intra and inter observer variability of the clinical examination of the knee among clinicians with different levels of rheumatology expertise. ii) To test the intra and inter observer variability of the ultrasonographic examination. iii) to investigate the concordance between the ultrasonographic and clinical examination of the knee.

Patients and Methods: Twenty healthy volunteers and 21 patients with inflammatory arthritis of the knee were included in the study. A rheumatology nurse directed the clinical and ultrasonographic examination sequence in order to maintain blindness. Patients were asked to lie under sheets to conceal their identity and expose the knee joint areas only. 4 examiners (2 rheumatology attendings, 1 rheumatology fellow and 1 resident in internal medicine) examined 82 knee joints twice on the same day. Each examiner visually evaluated the presence of joint swelling, then performed clinical examination with a patellar tap and a sweep test. Two rheumatologists experienced in US and blinded to the clinical examination results did US examinations twice. Presence of effusion and synovial hypertrophy were checked at the suprapatellar, medial and lateral joint regions in standard longitudinal and transverse planes. A semiquantitative 0-3 scale was used for US evaluation for joint effusion and synovial hypertrophy. Data analysis was made by Kendall's coefficient of concordance and Kappa statistics for agreement.

Results: Intra observer agreement between the rheumatology attendings was better than that of the rheumatology fellow and the medicine resident (κ=0.57-1.00 and κ= 0.25-0.77 respectively). On the other hand, the inter observer agreement among the four clinicians was poor in any of the two-way comparisons. Ultrasonographic inter observer agreement (κ) varied between 0.73 and 0.91 in detecting synovial effusion and hypertrophy respectively. Intra observer agreement (κ) at 6 US examination planes differed between 0.39-1.00.

Conclusion: The inter observer variation in physical examination of the knee is considerably more than in US examination**.** The concordance of the physical examination findings is better among more experienced physicians.

Reference:

1. F. Gogus, J. Kitchen, R. Collins, D. Kane: Reliability of physical knee examination for effusion: verification by musculoskeletal ultrasound. Annual ACR Meeting, San Francisco, 2008.

Disclosure: F. Gogus, None; **G. Hatemi**, None; **K. Tascilar**, None; **M. Melikoglu**, None; **S. Yurdakul**, None; **H. Kilic**, None; **S. Yalim**, None; **M. Batumlu**, None; **H. Yazici**, None.

1466

The CUSP Study: Comparison of Ultrasound and Physical Findings in Inflammatory Arthritis. BM Lynch[1], J. Kitchen[2], U. Fearon[1], G. Renard[1], O. FitzGerald[1], D. Kane[2] and DJ Veale[1], [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Adelaide and Meath Hospital, Dublin, Ireland

Purpose: High-resolution gray-scale ultrasonography allows detection of erosions, synovitis and effusions in synovial joints in inflammatory disease. Power Doppler (PD) imaging allows functional depiction and assessment of inflamed joints and soft tissues. This study aimed to correlate clinical and ultrasound (US) findings and investigate if power Doppler imaging correlates with vascular endothelial growth factor (VEGF) in inflammatory arthritis.

Method: Patients with Rheumatoid (n=16) and Psoriatic arthritis (n=4) commencing biologic therapy underwent assessment at baseline, 6 and 12 weeks. Patient global and 28 joint counts were performed by an independent clinical assessor. C-reactive protein (CRP) was measured by nephelometry assay and DAS28(CRP) was calculated. US examination of seven joints (wrist, metacarpophalangeal joints 2 and 3, proximal interphalangeal joints 2 and 3, metatarsophalangeal joints 2 and 5) on the dominant hand was performed using standardised presets on a GE Logiq 9 machine with a high frequency (15MHz) linear array transducer by two trained investigators. Gray-scale (GS) and PD synovitis were graded semi-quantitatively. Serum VEGF was measured by ELISA. The results are expressed as mean ± SEM.

Results: GS and PD synovitis scores significantly correlated with DAS28(CRP) both alone and in combination ($p<0.05$). DAS28(CRP) decreased from 4.58 ± 0.27 at baseline to 3.47 ± 0.26 and 3.53 ± 0.27 at 6 and 12 weeks respectively. Similarly, PD scores decreased from 0.76 ± 0.11 at baseline to 0.71 ± 0.13 and 0.72 ± 0.12 at 6 and 12 weeks respectively. Inter-observer variability was very good ($r=0.94$). At baseline, VEGF was 719.28 ± 82.96pg/ml , and at 6 and 12 weeks post biologic therapy was 609.47 ± 75.94pg/ml and 658.82 ± 69.43pg/ml respectively. VEGF did not significantly correlate with power Doppler at any time point in ACR responders and non-responders.

Conclusion: The simplified 7 joint US score used, significantly correlated with DAS28(CRP) validating it as a useful score for assessing synovitis in inflammatory arthritis. VEGF is released in inflammatory arthritis in response to TNF-α, and has been implicated in increasing endothelial permeability and swelling and stimulating angiogenesis. Although VEGF decreased at 6 and 12 weeks post biologic therapy compared to baseline, this did not correlate with PD which is in agreement with observations made by Strunk et al[1]. This suggests dissociation between VEGF secretion and PD or a delayed effect which may become apparent at a later time point.

[1]Strunk J et al. Rheumatology (Oxford), 2004 Dec;43(12):1480-3.

Disclosure: B. Lynch, None; **J. Kitchen**, None; **U. Fearon**, None; **G. Renard**, None; **O. FitzGerald**, Abbott Immunology Pharmaceuticals, 2, Wyeth Pharmaceuticals, Abbott Immunology Pharmaceuticals, BMS, 8 ; **D. Kane**, None; **D. Veale**, Wyeth Pharmaceuticals, Schering Plough, Glaxo SmithKline, 2, Wyeth Pharmaceuticals, Schering Plough, 5, Wyeth Pharmaceuticals, Schering Plough, 8 .

1467

Evaluation of the 7-Joint Ultrasound Score (US7) by One Year Follow-up Data with Regard to Disease Duration. Sarah Ohrndorf[1], Lydia Naumann[2], Ekkehart Dietz[3], Herbert L. Kellner[4], Johannes Strunk[5], Tina Backhaus[1], Wolfgang Hartung[6], Horst Sattler[7], Gerd R. Burmester[2], Wolfgang A. Schmidt[8] and Marina Backhaus[2], [1]Charité-University Medicine Berlin, Berlin, Germany, [2]Charite University Hospital, Berlin, Germany, [3]Berlin, Germany, [4]Munchen, Germany, [5]Cologne, Germany, [6]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, Bad Abbach, Germany, [7]Bad Dürkheim, Germany, [8]Med Ctr Rheumatol Berlin Buch, Berlin, Germany

Purpose: To further examine US7 of the clinically dominant hand and foot in daily rheumatologic practice by one year follow-up data with regard to disease duration.

Methods: US7 examines clinically dominant wrist, MCP and PIP II and III, MTP II, and V joints for synovitis, tenosynovitis/paratenonitis and erosions by grey scale (GS) and power Doppler (PD) ultrasound (US).

Patients both with early (< 2 years) and long-standing (≥ 2 years) rheumatoid arthritis (RA) and psoriatic arthritis (PsA) were examined at baseline and at 3, 6 and 12 months after start or change of DMARD and/or TNF-inhibitor therapy.

CRP, ESR, DAS28 and US7 were performed.

Results: N=64 patients with disease duration (dd) < 2 years (yrs) and n=137 patients (77% women) with dd ≥ 2 yrs of RA (95%) and PsA (5%) were evaluated.

Both patient groups had an initial moderate disease activity of DAS28=4.9 (dd < 2 yrs) or DAS28=4.8 (dd > 2 yrs).

The initial mean GS and PD synovitis scores of patients with dd < 2 yrs were 7.0 and 3.3, and they had a mean level of ESR=30 mm/h and CRP=19.8 mg/l.

Patients with dd ≥ 2 years had initial higher mean GS and PD synovitis scores of 8.5 and 4.3; their mean ESR was 28 mm/h and mean CRP was 13.5 mg/l.

With DMARD (53%) or TNF inhibitor+/-DMARDs (47%), all evaluated parameters significantly decreased, except for PD tenosynovitis/paratenonitis score as well as erosion score in patients with dd < 2 yrs (see tables 1 and 2).

Conclusion: US7 is a more sensitive tool for examining arthritic patients as it is able to identify disease activity in GS- and PD-US, although patients might seem to be in similar clinical status. By that, US7 is a tool which could influence therapeutic decisions in daily rheumatologic practice. It significantly reflects the therapeutic response.

Laboratory, disease activity and US data of patients with dd < 2 yrs

	Baseline	After 3 months	After 6 months	After 12 months
Mean ESR	30.0	19.2*	19.2*	18.2*
Mean CRP	19.8	7.7*	6.3*	5.5*
Mean DAS 28	4.9	3.5*	3.4*	3.1*
Mean GS synovitis score	7.0	4.7*	4.6*	4.3*
Mean PD synovitis score	3.3	1.8*	1.5*	1.3*
Mean GS tenosynovitis / paratenonitis score	1.2	0.8*	0.7*	0.4*
Mean PD tenosynovitis / paratenonitis score	0.6	0.4	0.4	0.2
Mean erosion score	0.9	1.2	1.0	1.2

**p-value < 0.05 to baseline examination by 2-sided exact Wilcoxon test*

Table 1

Laboratory, disease activity and US data of patients with dd ≥ 2 yrs

	Baseline	After 3 months	After 6 months	After 12 months
Mean ESR	27.9	21.8*	22.1*	23.3*

Mean CRP	13.5	8.7*	6.7*	7.8*
Mean DAS 28	4.8	3.8*	3.7*	3.6*
Mean GS synovitis score	8.5	6.2*	5.5*	5.2*
Mean PD synovitis score	4.3	2.5*	2.0*	1.8*
Mean GS tenosynovitis / paratenonitis score	1.3	0.7*	0.7*	0.7*
Mean PD tenosynovitis / paratenonitis score	0.8	0.3*	0.3*	0.3*
Mean erosion score	4.2	4.0	3.9	3.8*
**p-value < 0.05 to baseline examination by 2-sided exact Wilcoxon test*				

Table 2

Disclosure: S. Ohrndorf, Abbott GmbH & Co. KG, Max-Planck-Ring 2a, 65205 Wiesbaden, Germany, 2 ; **L. Naumann**, None; **E. Dietz**, None; **H. L. Kellner**, Abbott Immunology Pharmaceuticals, 8, Abbott Immunology Pharmaceuticals, 2 ; **J. Strunk**, Abbott GmbH & Co. KG, Max-Planck-Ring 2a, 65205 Wiesbaden, Germany;, 2 ; **T. Backhaus**, None; **W. Hartung**, None; **H. Sattler**, Abbott GmbH & Co. KG, Max-Planck-Ring 2a, 65205 Wiesbaden, Germany;, 2 ; **G. R. Burmester**, None; **W. A. Schmidt**, Abbott, Actelion, Bristol Myers Squibb, Chugai, Esaote, Essex, Ibsen, Lilly, Medac, Merck (USA), Merck (Germany), Novartis, Pfizer, Roche, Wyeth , 9, Abbott, Esaote, Ibsen, Novartis , 9, Abbott, Bristol Myers Squibb, Esaote, Essex, General Electric, Medac, Novartis, Roche, Wyeth, 9 ; **M. Backhaus**, None.

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Colour Duplex Ultrasonography in the Diagnosis and Management of Giant Cell Arteritis. Giovanni Ciancio[1], Matteo Colina[1], Renato La Corte[1], Francesco De Leonardis[1], Stefania Volpinari[1], Maria Fotinidi[1], Alessandra Bortoluzzi[1], Savino Occhionorelli[2], Antonietta Vanini[3], Marcello Govoni[1] and Francesco Trotta[4], [1]Rheumatology Section, Ferrara, Italy, [2]General Surgery-University of Ferrara, Ferrara, Italy, [3]Non Invasive Vascular Diagnostic Service-S.Anna Hospital, Ferrara, Italy, [4]Rheumatology Section, Ferrara

Purpose: Though several studies have emphasized the diagnostic potentialities of color duplex sonography (CDS) in giant cell arteritis (GCA) biopsy remains the gold standard for the diagnosis. Recently it has been suggested that the dark hypoechogenic halo is strongly related to the acute phase of the disease so CDS of the temporal artery may be a useful tool in monitoring and assisting glucocorticoid tapering in patients with GCA. To date, acute phase reactants are generally used for this purpose but they are not absolute indicators of disease activity. The aim of our study was to evaluate the role of color duplex ultrasonography in diagnosis and follow-up in patients with GCA

Methods: Thirteen consecutive outpatients aged more than 50 years who presented in the last 18 months with suspected GCA were prospectively studied. All patients satisfied the American College of Rheumatology (ACR) classification criteria for GCA. Bilateral CDS examination to check for halo's thickness, ESR and CRP were performed at baseline, 2, 4 and 6 weeks after initiation of corticosteroid treatment. Temporal artery biopsy was performed in all the 13 patients and it was directed to a particular arterial segment in the cases with evidence of halo.

Results: A dark halo of variable size (0.7–2.0 mm) around the vessel lumen was evident at baseline in 10 patients (bilaterally in 7,unilaterally in 3). No CDS alterations were found in 3 patients. Biopsy did prove positive for GCA in all the 10 patients with halo and negative in the 3 patients without CDS changes. During follow-up, halo's thickness decreased progressively and returned to normal earlier than ESR and CRP. Patients without CDS changes and biopsy negative were finally diagnosed as polymyalgia rheumatica (two) and crowned dens syndrome (one).

Conclusion: According to other studies, our data confirm that CDS may be considered a very useful tool in the diagnostic assessment of GCA and follow-up. It may be useful in guiding the site for biopsy . Since it has demonstrated to be more sensitive than VES and PCR it may allow a better monitoring and tapering glucocorticoid therapy.

Disclosure: G. Ciancio, None; **M. Colina**, None; **R. La Corte**, None; **F. De Leonardis**, None; **S. Volpinari**, None; **M. Fotinidi**, None; **A. Bortoluzzi**, None; **S. Occhionorelli**, None; **A. Vanini**, None; **M. Govoni**, None; **F. Trotta**, None.

1469

Synovial Hypertrophy of Metatarsophangeal Joints Is Not Specific of Inflammatory Rheumatism. Frédérique Gandjbakhch[1], Violaine Foltz[1], Sylvie Rozenberg[1], Pierre Bourgeois[2] and Bruno Fautrel[3], [1]MD, Paris, France, [2]Rheumatology, Pierre et Marie Curie University-Paris VI, Paris, France, [3]MD, PhD, Paris, France

Purpose: Ultrasonography practice has considerably increased in the past few years to manage inflammatory rheumatism. Only few data concerns the impact of metatarsophlangeal joints examination for diagnosis of inflammatory rheumatism.

Method: We underwent a case control study performed on 14 rheumatoid arthritis (RA) patients and 13 runners. Exclusion criteria of the runners consisted in history of tender or swollen joint of the feet and hands and history of inflammatory rheumatism. Ultrasonography (US) examination of metatarsophalangeal (MTP) joints was realized by the same rheumatologist with 4 years experience in RA ultrasonography practice. MTP 1 to 5 were examined bilaterally with a My Lab70 ESAOTE equipment in grey scale and in Power Doppler (PD) mode and scored in a semiquantitative score (0-3) according to OMERACT recommandations. Synovial hyperthrophy thickness was measured in dorsal plane perpendicularly to cortical bone at the maximum synovial thickness point. Statistics analysis was performed on a SAS 9.1 software.

Results: 85% of RA patients were female, mean age was 43+/-12 years old, mean disease duration was 6+/-6 years, 78% were positive for FR, 71% were erosive on Xrays. They were all treated by DMARD and one of them were treated by Adalimumab. 50% of them had corticosteroid treatment with a mean posology of 3 mg/day. Runners were female in 46% and mean age was 37+/- 9 years. MTP B- mode Synovitis was not specific of inflammatory arthritis and was detected in most of the runners (table 1). The location of synovitis differed between RA patients and runners. Synovitis appeared mostly in MTP 1 to 3 in runners, while it affected all MTP joints in RA patients, especially MTP5. There was a statistical significant difference concerning the number of synovitis between RA patients and runners in B mode (p=0.0012) and in Doppler mode (p=0.0008). There was also a significant difference between the 2 groups concerning the total score in Bmode (p=0.0121) and in Dopler mode (p=0.0008) and concerning the synovial thickness (p=0.0024). Roc curves were undertaken to determine a cut-off for synovial thickness and total score of B-mode synovitis discrimating between RA and runners. A cut-off were respectively 16 mm for synovial thickness and 10 for Bmode score.

Percentage of patients with at least one synovitis on MTP1 to5

		S Mtp1	S Mtp2	S Mtp3	S Mtp4	S Mtp5
B mode	RA	100	100	100	78	56
	runners	100	92	84	53	8
PD mode	RA	29	23	42	35	35
	runners	7,69	0	0	0	0

Conclusion: MTP Synovitis were not specific of inflammatory rheumatism and could be detected in runners. Yet, runners MTP synovitis and RA MTP synovitis differed in thickness and B-mode score. A cut-off has been determined to distinguish them. Doppler signal was nearly insignificant in runners. This data should be taken into account to help RA diagnosis.

Disclosure: F. Gandjbakhch, None; **V. Foltz**, None; **S. Rozenberg**, None; **P. Bourgeois**, None; **B. Fautrel**, None.

ACR/ARHP Poster Session C

Miscellaneous Rheumatic Inflammatory Diseases I

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Is Familial Mediterranean Fever (FMF) Associated with Non-Alcoholic Fatty Liver Disease (NAFLD) ? Doron Rimar[1], Itzhak Rosner[1], Michael Rozenbaum[1] and Eli Zuckerman[2], [1]Bnai Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel, [2]Carmel Medical Center, Faculty of Medicine, Technion, Haifa, Israel

Purpose: FMF is a periodic febrile disease. Liver disease is not considered a part of the spectrum of clinical manifestations of FMF and only rarely such an association has been described. The purpose of this study is to describe and characterize the chronic liver disease which may be associated with FMF.

Method: 26 patients (mean age 48±4.1 years, F:M 16:10) with FMF who were referred to the Liver Unit in Carmel Medical Center for assessment of chronically abnormal liver tests were studied. Data regarding FMF and liver disease were obtained from patient medical files. Liver biopsy was performed in 19 of 26 patients, avoided in 5 (cirrhotic coagulopathy) and was not done in two patients who refused).

Results: Most patients had definite FMF (23) with mean Tel Hashomer severity score of 1.7. Age of onset of FMF was 18 ±8.2.The mean daily dose of colchicine was 1.4±0.3 mg over a mean duration of 22 years ± 8. In 15 of 23 patients there was evidence of NAFLD: 4 with "simple" steatosis, 4 with NASH (one with HBsAg+) and 7 with NASH-cirrhosis. Additional 5 patients had "cryptogenic" cirrhosis (2 with HBcAb+), 4 had chronic "cryptogenic" hepatitis and one had normal liver tissue. Only 5 patients had metabolic syndrome (4 had NASH-cirrhosis) and the mean BMI was 26 ±4.1. Congo red staining for amyloid was negative in all liver biopsies. Seven of 11 patients who underwent mutation analysis for FMF were homozygous for M694V.

Conclusion: 76% of our FMF patients with chronic abnormal liver tests had NAFLD (biopsy proven in most of them) (58%) or "cryptogenic" cirrhosis (19%), which in many patients represents the end result of unrecognized NASH. The extremely high proportion of NAFLD and cryptogenic cirrhosis in our cohort of FMF patients without overt metabolic syndrome may indicate an unappreciated novel association between FMF and NAFLD, which may be related to inflammation induced by IL-1, prolonged colchicine treatment or genetic predisposition.

Disclosure: D. Rimar, None; **I. Rosner**, None; **M. Rozenbaum**, None; **E. Zuckerman**, None.

1471

Serum Cartilage Oligometric Matrix Protein (COMP) Level Is a Marker of Disease Activity in Relapsing Polychondritis. Fernando Kemta Lekpa[1], Jean -Charles Piette[2], Sylvie Bastuji-Garin[1], VB Kraus[3], T. Stabler[4], A. Robin Poole[5], André Marini-Portugal[1] and Xavier Chevalier[6], [1]Hopital Henri Mondor, Creteil, France, [2]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [3]Duke University Medical Center, Durham, NC, [4]Duke University Medical Center, Durham, [5]McGill University, Lancaster, [6]Hopital Henri Mondor, Créteil, France

Purpose: Relapsing polychondritis (RP) is a rare and severe disease which may lead to destruction of elastic cartilages. Until now, no reliable biomarker of disease activity in RP has been available. This study was designed to measure serum levels of cartilage biomarkers during both active and inactive phases of the disease.

Method: Serum levels of cartilage oligomeric matrix protein (COMP), chondroitin sulfate 846 epitope (CS846) of proteoglycan aggrecan and collagen type II collagenase cleavage neoepitope (C2C) were measured retrospectively in 21 subjects with RP. The Wilcoxon matched-pairs signed-rank test was used for statistical comparisons of biomarker levels in active and inactive phases of RP.

Results: Table 1 shows serum biomarker levels in the active and inactive phases of RP. Only the serum level of COMP was significantly increased during disease flares (*p = 0.05*). Steroids did not alter the serum cartilage-related biomarker levels. However, during the active phase, C2C levels were significantly higher in steroid treated patients compared with non-steroid treated patients (66.7 [44.6-81.4] vs 109 [92.6-135.9], *p*=0.011).

Table 1. Serum biomarker levels in the active and inactive phases of relapsing polychondritis.

	Phase of Disease		*p value**
Biomarkers	Active phase (n=21)	Inactive phase (n=21)	Active phase vs. Inactive phase
COMP ng/ml	694.8 [446.4-754.6]	335.7 [241.8-479.3]	0.05
CS846 epitope µg/ml	0.227 [0.147-0.266]	0.189 [0.131-0.227]	0.51
C2C pmol/ml	82.5 [56.5-121.7]	95.6 [68.8-107.2]	0.49

Concentrations are expressed as median [interquartile range]

* *p values* of the Wilcoxon matched-pairs signed-rank test.

Conclusion: This study suggests that serum COMP level may be useful for monitoring disease activity of RP. Further prospective studies are required to confirm this result.

Disclosure: F. Kemta Lekpa, None; **J. -. C. Piette**, None; **S. Bastuji-Garin**, None; **V. Kraus**, None; **T. Stabler**, None; **A. R. Poole**, None; **A. Marini-Portugal**, None; **X. Chevalier**, None.

1472

Immunosuppressant Related Neurological Involvement in Behçet's Disease. Akiko Suda[1], Haruko Ideguchi[2], Mitsuhiro Takeno[1], Shigeru Ohno[2] and Yoshiaki Ishigatsubo[1], [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Yokohama City University Medical Center, Yokohama, Japan

Purpose: Immunosuppressants such as cyclosporin A (CsA) are efficient for ocular lesions in Behçet's disease (BD), though the agents often cause neurological involvement, which is hardly distinguishable from neuro- Behçet's disease in a natural history.

Methods: Based on clinical charts, clinical features, therapeutic agents, outcomes and other backgrounds were retrospectively reviewed in a total of 412 BD patients who were under care at two Yokohama City University Hospitals from 1991 to 2007.

Results: Fifty-four (13.1%, 21 female, 33 male) of 412 patients had neurological symptoms. Of them, 24 patients had received CsA (20 patients) or Tac (4 patients) before onset of neurological manifestations. While the frequency of neurological symptoms was 26% (24 patients) in 93 patients who had previous medication with CsA or Tac, 9% (30 patients) of 319 patients had never received the immunosuppressive agents ($p<0.001$). No association was found between blood CsA levels and neurological manifestations. Although most of the patients receiving the immunosuppressive agents had uveitis, the incidence of neurological involvement was no different than in the other patients with ocular lesions. There was no association of development of the immunosuppressant related neurological with other

clinical backgrounds such as age, gender, disease duration and HLA-B typing. While 20 of 24 patients had meningitis and/or brainstem encephalitis, which were categorized as the acute type, three patients had a chronic progressive course. Discontinuation of the agents led to remission in 4 patients, and additional corticosteroid therapy resulted in remission in another 9 patients.Re-administration of CsA caused another neurological attack in one patient, whereas 6 patients relapsed acute type episode without these agents.

Conclusion: Our study revealed that treatment with CsA and Tac significantly increased the frequency of neurological manifestations in BD, though the immunosuppressants rarely cause CNS complication in other diseases. Latent CNS lesions may be responsible for the drug related neurological involvement in BD.

Disclosure: A. Suda, None; **H. Ideguchi**, None; **M. Takeno**, None; **S. Ohno**, None; **Y. Ishigatsubo**, None.

1473

Subgroup Analyses Demonstrate Consistent Response to Rilonacept (IL-1 Trap) in Patients with Cryopyrin-Associated Periodic Syndromes (CAPS). Hal M. Hoffman[1], Kristen M. Scheble[2], Douglas Nadler[3] and Steven P. Weinstein[4], [1]University of California at San Deigo, La Jolla, CA, [2]Regeneron Pharmaceuticals, Tarrytown,, NY, [3]Regeneron Pharmaceuticals, Tarrytown,, [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Purpose: The IL-1 inhibitor rilonacept (IL-1 Trap) 160 mg/week effectively controlled symptoms in 47 patients with CAPS (44 with familial cold auto-inflammatory syndrome [FCAS] and 3 with Muckle-Wells syndrome [MWS]) in a randomized, double-blind, placebo-controlled trial. An analysis of correlations between baseline patient/disease characteristics and treatment response was undertaken to determine whether any factor influenced response to rilonacept in this study.

Method: Forty-seven CAPS patients were randomized to 6 weeks of treatment with rilonacept 160 mg/week SC (after a loading dose of 320 mg) or placebo. Primary end point was change in key symptom score (KSS), a mean of patient-reported severity score for the 5 key CAPS symptoms (rash, fever/chills, eye redness/pain, joint pain, fatigue), between baseline and week 6, assessed using the Daily Health Assessment Form (DHAF). For the current analysis, change in KSS was compared in different subgroups of patients receiving rilonacept or placebo. Linear regression analysis was used to evaluate the impact of continuous baseline variables (age, weight, height, C-reactive protein [CRP] or serum amyloid A [SAA] level at baseline) on baseline KSS and change in KSS at week 6. Generalized linear modeling was used to undertake correlation analysis for categorical variables: region of residence, gender, presence of high CRP (>20 mg/L) or SAA (>100 mg/L) level at baseline or L353P mutation.

Results: Response to rilonacept was consistent and significant vs placebo in all patient subgroups (Table) analyzed by age, gender, CAPS diagnosis (FCAS or MWS) or baseline disease severity. No correlation was found between mean KSS at baseline and region of residence, age, weight, height, gender, CRP or SAA level at baseline, presence of high CRP (>20 mg/dL) or SAA (>100 mg/dL) level or L353P mutation (P>0.2 for all), nor was there any correlation between any baseline factor and the response to treatment at week 6 in the whole cohort (n=47) or rilonacept-treated patients (n=23) [all non-significant]. The response in patients with MWS (n=3) was similar to that in patients with FCAS.

Conclusion: In a representative population of US CAPS patients, response to rilonacept was consistent in all patients and not influenced by baseline disease or patient characteristics.

Subgroups	**Placebo**		**Rilonacept**		**P-value**
	N	**Change from baseline in KSS**	**N**	**Change from baseline in KSS**	
All patients	24	–0.3	23	–2.6	<0.0001
Males	8	–0.3	8	–2.6	0.002
Females	16	–0.3	15	–2.6	<0.0001
Age 51 years (mean)	14	–0.3	10	–2.0	<0.0001
Age < 51 years (mean)	10	–0.4	13	–3.1	0.0006

Baseline KSS <2.4 (mean)	14	–0.2	10	–1.1	<0.0001
Baseline KSS □2.4 (mean)	10	–0.5	13	–3.8	<0.0001

Disclosure: H. M. Hoffman, Regeneron Pharmaceuticals, 5 ; **K. M. Scheble**, Regeneron Pharmaceuticals, 3 ; **D. Nadler**, Regeneron Pharmaceuticals, 3 ; **S. P. Weinstein**, Regeneron Pharmaceuticals, Inc., 1, Regeneron Pharmaceuticals, Inc., 3 .

1474

The IFN-Inducible Gene Signature Is Elevated in SCLE and DLE and Correlates with CLASI Score. Inbal Braunstein, Rachel Klein, Misha Rosenbach, Joyce Okawa and Victoria P. Werth, University of Pennsylvania, Philadelphia, PA

Purpose: To study a set of five interferon (IFN)-inducible genes (LYGE, OAS1, OASL, MX1 and ISG15) in the blood of patients with different subsets of cutaneous lupus erythematosus (CLE) and to correlate expression levels with clinical activity and levels of IFN-inducible chemokines in the skin. Prior studies in SLE show a nonsignificant increase in IFN-inducible gene expression in patients with a history of malar or discoid rash (Feng et al, A&R 2006).

Method: Peripheral blood was obtained from 10 healthy controls and 33 patients with CLE (12 SCLE, 14 DLE, 4 TLE, 3 ACLE). Three subjects (1 SCLE, 2 DLE) were enrolled in a clinical study of lenalidomide for CLE. Total RNA was extracted and reverse transcribed into complimentary DNA. Gene expression levels were measured by real time PCR and normalized to GAPDH. An IFN-score was calculated using published methods. Disease activity was assessed with the Cutaneous Lupus Area and Severity Index (CLASI). Indirect immunohistochemical staining was performed on formalin-fixed, paraffin-embedded skin biopsy samples using anti-human CXCL10 polyclonal antibody. Staining was quantified on 6 high power images (200x) using ImagePro software.

Results: SCLE and DLE patients had significantly elevated IFN-scores as compared to healthy controls ($p<0.05$). The IFN-score correlated with CLASI scores when all 33 patients were analyzed (Spearman $r = 0.5553$, $p = 0.0008$). SCLE subjects who were actively smoking had higher IFN-scores (Spearmans $r = 0.8193$, $p = 0.0011$). The IFN-score did not correlate with expression of CXCL10 in the skin. Three subjects in an ongoing clinical study of lenalidomide for CLE exhibited a dramatic decrease in the IFN-score after two weeks of therapy. (Average baseline IFN score ± SEM: 29.53±1.39, average week two IFN score ± SEM:7.32 ± 2.42). Two of these subjects had concomitant clinical improvement. Levels of CXCL10 staining also decreased from baseline to week 6 in the study subjects, however one subject who did not have clinical improvement with treatment had a robust increase in CXCL10 expression at week 2.

Conclusion: The 5 IFN- inducible genes that are highly expressed in patients with SLE are also highly elevated in patients with DLE and SCLE as compared to healthy controls. These findings point towards a shared pathogenesis between SLE and some subtypes of CLE. In addition this gene signature correlates with CLASI scores, suggesting a potential biomarker of disease activity. We did not find a correlation between IFN-score and IFN-inducible chemokine expression in the skin. This may reflect the variability in the expression of CXCL10 in the skin, and/or suggest a complex relationship between levels of IFN-inducible genes and levels of IFN-inducible chemokines in the skin. Further study is needed to understand the role of elevated IFN-inducible gene expression in CLE.

Disclosure: I. Braunstein, None; **R. Klein**, None; **M. Rosenbach**, None; **J. Okawa**, None; **V. P. Werth**, None.

1475

Correlates of Clinical Response in the Circulating Leukocyte Profile of Subjects On Lenalidomide for Cutaneous Lupus Erythematosus. Inbal Braunstein[1], Noah G. Goodman[2], Misha Rosenbach[1], Joyce Okawa[1], Eline T. Luning Prak[2] and Victoria P. Werth[1], [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia

Purpose: Lenalidomide has been shown to be a potential alternative or adjunctive treatment for patients with severe generalized DLE that is refractory to standard therapies (Shah et al, 2009). Lenalidomide is a thalidomide analogue with potentially fewer side effects than thalidomide. Here we investigated the use of lenalidomide in a larger group of patients with different subtypes of treatment refractory CLE (DLE, SCLE and TLE).

Method: Five subjects with refractory CLE were treated with lenalidomide in an off-label trial using 5 or 10 mg of lenalidomide daily. Immunophenotyping was performed on fresh whole blood samples at baseline and at weeks 2 and 6 of treatment. Antibodies directed against cell surface markers of Dendritic Cells, T-cells, B-cells, regulatory T-cells (Tregs), Cutaneous Lymphocyte Antigen, Natural Killer cells, and T-cell activation markers were used.

Results: Four of the five subjects demonstrated skin improvement. One subject with skin improvement developed worsening arthralgias and new-onset proteinuria and was withdrawn from the study. Here we report trends in the circulating leukocyte subsets in four subjects with skin improvement and unique features of the leukocyte profile in the subject who developed arthralgias and proteinuria. In the subjects showing skin improvement the following trends were observed: decreased percentage of plasmacytoid dendritic cells (pDCs) (mean±SEM: -74% ± 7%) and a mean 4-fold increase in Treg percentage (mean±SEM: 4.1-fold increase ± 1.8-fold increase). Results for the non-responding subject did not follow these trends. Four subjects with available data showed an increase in CD4+ CD25+ HLA-DR+ percentage. This increase was more marked in the three who had responded clinically (mean±SEM: 3-fold increase ± 0.5-fold increase in three responders vs. 0.9-fold increase in the nonresponder). The subject who developed arthralgias and new-onset proteinuria had elevated numbers of resting memory B cells at baseline (~14%), and a robust and unique increase in activated pDCs at week 6.

Conclusion: Here we see evidence that increases in circulating Tregs and T-cell activation markers, and decreases in circulating pDCs may serve as biomarkers of clinical response to lenalidomide in some patients with CLE. Furthermore, these preliminary data suggest that lenalidomide activates T-cells and may activate pDCs, potentially triggering systemic disease in a subset of susceptible CLE patients.

Disclosure: I. Braunstein, None; **N. G. Goodman**, None; **M. Rosenbach**, None; **J. Okawa**, None; **E. T. Luning Prak**, None; **V. P. Werth**, None.

1476

Anti-Inflammatory Effect of Alpha-2 Adrenergic Agonists On Endothelial Cells. Ada Herrera-García[1], María-Jesús Domínguez-Luis[1], Ana Díaz-Martín[1], Maria Teresa Arce-Franco[1], Manuel Feria-Rodríguez Sr.[2] and Federico Diaz-Gonzalez[1], [1]Hospital Universitario de Canarias, Tenerife, Spain, [2]Faculty of Medicine, Tenerife, Spain

Purpose: Two stress pathways, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system regulate the immune response through the release of corticosteroids and norepinephrine, respectively. Norepinephrine recognizes adrenergic receptors (alpha and beta1) expressed in the surface of cells involved in the inflammatory response. Our group has observed that alpha 2 adrenergic agonists are able to modulate the inflammatory response in animal models of inflammation. However, the mechanism through which these compounds reduce the inflammatory response has not been clarified. OBJECTIVES: To study the potential anti-inflammatory effect of alpha$_2$ adrenergic agonists in human neutrophils and endothelial cells.

Method: Human neutrophils were isolated from peripheral blood of normal donors and incubated at 37ºC for 20´ in medium alone or in the presence of the alpha 2 agonists, xylazine or UK14.304 and/or the alpha2 antagonist, RX821002. Human umbilical venous endothelial cells (HUVEC) isolated from donors were activated with TNF- alpha (20ng/ml) for 6-12h in medium alone, in the presence of one of the alpha2 agonists and/or RX821002. The effect of xylazine and UK14.304 on the basal expression of VCAM-1, ICAM-1 in HUVEC, was assessed by flow cytometry analysis. The strength of endothelial intercellular junctions was analyzed by VE-Cadherin staining and confocal microscopy. Neutrophil migration capability through activated endothelium was assessed by transwell assay (5µm) where IL-8 was the chemotactic factor. Variation in the L-Selectin and CD11b expression in neutrophis activated with TNF-alpha (20ng/ml, 20min) in basal conditions, in presence and absence of Xilazine and UK14.304 were assessed by flow cytometry. Wilcoxon test ($p<0.05$) was used to evaluate the statistical significance.

Results: Both alpha$_2$ adrenergic agonists prevent the variations in L-selectin and CD11b basal expression in a doses-dependent manner in human neutrophils activated with TNF- alpha. In activated HUVEC, the presence of xylazine significantly reduced the up-regulation of ICAM-1 in a doses-dependent manner, with a maximum of 0.8 microM ($p<0.01$). The basal migration of human neutrophils through activated HUVEC was decreased up to 40±8% in presence of UK14.304. This effect was reverted by RX821002. The endothelial intercellular surface positive for VE-Cadherin staining was increased in a 50% by UK14.308 respect to the basal.

Conclusion: The alpha$_2$ adrenergic agonists are able to modulate the inflammatory response at endothelium level. These compounds cause a reduction in the neutrophil movement across the endothelial barrier. This finding supports the endothelium as a therapeutic target for developing new anti-inflammatory agents potentially useful for rheumatic diseases.

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Evaluation of Lasting High Levels of CRP Among the Patients with Metabolic Syndrome. Osamu Saiki[1], Makihiko Kuhara[1] and Hiroshi Uda[2], [1]Osaka Prefecture University, Habikino, Japan, [2]Sakai Onshinkai Hospital, Sakai, Japan

Purpose: "Low grade" systemic inflammation is very common findings in patients with metabolic syndrome (MetS). The elevation of CRP levels in these patients is one of causes of several cardiac and metabolic diseases. However, the elevation of CRP is limited (usually less than 10mg/L). Among these patients, we found several patients who presented high levels of CRP without significant clinical symptom of inflammatory diseases for a long time.

The main focus of present study is to determine whether the lasting high levels of CRP is due to MetS or to the other inflammatory diseases, and also to determine whether the treatment for the elevated CRP levels is necessary in these patients.

Method: The patients who met the Japanese criteria for MetS (n = 256) were assessed. Determination of CRP level was mainly based on a high sensitivity enzyme-linked immunosorbent assay. Carotid plaques were evaluated by ultrasound of cervical artery. The abdominal fat distribution was assessed by computed tomography and the scan was performed at the abdominal level. Some patients with high levels of CRP were treated with anti-inflammatory drugs including methotrexate (MTX).

Results: Among 256 patients with MetS, we found eight patients who showed high levels of CRP (40~10mg/L) for more than 5 years. In these patients, the levels of CRP have not changed significantly and are between 40 and 10 mg/L throughout the observation. The levels of serum amyloid A, fibrinogen, and CH50 were also elevated. In the rest of the patients, the levels of CRP were less than 10 mg/L as reported elsewhere. These eight patients have not shown subfever, cough, or other clinical symptoms characteristics for inflammatory diseases. Indeed, no patients have swollen joint or radiographic bone change, but three out of eight patients complained moderate arthralgia of large joint such as knee, shoulder or hip. The levels of rheumatoid factor and anti-CCP antibody were within normal limits and these patients have not satisfied any criteria of inflammatory diseases such as rheumatoid arthritis or collagen disease. Five patients received MTX for more than 1 year but the levels of CRP or the clinical symptom did not improved. In all eight patients, the area of visceral fat was more than 200cm^2. However, the other patients of visceral fat over 200cm^2 presented low levels of CRP. The eight patients showed insulin resistance as was seen in other patients. Ultrasound study of carotid plaques showed no differences between patients of high CRP levels and those of low CRP levels.

Conclusion: There are a series of patients who show high levels of CRP for a long time without clinical symptoms of inflammatory diseases. High levels of CRP merely cannot explain by visceral fat area, insulin resistance, or carotid plaques. MTX treatment was not effective for those patients and it is necessary to clarify the mechanism of elevation of CRP levels and how we take care of these patients.

Disclosure: O. Saiki, None; **M. Kuhara**, None; **H. Uda**, None.

1478

The Genetics and Clinical Presentation of a Novel TRAPS Mutation. Rachel Glaser, Anna Simon, John G. Ryan, Richard M. Siegel and Daniel L. Kastner, National Institutes of Health, Bethesda, MD

Background: The TNF receptor associated periodic syndrome (TRAPS) is an autoinflammatory disorder characterized by recurrent febrile episodes caused by autosomal dominant mutations of *TNFRSF1A*. TRAPS attacks are distinguished from other periodic fever syndromes by their prolonged duration of attacks, and association with abdominal pain, pleuritis, arthritis, and a centrifugally migrating myalgia and rash.

Purpose: To investigate the genetics, protein expression, and clinical phenotype of a novel mutation in *TNFRSF1A*.

Methods: The index patient was identified as having suspected TRAPS based on his clinical presentation. Data including demographics, flare characteristics, laboratory findings, and treatment were obtained from family members with symptoms consistent with TRAPS. Sequencing of *TNFRSF1A* was performed. Western blot analysis of whole cell lysates from peripheral blood mononuclear cells (PBMCs) of two of the patients was performed.

Results: We identified six affected family members in three generations (see Figure 1). Western blot analysis demonstrated intracellular accumulation of the TNFR1 protein, similar to that seen in other known *TNFRSF1A* mutations. Genetic analysis of the *TNFRSF1A* gene confirmed the presence of a C52G mutation in the 3 symptomatic family members tested. An asymptomatic first degree relative did not carry the mutation. This mutation has not been previously described. The clinical phenotype of the C52G mutation includes fever of 1-4 weeks duration, abdominal pain, diarrhea, and myalgia. .Rash was present in a single patient. Ocular symptoms, oral ulcers, sore throat, pleurisy, and arthralgia were absent. Frequency and intensity of attacks were most severe in the index patient. Inflammatory markers and acute phase reactants were elevated during times of flare with subsequent normalization during periods of remission in the patient for whom data was available.

Conclusion: The novel C52G mutation in *TNFRSF1A* is associated with a phenotype typical of TRAPS and behaves similarly to other cysteine mutations at the protein level, suggesting a trafficking defect with accumulation of the mutant protein in the endoplasmic reticulum. The observed differences in severity of attacks amongst the identified patients may indicate a variable penetrance of this mutation. Western blot analysis of PBMCs is consistent with the accumulation of TNFR1 seen in patients with other severe structural mutations. Exploration of the specificity of Western blot for diagnosis may be of clinical interest.

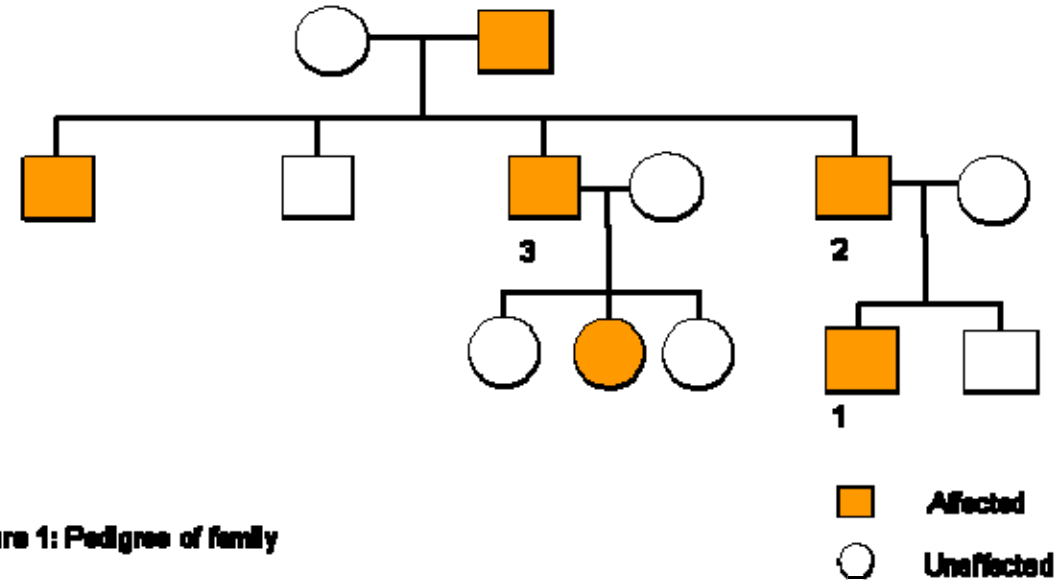

Figure 1: Pedigree of family

Disclosure: R. Glaser, None; **A. Simon**, None; **J. G. Ryan**, None; **R. M. Siegel**, None; **D. L. Kastner**, National Institutes of Health, 9 .

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Are Azathioprine, Cyclophosphamide and Chlorambucil Effective for the Treatment of NON Infectious Autoimmune Uveitis? A Systematic Literature Review. Esperanza Pato[1], Ana M. Ortiz[2], Miguel Abad[3], Loreto Carmona[4], Estibaliz Loza[4], Jesús Maese[4], Santiago Muñoz-Fernández[5] and Felix Francisco[6], [1]Hospital Clínico San Carlos, Madrid, Spain, [2]Hospital de la Princesa, Madrid, Spain, [3]Caceres, Spain, [4]Fundación Española de Reumatología, Madrid, Spain, [5]Madrid, Spain, [6]Rheumatology Section, Hospital Doctor Negrin, Las Palmas de Gran Canaria, Spain

Non infectious autoinmune uveitis (NIAU) might develop a severe course with poor visual prognosis if an adequate control of the disease is not achieved. The treatment of autoimmune uveitis are corticosteroids and immunossupressive agents (IS). Azathioprine (AZA), cylophospamide (CY) and chlorambucil (CB), are IS used for the treatment of these uveitis.

Purpose: To systematically review the published evidence regarding the efficacy of AZA, CY and CB in NIAU.

Method: Systematic review of studies retrieved by a sensitive search strategy in Medline, Embase and Cochrane Library, up to October 2007. Randomized controlled trials, observational studies and case series were included. Selection criteria: population: patients with NIAU (intermediate, posterior and panuveitis); intervention: studies had to test cyclosporine A, tacrolimus, sirolimus, methotrexate, mycophenolate

mofetil, AZA CY and CB; outcomes: visual acuity, Tyndall, vitreous haze, retinal vasculitis, macular edema, pars planitis and adverse events. Three reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently and collected the data by using *ad hoc* standard forms. One of them also graded the quality of the selected studies using a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update.

Results: A total of 128 articles were studied in detail, of which 39 were studies of NIAU with AZA, CY or CB. 13 studies were excluded (literature review, combined treatment), and 26 were included (2 randomized controlled trials, 1 clinical trial, 5 prospective studies,18 retrospective case series). A total of 443 patients with NIAU were analyzed (associated with Beçhet disease, Vogt-Koyanagi-Harada, serpiginous choroiditis, sympathetic ophthalmia and other diagnosis). in spite of the great variability regarding the study design, study samples, treatment duration and outcomes, most patients on AZA, CY or CB showed an stabilization or improvement in the visual outcomes. Minor adverse events were reported.

Conclusion: Treatment with AZA is effective and safe in the treatment of patients with Behçet associated uveitis (level of evidence 1A, grade of recommendation A), and is effective and safe for the treatment of NIAU (level of evidence 4, grade of recommendation C).

Treatment with CY and CB are effective and safe in the treatment of NIAU (level of evidence 4, grade of recommendation C).

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Effect of Infliximab On the Treatment of Refractory Posterior Uveitis After Withdrawal of Infusions Due to Remission. Mª Victoria Hernández[1], Juan José Molina[2], Gerard Espinosa[3], Virginia Ruíz-Esquide[1], José A. Gómez-Puerta[1], Josefa Martin[1], Alfredo Adán[2], Ricard Cervera[3], Juan D. Cañete[1] and Raimon Sanmartí[1], [1]Arthritis Unit. Rheumatology Department. Hospital Clínic, Barcelona, Spain, [2]Ophthalmology Department. Hospital Clínic, Barcelona, Spain, [3]Autoimmune Diseases Department. Hospital Clinic, Barcelona, Spain

Purpose: Although efficacy of infliximab (INF) therapy has been demonstrated in some cases of refractory posterior uveitis, it is not established how long treatment should be administered once remission has been achieved and when it should be discontinued. Our objective was to determine the efficacy of INF treatment and outcomes in patients with refractory posterior uveitis after withdrawal of infusions

Method: : 17 patients with posterior uveitis refractory to immunosuppressive drugs (IMS) and/or oral glucocorticoids (GC) were treated with INF (at a dose of 5 mg/kg/iv at 0, 2, 6 and every 8 weeks thereafter), for a minimum of 12 months, until complete remission was achieved. In those patients that showed a good response to INF, therapy with IMS and GC was progressively discontinued. When remission was achieved and maintained during at least six months, INF was discontinued and patients were subsequently evaluated monthly. The main outcome measures were: intraocular inflammation (assessed using the binocular indirect ophthalmoscopy score), best corrected visual acuity (BCVA), and foveal thickness measured by optic coherence tomography (OCT)

Results: Seven out of 17 patients achieve remission and therapy with IMS, GC and INF were discontinued in a progressive form. Of the seven patients, four were female; mean age was 31 ± 5.4 years (range 25-38) and the mean follow-up after INF discontinuation was 8.7 ± 5.2 months (range 4-18). Four patients had posterior uveitis associated with Behçet disease, 2 diffuse subretinal fibrosis syndrome and 1 idiopathic posterior uveitis. Mean INF treatment was 13 infusions (range 9-18). Four out of 7 patients (57.2%) remained in complete remission with no relapses during the follow-up, and are currently without therapy. BCVA was stable in 10 eyes and deteriorated in three. The OCT showed worsening in the macular edema in the three patients with reactivation.

Conclusion: INF is an efficient long-term treatment of refractory posterior uveitis. Repeated infusions are required to maintain long-term remission, which may be sustained, leading to drug discontinuation in a significant percentage of patients.

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Dysfunctional Chemotaxis in Familial Mediterranean Fever. Nona T. Colburn[1], Jae Jin Chae[2], Kristina Zaal[2], James Balow Jr.[2], John McManigle[3], Ivona Aksentijevich[2], Hong-Wei Sun[4], Beverly K. Barham[2] and Daniel L. Kastner[2], [1]National Institutes of Health, Bethesda, MD, [2]NIAMS/NIH, Bethesda, MD, [3]Durham, NC, [4]NIH | NIAMS, Bethesda, MD

Purpose: Familial Mediterranean fever (FMF) is a heritable autoinflammatory disease characterized by substantial neutrophil influx at sites of serosal and synovial involvement. Inflammatory attacks are usually prevented by prophylaxis with colchicine, a microtubule inhibitor. Pyrin, the FMF protein, colocalizes with microtubules and may impact leukocyte cytoskeletal functions such as adhesion and migration. We therefore sought to further investigate leukocyte migration in FMF.

Method: Peripheral blood samples were obtained from 25 treated patients, 10 untreated patients, and 16 controls. Subsets of patients were studied in several assays. Mononuclear cells were stimulated for 24 hours with TLR ligands 2, 4, 5, 7, and 9. Chemokines produced from cultured supernatants and from serum samples were evaluated with the Luminex immunoassay. Analysis of gene expression sequences with the Affymetrix system was utilized in 8-paired patient samples who underwent colchicine withdrawal. Chemotaxis assays included a transwell system and a live imaging protocol with both patient granulocytes and the neutrophil-like PLB cell line transfected with V726A, M680I, and M694V pyrin mutations, stimulated to various chemoattractants, including MIP-1 alpha, IL-8 and fMLP.

Results: Microarray analysis revealed a “chemotactic signature” induced by colchicine withdrawal with upregulation of major chemotactic genes including CRK and Integrin beta-1, and downregulation of genes involving chemokine receptors and cell adhesion molecules such as CCR 7 and CXCR3. Moreover, neutrophil activation was increased, as seen with the downregulation of the L-selectin marker, CD 62L. Asymptomatic FMF patients on colchicine showed elevated serum levels of the chemokines, MIP-1 alpha and beta, as compared to controls. In addition, mononuclear cells from treated patients stimulated ex-vivo, suggest a role for TLR4, 5, and 9 in the modulation of chemokines, specifically MIP-1 alpha and beta. Patients off colchicine demonstrated significant hyperresponsive cell movement compared with treated patients and controls, although such movement was found to be random (chemokinetic) and less directed (chemotactic) when visualized. By transwell analysis of the transfected neutrophil-like PLB cell line hypermobility was more apparent with the V726A mutation.

Conclusion: A cascade of intracellular events involving chemokine signaling can impact leukocyte migration in FMF. This study has focused on determining the extent to which these effects represent the underlying pathophysiology of FMF, independent of colchicine.

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Improved Health-Related Quality of Life in Patients with Cryopyrin-Associated Periodic Fever Syndrome (CAPS) After Treatment with Canakinumab (Ilaris) – A Fully Human Anti-IL-1beta Monoclonal Antibody. H.J. Lachmann[1], I. Koné-Paut[2], J. Kuemmerle-Deschner[3], K. Leslie[4], E. Hachulla[5], P. Quartier[6], A. Ferreira[7], N. Patel[8], K. Lheritier[7], R. Preiss[8] and P.N. Hawkins[1], [1]National Amyloidosis Centre, UCL Medical School, London, United Kingdom, [2]Hopital, Kremlin Bicetre, Le Kremlin Bicetre, France, [3]Pediatric Rheumatology, Universitätsklinik, Tübingen, Germany, [4]UCSF, School of Medicine, San Francisco, CA, [5]Hopital Claude Huriez, Lille Cedex, France, [6]Unité d'Immunologie, Hopital Necker-Enfants Malades, Paris, France, [7]Novartis, Basel, Switzerland, [8]Novartis, East Hanover, NJ

Background: The direct impact of CAPS on patients' well-being is often underestimated due to limited available data on patients' perception of the disease. In the 48 weeks pivotal Phase III study with canakinumab in CAPS, health reported quality of life (HRQoL) was assessed as an exploratory endpoint at baseline and during treatment using a variety of patient reported outcomes to evaluate the direct impact of the disease on patients' well-being and the improvements observed following treatment with canakinumab.

Purpose: To evaluate the improvement in HRQoL in CAPS patients during treatment with canakinumab.

Methods: In this 3-part study patients received canakinumab 150 mg s.c. or 2 mg/kg s.c. (body weight ≤40 kg) every 8 weeks. HRQoL was assessed in adults using the following domains: general mental and physical health (SF-36®), fatigue (FACIT-Fatigue®) and functional disability (HAQ-DI®).

Results: Baseline scores for general mental and physical health (SF-36®) and fatigue (FACIT-Fatigue®) were considerably lower than those expected in the general population and demonstrates the significant impact that CAPS has on patients' well-being (Table). Following the first canakinumab dose, SF-36 and FACIT-Fatigue® scores improved to the levels expected in the general population. An improvement in functional disability was observed as shown by HAQ-DI scores. HRQoL scores at the end of this 1 year study (48 weeks) were comparable

to those observed following the first injection, and suggest that patient's well-being is improved to levels seen in the general population without chronic disease.

Conclusion: CAPS has a significant impact in patient's well being due to the physical effects of systemic inflammation mediated by direct neurotrophic effects of IL-1beta leading to the deleterious effects on patients physical and mental health. Canakinumab every 8 weeks provides improvement in quality of life, to that of the general population, across a variety of standardized measurement tools addressing physical and emotional well-being as well as fatigue.

Table: Comparison of HRQoL scores of CAPS patients treated with canakinumab

Component	General US population Mean (SD)	n	Baseline Mean (SD)	End of study (48 weeks) Mean (SD)	Change from baseline Mean (SD)
SF-36 (0-100)					
Physical Component	50.0 (10.0)[1]	22	40.4 (9.3)	48.5 (12.6)	8.2 (9.4)
Mental Component	50.0 (10.0)[1]	22	42.6 (12.4)	48.9 (12.4)	6.3 (12.4)
- Physical Functioning	84.2 (23.3)[1]	23	74.1 (28.8)	82.6 (25.7)	8.5 (23.0)
- Role-Physical	80.9 (34.0)[1]	26	50.0 (48.0)	76.0 (40.3)	26.0 (47.7)
- Bodily Pain	75.2 (23.7)[1]	25	48.0 (23.0)	76.5 (30.2)	28.6 (31.8)
- General Health	71.9 (20.3)[1]	25	46.4 (17.2)	60.8 (23.2)	14.4 (17.6)
- Vitality	60.9 (20.9)[1]	26	42.5 (22.2)	60.0 (28.5)	17.5 (30.5)
- Social Functioning	83.3 (22.7)[1]	25	67.5 (29.1)	77.5 (33.5)	10.0 (36.3)
- Role-Emotional	81.3 (33.0)[1]	25	58.7 (46.4)	73.3 (41.9)	14.7 (46.2)
- Mental Health	74.7 (18.1)[1]	26	64.5 (21.5)	74.2 (21.7)	9.7 (20.5)
FACIT-Fatigue®	43.6 (9.4)[2]	26	27.4 (13.0)	39.5 (14.7)	12.2 (16.9)
HAQ-DI (0-3)	Not Available	26	0.41 (0.6)	0.27 (0.5)	-0.14 (0.4)

n = number of patients who had both the baseline and end of study values

[1]Adapted from Ware J, Kosinski, M., Keller, SK. . SF-36® Physical and Mental Health Summary Scales: A User's Manual. *Boston, MA: The Health Institute.* 1994

[2]Adapted from Cella D, Lai J, Chang C, Peterman A, Slavin M. Cancer 2002;94:528-38

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Effect of Canakinumab (Ilaris, a Fully Human Anti-IL-1 beta Monoclonal Antibody) On the Health-Related Quality of Life (HRQoL) in Cryopyrin-Associated Periodic Syndrome (CAPS) Patients. J.B. Kuemmerle-Deschner[1], J. Hoyer[2], E. Hachulla[3], R. Chaturvedi[4], N. Blank[5], F. Hiepe[6], A. Ferreira[7], S. D. Felix[7], A.M. Wright[7], T. Jung[7] and C. Rordorf[7], [1]Universitätsklinikum Tübingen, Klinik fuer Kinder- und Jugendmedizin, Tübingen, Germany, [2]Univ.-Klinikum Gießen und Marburg, Marburg, Germany, [3]Hôpital Claude Huriez CHRU, Lille, France, [4]Pushpawati Singhania Research Institute, New Delhi, India, [5]Medizinische Klinik 5, Universitätsklinikum Heidelberg, Heidelberg, Germany, [6]Charité- Universitätsmedizin Berlin, Berlin, Germany, [7]Novartis, Basel, Switzerland

Purpose: Patient's QoL is markedly affected by the persistent disease features of CAPS. Canakinumab treats the underlying causes of CAPS by potent, rapid, and selective blockade of IL-1β. This Phase II, open-label study evaluated the improvement in the HRQoL following canakinumab treatment in CAPS patients.

Method: The study was conducted in CAPS patients with confirmed NLRP3 mutation. Patients received a single dose of canakinumab 150 mg or 2 mg/kg s.c. (patients ≤16 yrs) with redosing upon each relapse. HRQoL of adult patients were assessed at baseline and during treatment by patient reported outcomes for fatigue (FACIT-Fatigue©), general mental and physical health (SF-36©), and functional disability (HAQ-DI©). Increases from baseline FACIT-Fatigue and SF-36 scores, and decrease from baseline HAQ-DI scores indicate improvement in HRQoL.

Results: The mean baseline scores for FACIT-Fatigue (31.22) and SF-36 mental (43.02) and physical (37.98) component scores were significantly lower than scores expected in the general population (*i.e.*, 43.6 for FACIT-Fatigue and 50 for both SF-36 component scores, respectively)[1,2], confirming the detrimental impact CAPS has on patient's quality of life. HAQ-DI baseline mean score was 0.42 on a scale of 0 (no disability) to 3 (maximum disability). Ten out of 18 patients had functional disability as assessed by HAQ-DI (range 0.13 to 2.5). Canakinumab patients improved their HRQoL scores following a single injection (See Table). Improvements were seen as early as one day after the first single dose and maintained for 5 weeks. FACIT-Fatigue (45.6) as well as SF-36 mental (54.84) and physical component scores (49.52) reached levels comparable to average scores of the general population. Similarly, HAQ-DI improved by 0.2 units 5 weeks after canakinumab administration. HRQoL decreased again prior to canakinumab re-dosing when patients started experiencing a disease flare.

Conclusion: Canakinumab improved the HRQoL in CAPS patients assessed by FACIT- Fatigue, SF-36 mental and physical scores to a level of average scores of the general population and improved functional disability index.

Table. Summary of FACIT-Fatigue, SF-36 and HAQ-DI summary scores by time following a single dose of canakinumab (1st period)

Dose regimen	Time-point		FACIT-Fatigue 0-52		SF-36 (MCS) 0-100		SF-36 (PCS) 0-100		HAQ-DI 0-3	
		Average general population score[1,2] (SD)	43.6 (9.4)		50* (10)		50* (10)		NA	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Canakinumab 150mg sc	Baseline		18	31.22 (13.41)	18	43.02 (10.39)	18	37.98 (11.14)	18	0.42 (0.79)
	1 day post-dose		19	35.63 (15.31)	15	41.02 (11.22)	15	41.20 (12.69)	19	0.36 (0.72)
	1 week post-dose		19	45.05 (11.01)	18	47.75 (8.46)	18	45.86 (9.49)	19	0.19 (0.53)
	5 weeks post-dose		15	45.60 (9.50)	14	54.84 (7.25)	14	49.52 (8.36)	15	0.23 (0.58)
	Prior re-dose		17	36.68 (12.56)	17	48.40 (9.43)	17	41.74 (13.48)	17	0.34 (0.62)

MCS, Mental component; PCS, Physical component; NA, Not available; *Scores were normalized so that a score of 50 represented an average US person with no chronic disease; The 1st period includes data from inclusion when patient was flaring to the first relapse ; Prior re-dose= assessment when patient experienced next flare

References:
1. Ware J, Kosinski, M., Keller, SK. . SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute. 1994
2. Cella D, Lai J, Chang C, Peterman A, Slavin M. Cancer 2002;94:528-38

Disclosure: J. B. Kuemmerle-Deschner, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5 ; **J. Hoyer**, None; **E. Hachulla**, Novartis Pharmaceutical Corporation, 5 ; **R. Chaturvedi**, Novartis Pharmaceutical Corporation, 2 ; **N. Blank**, Novartis Pharmaceutical Corporation, 2 ; **F. Hiepe**, None; **A. Ferreira**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **S. D. Felix**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **A. M. Wright**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **T. Jung**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **C. Rordorf**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 .

1484

MRI Imaging Findings in Neuro- Behçet's Disease. Akiko Suda[1], Haruko Ideguchi[2], Mitsuhiro Takeno[1], Shigeru Ohno[2], Atsushi Ihata[1], Atsuhisa Ueda[1] and Yoshiaki Ishigatsubo[1], [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Yokohama City University Medical Center, Yokohama, Japan

Purpose: Neurological involvement is one of the most serious manifestations Behçet's disease (BD). The incidence is ranged from 5 to 10 % of BD patients. The clinical symptoms and lesions are diverse from patient to patient. We here assessed the MRI imaging and clinical manifestations in BD patients with central nervous involvement.

Methods: Brain MRI imaging were conducted in 27 NBD patients (16 male, 11 female) under care in Yokohama City University Hospital from 1991 to 2007. The imaging conditions included T1 WI, T2WI, and FLAIR images. We analyzed abnormal signals in individual imaging conditions, the anatomical localization, and morphological abnormalities of the parenchymal brain system including atrophy. Neurological symptoms and signs were also reviewed based on clinical charts when the MRI was taken.

Results: A total of 77 abnormal signals were identified by any imaging conditions in the 27 patients. The lesions were most frequently detected in the cerebrum (77.8%), followed by the brain stem (59.3%), the basal ganglia (37.0%) and the cerebellum (22.2%). The most common abnormality was T2 high intensity in the cerebral subcortex. Cerebellar and cerebral brain atrophy was found in 8 (38.1%) and 3 patients (14.2%) of 27 patients, respectively. Of neurological clinical features, cranial nerve involvement was more common in patients with the brainstem lesions than the others ($p=0.027$). Cerebellar and/or cerebral brain atrophy was associated with personality changes ($p=0.005$) and speech disorder ($p=0.018$). The other symptoms such as headache and meningeal signs were not related with any abnormal MRI findings. There was no significant association of abnormal MRI findings with gender, age and HLA-B phenotype.

Conclusion: : MRI is useful to detect the brainstem lesions, which are responsible for cranial nerve injury, and he parenchymal brain atrophy, which causes personality changes and speech disorder in patients with BD.

Disclosure: A. Suda, None; **H. Ideguchi**, None; **M. Takeno**, None; **S. Ohno**, None; **A. Ihata**, None; **A. Ueda**, None; **Y. Ishigatsubo**, None.

1485

Late Improvement in Processing Functions in Patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Treated with the Recombinant IL-1 Receptor Antagonist Anakinra. SM Paul[1], J. Snow, H. Hildenbrand[1], M. Jain[1], C. O'Shea, M. Smith[1], E. Wiggs, C. Henderson[2], L. Comis[1], T.H. Pham[2], N. Plass[2], D. Chapelle[2], D. Stone[2], R. Wesley[2] and R. Goldbach-Mansky[2], [1]CC/NIH Bethesda,MD, [2]NIH | NIAMS, Bethesda, MD

Purpose: To determine the cognitive outcomes after 3 years of treatment with the recombinant interleukin-1 receptor antagonist anakinra of patients with NOMID, an auto-inflammatory syndrome caused by mutations in *CIAS1*, a gene associated with up-regulation of IL-1β production.

Methods: These results come from an ongoing open label prospective treatment trial of 23 subjects between 4 to 28 years with NOMID. Subjects received daily subcutaneous injection of anakinra starting between 2.5mg/kg/day, increasing to 5 mg/kg/day if symptoms persisted. Functional outcome measures included the Assessment of Motor and Process Skills (AMPS), the Pediatric Evaluation of Disability Inventory (PEDI), and standard IQ testing obtained at baseline then 12, 24 and 36 months. Only patients with paired data were included in the analysis.

Results: An early and significant improvement in motor function was already seen within 6-12 months of treatment, however only a trend in the improvement was seen in assessments that required higher cerebral functions. However after 3 years of therapy with anakinra, the mean z-scores for the AMPS processing which were below age expected norm values at baseline, processing score increased from a score of 1.3 (SE 0.1) at baseline to 1.46 (SE 0.1) ($p<0.001$). Mean PEDI scaled scores were below normal at baseline and improved not only in the mobility domain from 73.4 (SE 5.1) to 101.7 (SE 6.1) ($p<0.001$) at 36 months but also the PEDI self care and social functions significantly improved in patients at 36 months ($p<0.001$ respectively). However, the mean IQ which was in the low normal range at baseline remained stable at 85 (SE, 4.1) at baseline and 87.5 (SE, 4.1) at 3 years ($p=0.3$).

Conclusion: Improvement in the functional performance and reduction in disability were rapid effects shortly after the initiation of treatment with anakinra. Interestingly, an improvement in the AMPS process z-score, the PEDI social and self-care scaled scores, were only observed at 3years but had not significantly changed at 12 months. Our data suggest that, the recovery of some CNS function may take adaptive behavioral steps to translate into an improvement of measurable functional improvement in areas where higher cognitive functions are involved including improved processing in performing activities of daily living.

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1486

Infliximab Therapy Significantly Suppresses Ocular Inflammation in Behçet's Disease. Takeaki Uehara[1], Mitsuhiro Takeno[2], Sei Samukawa[3], Maasa Hama[2], Kenji Ohmura[4], Akiko Suda[2], Atsushi Ihata[5], Atsuhisa Ueda[4] and Yoshiaki Ishigatsubo[2], [1]Senior resident, Yokohama, Japan, [2]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [3]Graduate student, Yokohama, Japan, [4]not Trainee, Yokohama, Japan, [5]Yokohama City University Med, Yokohama

Purpose: There is accumulating evidence that infliximab (IFX) is effective on uveitis in Behçet's disease (BD). We evaluated clinical efficacy and safety issues in IFX therapy for BD patients.

Method: IFX therapy was conducted in 13 BD patients (female 2, male 11, age 37+15 yo) who met he International Study Group criteria for diagnosis of Behçet's disease and refractory uveitis to conventional therapies. After screening latent tuberculosis by chest CT scan and tuberculin skin test (TST), 5 mg/kg of IFX was given at 0, 2, 6, weeks and thereafter every 8 weeks. Patients who had suggestive tuberculosis lesions and/or positive TST received anti-tuberculosis chemophylaxis during the first 9 months of IFX therapy. We assessed frequency of ocular attacks and visual acuity before and after infliximab therapy. Surgical operation and adverse events were also noted during infliximab therapy.

Results: Mean duration was 7.4+6.0 years from the disease onset to initiation of infliximab therapy. Before the infiliximab therapy, all patients had received colchicines, 7 patients had cyclosporine A, and 3 patients had prednisolone. The oral agents were discontinued except colchicines in 6 patients and prednisolone in one. Either of isoniazide or refampicin was given to 6 of 13 patients as anti-tuberculosis chemophylaxis because of positive TST. Frequency of ocular attacks was reduced from 2.4 + 0.6/6 month before the IFX therapy to 0.8 + 0.8/6 months after the therapy. Most of ocular attacks, which were commonly accompanied by extraocular symptoms such as oral aphthosis, folliculitis and eryhema nodosum, were found after 6 weeks form the last infusion. Therefore, the infusion intervals were shortened from 8 to 6 weeks in 4 patients. Visual acuity were improved in 12 eyes, unchanged in 11 eyes, and deteriorated in 3 eyes. Especially, early introduction of IFX therapy led to good visual prognosis. Surgical ocular operations were performed in 3 eyes for cataract and glaucoma, respectively, without operation-related ocular attacks. Serious adverse events including tuberculosis were not observed except for cytomegalovirus infection in a patient.

Conclusion: IFX therapy significantly suppresses ocular attacks, leading to improved visual acuity in BD patients with uveitis. Particularly, early introduction of IFX therapy is encouraged in BD patients with serious uveitis.

Disclosure: T. Uehara, None; **M. Takeno**, None; **S. Samukawa**, None; **M. Hama**, None; **K. Ohmura**, None; **A. Suda**, None; **A. Ihata**, None; **A. Ueda**, None; **Y. Ishigatsubo**, None.

1487

Rilonacept Treatment of Refractory Adult Onset Still's Disease. Petros Efthimiou[1] and Olga Petryna[2], [1]Weill Cornell Medical College/Lincoln Med & Mental Hlth Ctr, New York, NY, [2]Lincoln Med & Mental Hlth Ctr, New York, NY

Purpose: Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterized for spiking fever, rash, and arthritis. While glucocorticoids remain the cornerstone for treatment, refractory cases abound and have been treated with biologics with varying success. We are reporting successful use of a novel Interleukin (IL)-1 inhibitor, rilonacept, in 2 patients with AOSD after failure of treatment with glucocorticoids, immunosuppressors and biologics, including anakinra.

Methods: We identified through chart review 2 patients with refractory AOSD that were treated with rilonacept. The retrospective study was approved by the institutional review board (IRB)

Results: *Patient 1*: A 36 y/o hispanic female with daily spiking fevers, arthritis of knees, wrists, and MCPs, maculopapular rash and elevated serum ferritin (4253 ng/ml) failed treatment with glucocorticoids, methotrexate and responded partialy to anakinra 100 mg SQ twice daily. Anakinra was switched to rilonacept (220mg SQ loading and 160mg sq weekly maintenance) with dissapearance of rash and arthritis. Prednisone was tapered to 10mg daily and ferritin values normalized (67.3ng/ml).

Patient 2: A 44 y/o hispanic female with daily fever, arthritis and erythematous rash of upper chest and lower extremities was treated with oral prednisone, methotrexate, daily anakinra and abatacept with inadequate response. Rilonacept (220mg SQ loading and 160mg sq weekly maintenance) was added to oral prednisone and methotrexate with amelioration of rash and arthritis that allowed for a significant tapering of the prednisone dose, normalization of acute phase reactants and facilitated weight loss.

Conclusion: Rilonacept, through its long acting IL-1 inhibition, may be an effective treatment of refractory AOSD, even in anakinra treatment failures. To our knowledge this is the first published report of the use of rilonacept in AOSD. Controlled trials, through international collaboration, are warranted.

Disclosure: P. Efthimiou, None; **O. Petryna**, None.

ACR/ARHP Poster Session C

Orthopedics, Low Back Pain and Rehabilitation

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1488

Healthcare Costs After Closed Fracture in Commercially Insured and Medicare Advantage Populations From a National Health Plan. Laura L. Christensen[1], Sheikh Usman Iqbal[2], Ying Fan[3] and David Macarios[2], [1]i3 Innovus, Ann Arbor, MI, [2]Amgen, Thousand Oaks, CA, [3]i3 Innovus, Eden Prairie, MN

Purpose: To determine annual total health care costs following hip, vertebral and non-hip/non-vertebral (NHNV) fractures (fx) among commercial (COM) and Medicare Advantage Plan (MAP) enrollees

Method: Administrative claims from a large, national health plan were analyzed. Men and women 45 or older with at least one medical claim for a new closed fracture (identified through primary ICD-9-CM diagnosis indicating closed hip, vertebral, or NHNV fracture) at a single site between June 30, 2002 and June 30, 2006, were continuously enrolled with the plan for 12 months before and after the fracture, and had at least two fracture-related outpatient visits during the follow-up period were included. Those with hip, femur, tibia and humerus fractures were required to have inpatient care associated with the first fracture claim. COM and MAP members were analyzed separately. Costs were calculated and stratified for hip, vertebral, and NHNV fx as paid amounts and were adjusted to 2006 dollars. Costs were considered fracture-related if there was a primary fx diagnosis code or a procedure code related to fx.

Results: The study identified 46,681 (COM 36,521; MAP 10,160) closed fragility fx during the study period. Mean post-fracture annual healthcare cost greatly exceeded the cost incurred prior to fracture, increasing 64% from $10,983 to $18,010 in COM patients and 112% from $8,979 to $19,077 in MAP patients.

The sample comprised mostly women (64% COM, 77% MAP) and mean age was 58 yrs and 76 yrs for COM and MAP, respectively. Compared to COM (relatively younger) patients, MAP patients had higher proportions of hip fractures (17% vs 5%) and vertebral fractures (26% vs 16%) and lower proportions of NHNV fractures (58% vs 79%).

In both populations, mean healthcare cost per fracture was highest for hip fractures, followed by vertebral fx (table). Inpatient cost comprised the major portion of total cost for hip and vertebral fx. Average total health care costs per fracture were higher for COM than for MAP patients (14% higher for hip, 40% higher for vertebral). Vertebral fx had the highest mean outpatient and pharmacy costs (table). Mean fx-related medical cost comprised 45-75% of the total medical cost.

Conclusion: Total and fracture-related healthcare costs pose a substantial burden to patients and the healthcare system.

	Hip		Vertebral		NHNV	
	COM	MAP	COM	MAP	COM	MAP

Mean follow-up costs						
Inpatient	23,837	22,827	11,286	9,806	4,921	6,571
Outpatient	7,097	3,578	10,001	5,543	6,619	4,497
Pharmacy	2,801	1,056	3,327	1,166	2,055	896
Emergency	626	1,251	433	858	389	962
LTC	1,723	3,611	272	888	156	869
Other	2,615	1,652	1,642	1,021	834	870
Follow-up fracture-realted medical cost	23,671	24,317	10,760	8,906	6,434	6,735
Total follow-up medical cost	35,898	32,919	23,634	18,117	12,918	13,769
Total follow-up health care cost (medical+pharmacy)	38,699	33,975	26,961	19,283	14,973	14,665

Disclosure: L. L. Christensen, None; **S. U. Iqbal**, Amgen, Inc, 3 ; **Y. Fan**, None; **D. Macarios**, Amgen, 1, Amgen, 3 .

1489

Radiocarpal and First Metatarso-Phalangeal Arthrocentesis Site Confirmation with Fluoroscopy. Augustine M. Manadan, Saulat Mushtaq and Joel A. Block, Rush University Medical Center, Chicago, IL

Purpose: Rheumatologists routinely perform arthrocentesis. We attempted to determine the accuracy of routine arthrocentesis of the radiocarpal (RC) and first metatarso-phalangeal joint (MTP).

Method: All board certified attending rheumatology physicians with privileges at John H. Stroger Jr. Hospital of Cook County were asked to complete a voluntary short survey with the following questions:

(1) Have you ever obtained synovial fluid from a wrist joint aspiration?

(2) Which joint in the wrist do you usually aspirate?

(a) RC joint

(b) Intercarpal joint

(c) Carpo-metarcapal joint

(3) What is your estimated success rate during wrist aspiration?

(4) Have you obtained synovial fluid from the first MTP joint?

(5) What is your estimated success rate during first MTP joint aspiration or injection?

Subsequently, they were asked to mark their usual site of arthrocentesis on the skin overlying the right RC and right first MTP joints of the two primary investigators. The actual joint lines had been previously identified fluoroscopically, and had been marked using ink invisible to normal light but visible under ultraviolet illumination (LDP, Inc., www.maxmax.com).

Results: All 10 eligible rheumatologists agreed to participate; they had a mean of 17.9 (range 3-32) years of clinical rheumatology experience and originated from 7 fellowship programs. All reported having obtained synovial fluid during wrist aspiration and 90% reported having obtained synovial fluid during MTP aspiration. In the wrist, 8/10 (80%) preferred to aspirate at the RC joint and 2/10 (20%) preferred the intercarpal joint. The self reported success rates for wrist and MTP arthrocentesis were 61% (range 25-90%) and 37% (range 0-80%), respectively. Each rheumatologist marked the site of preferred aspiration on two wrists and two MTPs. Data from a total of 18 RC markings and 20 MTP markings were obtained. Two physicians reporting intercarpal joint aspiration as their preferred technique were excluded from wrist marking analysis. The sites marked by the rheumatologists were a mean of 0.85 cm (range 0-1.6) from the fluoroscopically identified radiocarpal joint and 0.33 cm (range 0-1.3) from the fluoroscopically identified MTP joint. Review of the data indicated that 7/8 (88%) of physicians had marked the wrist intercarpal joint when they had intended to mark the RC joint.

Conclusion: Blind joint aspiration may be inaccurate, even in superficial joints that are thought to be easily accessible. Fluoroscopic guidance has the potential to improve accuracy of arthrocentesis. Nonetheless, generalizability may be limited because during actual arthrocentesis, the needle angle is frequently adjusted *in situ* to accommodate inaccurate site selection. Moreover, many articular capsules are sufficiently large that it is often not necessary to aspirate directly at the joint margin in order to obtain synovial fluid. Nonetheless, experienced rheumatologists often mistake the wrist intercarpal joints for the RC joint, and misidentify the MTP joint line.

Disclosure: A. M. Manadan, None; **S. Mushtaq**, None; **J. A. Block**, Novartis, 9, Wyeth, 9, Anika, 9, Lilly, 9, Abbott, 9 .

1490

Ultrasound-Guided Percutaneous Injection, Hydrodissection, and Fenestration for Carpal Tunnel Syndrome. Daniel G. Malone[1], Thomas B. Clark[2] and Nathan Wei[3], [1]University of Wisconsin, Madison, WI, [2]MSKUS, Vista, CA, [3]Arthritis & Osteo Ctr of MD, Frederick, MD

Purpose: Carpal tunnel syndrome, caused by compression of the median nerve deep to the flexor retinaculum, is the most common entrapment neuropathy. Most patients are initially treated with conservative measures such as splinting. When conservative measures fail, interventional techniques are considered the next step. Many studies have appeared comparing open surgical flexor retinaculum release to blind injections of corticosteroids into the carpal tunnel, but neither technique has proven superior to the other. Advantages of injection are: lower level of invasiveness, faster recovery, and ease of the technique. Occasional failures and complications occur with all techniques.

Method: We have been using an ultrasound-guided procedure of percutaneous hydrodissection of the median nerve away from the deep surface of the flexor retinaculum, followed by fenestration of the flexor retinaculum along a path parallel to the long axis of the arm, starting from the level of the distal palmar crease and progressing proximally to the level of the radio-lunate joint, the intent being to lower the pressure exerted by the flexor retinaculum on the nerve (panel 1). We have treated a series of 39 wrists in 29 patients with electrically-proven carpal tunnel syndrome, using this technique of hydrodissection and fenestration, performed using standard injection equipment and a GE LogiQ e ultrasound system with a 12 MHz linear array probe. All patients had typical carpal tunnel syndrome symptoms and presented to us for interventional treatment, conservative measures having failed. No patient had had previous surgery, and 2 had had blind carpal tunnel steroid injections, without hydrodissection or fenestration. Outcomes were defined as:

Excellent-all symptoms resolved,

Fair-some residual symptoms, or return of symptoms, but improved compared to prior to procedure,

Failure-required open surgical release.

Follow-up periods after procedure ranged from 5-64 weeks, averaging 38 weeks (as of late June 09). Patients were contacted by telephone, or seen in follow-up in clinic, to determine outcomes.

Results: Excellent—31 wrists; Fair—5 wrists; Failure—3 wrists; No complications were encountered.

Conclusion: Ultrasound-guided hydrodissection and fenestration is a viable, easy, relatively non-invasive therapy for carpal tunnel syndrome that can result in prolonged symptom relief, and may be a way to postpone, or even obviate the need for, open release.

Disclosure: D. G. Malone, Grneral Electric, 5 ; **T. B. Clark**, General Electric, 5 ; **N. Wei**, None.

1491

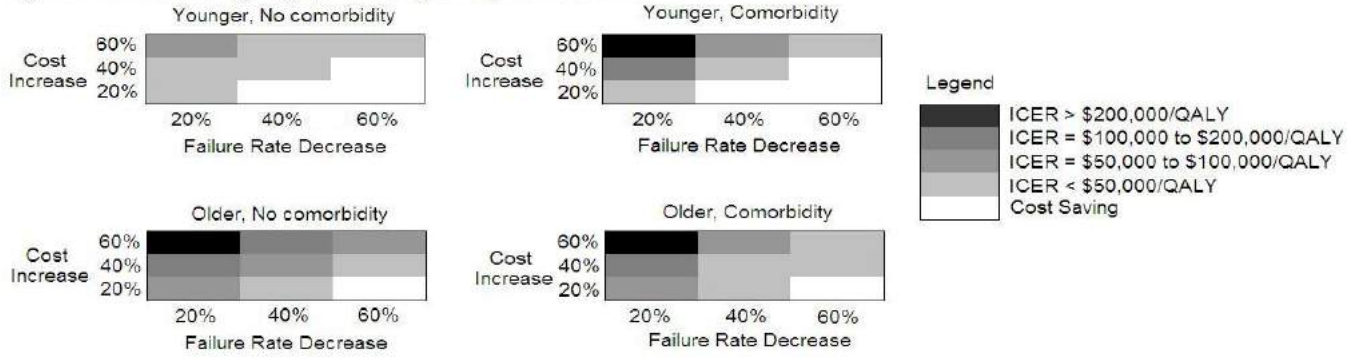
The Cost-Effectiveness of Innovative Implants in Total Knee Replacement. L.G. Suter[1], H. Gerlovin[2], J.N. Katz[3], I. Golovaty[2], N.N. Niu[2], H.L. Holt[2], L. Fraenkel[1], L. Weis[4], D.H. Solomon[2], T.S. Thornhill[2], A.D. Paltiel[5] and E. Losina[6], [1]Yale University and Veterans Affairs Healthcare System, New Haven, CT, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Veterans Affairs Health Care System, West Haven, CT, [5]Yale University, New Haven, CT, [6]Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA

Purpose: Total knee replacement (TKR) is a cost-effective but increasingly common and expensive treatment for end-stage knee osteoarthritis (OA). Newer, costlier implants promising reduced rates of long term prosthesis failure are under continual development. Our objective was to specify the cost, performance, and target population scenarios under which innovative implants might be cost-effective.

Methods: Using a Markov state-transition computer simulation model of knee OA, we projected failure-free survival, costs and quality adjusted life expectancy (QALE) in patients undergoing TKR using implants with varying failure rates and costs. We considered four populations: 1) younger (50-59 years) and no comorbidities; 2) younger with comorbidity (e.g., obesity and cardiovascular disease); 3) older (70-79 years) and no comorbidities; and 4) older with comorbidity. We considered prosthesis failure rate reductions ranging from 20-60% based upon laboratory data. Outcomes of standard (i.e., using currently available implants) TKR were derived from a national cohort of Medicare beneficiaries undergoing TKR. Using published literature, we derived the current cost of the implant (about 25% of total TKR cost) and considered cost increases ranging from 20-60% based upon published data. We estimated average per person lifetime medical costs (2008 USD) and QALE from a societal perspective with 3% discounting.

Results: Standard TKR resulted in average per person lifetime medical costs of $44,184 with QALE of 16.27 years in healthy 50-59 year olds and $39,782 with QALE of 7.24 years in comorbid 70-79 year olds. A 60% decrease in failure rate increased the proportion of failure-free individuals alive 20 years after TKR from 59.4% to 69.5% for healthy 50-59 year olds and from 9.6% to 11.2% for older individuals with comorbidities. The impact of decreasing TKR failure rates while simultaneously increasing implant cost on the incremental cost-effectiveness ratio (ICER) of innovative versus standard TKR is shown in Figure 1. Implants with high cost increases were less likely to be cost-effective (upper left corners), while those conferring the greatest reductions in failure rate were universally cost-effective or cost-saving (lower right corners).

Figure 1. ICERs according to age, comorbidity and implant characteristics



Conclusion: Age-specific mortality in older populations may limit long term benefits from innovative TKRs. Despite this, newer, costlier implants are likely to be cost-effective at currently acceptable thresholds if they reduce the true long-term TKR failure rate by 40% or more and cost no more than 60% over current implants.

Disclosure: L. G. Suter, None; **H. Gerlovin**, None; **J. N. Katz**, None; **I. Golovaty**, None; **N. N. Niu**, None; **H. L. Holt**, None; **L. Fraenkel**, NIH, AF, 2 ; **L. Weis**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 ; **T. S. Thornhill**, DePuy, 7, Conformis, 9 ; **A. D. Paltiel**, None; **E. Losina**, None.

1492

Effect of CYP2C9 and VKORC1 Genotypes On Early-Phase Warfarin Dosing of Rheumatoid Arthritis Patients with Elective Joint Surgery in Japanese. Asami Tokita, Taku Suzuki, So Tsukahara, Katsunori Ikari and Shigeki Momohara, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Elective joint surgery in rheumatoid arthritis (RA) is used to relieve severe pain and improve function of severely deformed joints that do not respond to medication. To prevent pulmonary embolism associated with deep venous thrombosis (DVT) following elective joint surgery, the optimized prophylaxis including warfarin therapy is absolutely essential. The two key enzymes in the metabolism of warfarin are cytochrome P450 (CYP) 2C9 (CYP2C9 gene) and the C1 subunit of the vitamin K 2,3 epoxide reductase complex (VKORC1 gene). These two genes contribute significantly to the variability among patients in dose requirements for warfarin. Recently, the International Warfarin Pharmacogenetics Consortium showed that the pharmacogenetic algorithm with CYP2C9 and VKORC1 genes were useful for estimation of the appropriate warfarin dose. The aim of this study was to investigate whether these genes were associated with the amount of required warfarin and the time to reach the target PT-INR of rheumatoid arthritis patients with elective joint surgery in Japanese.

Method: The study was approved by the Tokyo Women's Medical University Genome Ethics Committee. Written informed consent was obtained from all patients prior to enrollment in the study. The diagnosis of RA is based on the American College of Rheumatology 1987 revised criteria. Acute DVT was diagnosed according to color flow duplex ultrasonography. The initial warfarin treatment was started with a 1-day loading of a dose of 3.0 mg for acute DVT following surgery. The PT-INR measurement was repeatedly monitored with intervals of 3–4 days and then the dose was adjusted. Once it reached a stable dose, the time to reach the target PT-INR was estimated. The therapeutic target INR range of the patients was from 1.5 to 2.5. DNA samples were available from 31 patients treated with warfarin following total hip and knee arthroplasty. Genotyping of CYP2C9*1, CYP2C9*3, and VKORC1 1173C>T were performed using TaqMan SNP genotyping assay (Applied Biosystems, Tokyo, Japan).

Results: All patients were homozygous CYP2C9*1/*1 genotype. Of these, 8 patients were heterozygous VKORC1 C/T and 23 patients were homozygous T/T genotype. The daily warfarin doses were significantly different between VKORC1 C/T and T/T genotype (P=0.009, Table 1).

Conclusion: Patients with VKORC1 T/T genotypes need a lower maintenance dose of warfarin than patients with VKORC1 C/T genotype. Genetic variability helps predict the ideal therapeutic dose of warfarin in Japanese rheumatoid arthritis patients.

Table 1. Characteristics of 31 patients of rheumatoid arthritis in Japanese

Genotype	VKORC1 C/T (N=8)	VKORC1 T/T (N=23)	P
Daily warfarin dose (mg/day)	3 (3-3.6)	2 (1.75-3)	0.009
Days from initial dose (days)	11 (9.25-12.5)	15 (9.5-21)	0.13
Target INR	1.88 (1.7-2.2)	1.91 (1.7-2.1)	0.73

Values are given as median (interquartile range).

Disclosure: A. Tokita, None; **T. Suzuki**, None; **S. Tsukahara**, None; **K. Ikari**, Mitsubishi Tanabe Pharma Corporation, 8 ; **S. Momohara**, Astellas Pharma Inc., 8, Chugai Pharmaceutical Co., Ltd, 8, Dainippon Sumitomo Pharma Co., Ltd., 8, Kaken Pharmaceutical Co., Ltd., 8, Takeda Pharmaceutical Company Limited, 8, Mitsubishi Tanabe Pharma Corporation, 8, Sanofi-aventis K.K, 8, Santen Pharmaceutical Co., Ltd., 8, Wyeth K.K., 8 .

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Low Back Pain Patients Experience Lower Pain Intensity After Extensive Physical Testing. Thomas Maribo[1], Elena Iversen[2], Lone D. Jensen[1], Kristian Stengaard-Pedersen[3] and Berit Schiøttz-Christensen[2], [1]Aarhus University Hospital, Aarhus, Denmark, [2]Aarhus Clinic for Rheumatic Diseases, Aarhus, Denmark, [3]Rheumatology Universityhospital, Aarhus

Low back pain (LBP) is the most common and costly musculoskeletal complaint with a lifetime prevalence of 70-80 %.

Pain in LBP patients is influenced by many factors, including physical activity, core muscle endurance and physical fitness.

Endurance of core muscles is known to be reduced in LBP patients compared to healthy controls. With regards to physical fitness the results are less clear. No studies have analysed how LBP patients tolerate physical testing.

Purpose: To evaluate intensity of pain before and after physical testing in patients with recurrent LBP.

Method: The study population was 223 LBP patients of both gender and 18-63 years of age that were admitted to the Department of Rheumatology at Aarhus University Hospital. The patients were active on the labour marked and were advised to exercise after physical examination. The physical test battery included postural balance, core muscle endurance, and physical fitness. Postural balance was tested using one leg stand test and sway measures on a force platform. Core muscle endurance was tested using modified Sorensen test and supine isometric chest raise test as described by Ito. Physical fitness was tested using Astrand bicycle test. Every test session lasted 45 minutes.

Pain was recorded just before and 10 minutes after completion of the test battery using a 0-10 numeric rating scale (NRS).

The Mann-Whitney test was used to test for significant changes in pain before and after testing.

Results: Pain was recorded before and after physical testing on all 223 patients.

Patients rated mean initial pain as 2.23 (CI95 1.99; 2.48) and after the test pain was reduced to 1.76 (CI95 1.50; 2.02), the difference was statistically significant ($p<0.001$). Of all the patients 100 (44.8 %) reported decreased pain, 88 patients (39.5 %) reported unchanged pain and 35 patients (15.7 %) reported increased pain.

One hundred seventy six patients (74.8 %) reported none or mild initial pain (NRS ≤ 3) before the test this group rated mean pain as 1.37 (CI95 1.19; 1.54) and after test this was reduced to 1.00 (CI95 0.81; 1.19) this reduction was significant ($p<0.001$).

Fifty five patients (24.6 %) reported moderate initial pain (NRS ≥ 4), before the test this group rated mean pain as 4.82 (CI95 4.54; 5.10) and after test this was reduced to 4.04 (CI95 3.50; 4.58) this reduction was significant ($p=0.001$).

The presence of patients with severe initial pain (NRS ≥ 8) was negligible.

Conclusion: Physical testing for both postural balance, core muscle endurance, and physical fitness was safe in patients with recurrent LBP. Most patients reported the same or less pain after the 45 minutes of physical testing. Only 15.7 % reported an increase in pain.

Disclosure: T. Maribo, None; **E. Iversen**, None; **L. D. Jensen**, None; **K. Stengaard-Pedersen**, None; **B. Schiøttz-Christensen**, None.

1494

Dose Stability of Tapentadol ER for the Relief of Chronic Low Back Pain: Results of a Randomized, Active- and Placebo-Controlled Study. Robert Buynak[1], Mila Etropolski[2], Bernd Lange[3], Douglas Y. Shapiro[2], Akiko Okamoto[2], Achim Steup[3], Ilse Van Hove[4] and Christine Rauschkolb[5], [1]Northwest Indiana Center for Clinical Research, Valparaiso, IN, [2]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, [3]Grünenthal GmbH, Aachen, Germany, [4]Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica, N.V., Beerse, Belgium, [5]Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Raritan, NJ

Purpose: Tapentadol is a new centrally acting analgesic with μ-opioid receptor agonist and norepinephrine reuptake inhibitor activity. The efficacy, safety, and dose stability of tapentadol extended release (ER) in patients with moderate to severe chronic low back pain were evaluated.

Method: Patients were titrated over 3 weeks to an effective and tolerable bid dose of tapentadol ER (100-250 mg), oxycodone HCl controlled release (CR; 20-50 mg), or placebo, then maintained at that dose for 12 weeks; additional dose adjustments were allowed as needed under the supervision of the patients' physician to maintain an optimal balance of efficacy and tolerability. Efficacy was measured as change in mean pain intensity (0-10 NRS) from baseline to Week 12 of maintenance; in the event of early patient discontinuation, missing values were imputed using last observation carried forward. Dose stability was evaluated as the percentage of days patients took their modal (most frequently used) dose.

Results: The intent to treat population included 958 patients. Improvements in average pain intensity scores from baseline to Week 12 of maintenance were significant versus placebo in the tapentadol ER (least squares mean difference vs placebo, −0.8, P <0.001) and oxycodone CR (−0.9, P <0.001) groups. A total of 235 patients in the tapentadol ER group and 199 patients in the oxycodone CR group entered the maintenance period and were evaluated for dosing. During the maintenance period, median modal TDDs were 400 mg tapentadol ER and 80 mg oxycodone HCl CR. The median percentage of time on the modal dose was ≥93% for both active treatments, indicating that patients were on a stable dose for the majority of the maintenance period. The median number of the most consecutive days that patients took the modal dose was 49.0 days for tapentadol ER and 47.0 days for oxycodone HCl CR. The range of mean TDDs (tapentadol ER, 384.6-393.2 mg; oxycodone HCl CR, 72.3-74.5 mg) and mean pain scores (tapentadol ER, 4.4-4.2; oxycodone CR, 4.6-4.5) were relatively stable from Week 3 of maintenance to the end of the study. A higher percentage of patients completed treatment with tapentadol ER (54.1%) than with oxycodone CR (43.3%), mainly because of the lower rate of discontinuation due to adverse events (AEs) in the tapentadol ER group (16.7%) than in the oxycodone CR group (32.3%).

Conclusion: Tapentadol ER (100-250 mg bid) relieved moderate to severe chronic low back pain more effectively than placebo, with fewer AE-related discontinuations than oxycodone HCl CR (20-50 mg bid). Most patients maintained a stable TDD and a stable level of effective pain relief on tapentadol ER.

Disclosure: R. Buynak, Johnson & Johnson, 2 ; **M. Etropolski**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **B. Lange**, Grunenthal GmbH, 3 ; **D. Y. Shapiro**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **A. Okamoto**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **A. Steup**, Grunenthal GmbH, 3 ; **I. Van Hove**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **C. Rauschkolb**, Johnson & Johnson, 1, Johnson & Johnson, 3 .

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Long-Term Safety and Gastrointestinal Tolerability of Tapentadol Extended Release or Oxycodone Controlled Release in Patients with Chronic Low Back or Osteoarthritis Pain. Stefan Grond[1], Brigitte Kuperwasser[2], Bettyanne McCann[2], Robert Lange[3], Bernd Lange[3], Akiko Okamoto[2], Jane Gilbert[4], Achim Steup[3], Thomas Häufel[3] and Mila Etropolski[2], [1]Clinical Center Detmold-Lippe, Detmold, Germany, [2]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, [3]Grünenthal GmbH, Aachen, Germany, [4]Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag Ltd., High Wycombe, United Kingdom

Purpose: This phase 3, open-label study evaluated the safety and efficacy of tapentadol extended release (ER), a new, centrally acting analgesic with μ-opioid receptor agonist and norepinephrine reuptake inhibitor activities, and oxycodone controlled release (CR) for up to 1 year in patients with moderate to severe chronic low back or osteoarthritis hip or knee pain.

Method: Patients were randomized 4:1 to receive controlled, adjustable, oral bid doses of tapentadol ER 100-250 mg or oxycodone HCl CR 20-50 mg. Dose titration was performed in steps of 50 mg bid for tapentadol ER or 10 mg bid for oxycodone HCl CR to a dose providing an optimal balance of efficacy and tolerability. Efficacy was assessed as the average pain intensity score over the preceding 24 h; at each visit, patients indicated their pain score using on an 11-point numerical rating scale. Odds ratios (ORs) for specific gastrointestinal (GI) treatment-emergent adverse events (TEAEs) were estimated using a logistic regression model.

Results: Of 1,117 patients who received ≥1 dose of study drug and were analyzed for safety, 46.2% (413/894) and 35.0% (78/223) completed 52 weeks of treatment with tapentadol ER and oxycodone CR, respectively. Mean (SD) treatment duration was numerically longer with tapentadol ER (211 [157.4] days) than with oxycodone CR (161 [163.1] days). Mean (SD) daily doses were 326.7 (120.2) mg tapentadol ER and 51.5 (26.9) mg oxycodone HCl CR. Mean (SD) values of average pain scores decreased from 7.58 (1.54) with tapentadol ER and 7.61 (1.63) with oxycodone CR at baseline to 4.37 (2.57) and 4.52 (2.23), respectively, at study endpoint. Tapentadol ER was associated with significantly better GI tolerability than oxycodone CR based on estimated ORs for the incidence of all assessed GI TEAEs (52.0% vs 64.1%, respectively; OR [95% CI], 0.606 [0.45-0.82]; P = 0.001) and for specific GI TEAEs of constipation (22.6% vs 38.6%, respectively; 0.469 [0.34-0.64]; P <0.001), nausea (18.1% vs 33.2%, respectively; 0.447 [0.32-0.62]; P <0.001), vomiting (7.0% vs 13.5%, respectively; 0.490 [0.31-0.78]; P = 0.002), and the composite of nausea and/or vomiting (20.7% vs 37.2%, respectively; 0.441 [0.32-0.61]; P <0.001).

Conclusion: Tapentadol ER provided sustained long-term relief of chronic low back or osteoarthritis pain. Tapentadol ER 100-250 mg bid was associated with significantly lower ORs for the assessed GI TEAEs compared with oxycodone HCl CR 20-50 mg bid.

Disclosure: S. Grond, Johnson & Johnson, 5, Johnson & Johnson, 7, Grünenthal GmbH, 5, Grünenthal GmbH, 7 ; **B. Kuperwasser**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **B. McCann**, Johnson & Johnson, 3, Johnson & Johnson, 1 ; **R. Lange**, Grünenthal GmbH, 3 ; **B. Lange**, Grunenthal GmbH, 3 ; **A. Okamoto**, Johnson & Johnson, 1, Johnson & Johnson, 3 ; **J. Gilbert**, Johnson & Johnson, 3, Johnson & Johnson, 1 ; **A. Steup**, Grunenthal GmbH, 3 ; **T. Häufel**, Grünenthal GmbH, 3 ; **M. Etropolski**, Johnson & Johnson, 1, Johnson & Johnson, 3 .

1496

A 12-Month Randomized Controlled Trial of Balance Training in Elderly Women with Osteoporosis: Improvement of Quality of Life and Reduction of Falls. Melisa M. Madureira and Rosa M.R. Pereira, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil

Purpose: Physical and also psychological incapacity, including fear of falling was strongly related to self-reported decreased satisfaction with life in osteoporosis. The impact of a balance exercise prevention programs in improving quality of life is not well established. We therefore have investigated the effect of 12-month Balance Training Program in quality of life and falls in elderly women with osteoporosis.

Method: Sixty consecutive women with senile osteoporosis (age:65 to 85 years) were recruited from the Osteometabolic Disease Outpatient Clinic and randomized into two groups: Balance Training Group (BT) with 30 patients and Control Group (CG) with 30 patients. The Balance Training Program was focused mainly on techniques to improve balance, coordination and mobility and consisted of one-hour exercise session/week supervised by a physiotherapist for 12-months and oriented exercises to be performed at home 3 days/week. Both groups were sedentary before inclusion in the study and all patients were taking their prescribed medication for osteoporosis. The quality of life, in both groups, was evaluated before and at the end of the trial using the Osteoporosis Assessment Questionnaire (OPAQ). The quality of life scores are standardized into identical units ranging between 1 (good health status) and 10 (poor health status). Falls in the preceding year were noted and compared to the period of study.

Results: The groups BT and CG were similar in all basal scores domains of OPAQ, except for Social Interaction that was lower in BT compared to CG (2.69±1.42 vs. 3.49±1.47, p=0.013). The comparison of OPAQ domains variations (basal values – mean final values) revealed a significant improvement of quality of life in all parameters for BT group compared to CG: well being (1.61± 1.44 vs. -1.46 ± 1.32, p<0,001), physical function (1.30±1.33 vs. –0.36±0.82, p<0.001), psychological status (1.58±1.36 vs. –1.02±0.83, p<0.001), symptoms (2.76±1.96 vs. –0.63±0.87, p<0.001), social interaction (1.01±1.51 vs. 0.35±1.08, p<0.001). A significant progress was also observed regarding psychological status, fear of falls (3.78±3.15 vs. -0.72±1.89, p=0.001) and independence (-0.28±0.77 vs. -2.11±2.80, p=0.004) in BT group compare to CG. Of note, this overall improvement was paralleled by a reduction of falls in 50% of patients in BT group compared to 26.6% for the CG (OR: 7.50, p<0.025).

Conclusion: Our longitudinal prospective study demonstrated that 12-month Balance Training Intervention improve the quality of life and prevent falls in elderly people.

Disclosure: M. M. Madureira, CAPES, 2 ; **R. M. R. Pereira**, CNPQ, 2 .

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Acupuncture for Acute Non-Specific Low Back Pain: A Randomized, Controlled, Placebo Trial. Tatiana Molinas Hasegawa, Andreia Salvador Baptista, Marcelo Cardoso de Souza, Alexandre Massao Yoshizumi and Jamil Natour, Federal University of Sao Paulo, Sao Paulo, Brazil

Purpose: Acute non-specific low back pain (LBP) is defined as an episode of low back pain, not attributed to a recognizable or known specific disease, persisting for less than 6 weeks. Evaluate the effectiveness of Yamamoto's method of acupuncture on pain, functional status and quality of life using on patients with acute non-specific LBP.

Method: 80 patients with acute non-specific LBP were invited to participate in a randomized and blinded controlled clinical trial. The patients were randomized to an intervention-group (submitted to five real acupuncture sessions) or a control-group (placebo-submitted to five non-penetrating acupuncture sessions). The patients were evaluated by a blinded examiner in the beginning (T0), 3 (T3), 7 (T7), 14 (T14), 21(T21) and 28 (T28) days after intervention, using the following outcomes: visual analogue scale (VAS) for pain before (last week) and after intervention, Roland-Morris questionnaire (RM), SF-36, patient improvement by visual scale (LIKERT) and number of anti-inflammatory taken. The number of visits to the doctor was considered as co-interventions. Following treatment, patients were asked whether they thought they had undergone real acupuncture or the placebo treatment. The primary outcome was to detect a 2-point reduction in pain

VAS; the minimal clinically important difference (MCID) for the RM scale was a reduction of 2.5 points. Statistical analysis was performed using the Student's t-test to compare the baseline characteristics and analysis of variance (ANOVA) with repeated measurements to assess inter/intra-group changes.

Results: The groups were homogeneous at baseline. 80 patients completed the study and intention-to-treat analysis was performed. Until day 14, the only difference found between groups (p=0.03) was on VAS for pain before and after intervention what we call of immediate improvement; or all the other outcomes both groups improved and there was no significant difference between them. After 14 days the intervention group showed a significant improvement (p<0.05) in last week pain-VAS; RM; bodily pain and vitality domains of SF-36. Physical function domain of SF-36 revealed a meaningful difference after 21days, in the intervention-group (p<0.001). There was also a reduction in anti-inflammatory tables intake in the intervention-group (p=0.002). There was no meaningful differences between the groups concerning the variables LIKERT (p=0.67) and number of visits to the doctor (p=0.33). Thirty-six (90%) patients in the placebo group believed they had received real acupuncture, thereby supporting the credibility of non-penetrating placebo used in this study.

Conclusion: Acupuncture was more effective than placebo regarding decreasing pain and anti-inflammatory intake and improving functional status, bodily pain, vitality and physical function domains of SF-36. Acupuncture was ineffective regarding the others domains of SF-36, Likert scale and number of visits to the doctor.

Disclosure: T. M. Hasegawa, None; **A. S. Baptista**, None; **M. C. D. Souza**, None; **A. M. Yoshizumi**, None; **J. Natour**, None.

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The Effectiveness of a Weak Opioid Medication Versus a COX-2 Selective NSAID in Treating Flare-up of Chronic Low Back Pain: Results From a Randomized, Double-Blind, 6-Week Study. John B. O'Donnell[1], Evan F. Ekman[2], William M. Spalding[3], Pritha Bhadra[3], Dorothy McCabe[3], Manuela F. Berger[3] and Leigh Prevost[4], [1]Union Memorial Hospital, Baltimore, MD, [2]Southern Orthopaedic Sports Medicine, Columbia, SC, [3]Pfizer Inc., New York, NY, [4]Parexel, Worthing, United Kingdom

Purpose: To compare the analgesic efficacy, safety, and tolerability of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for the treatment of chronic low back pain (CLBP).

Method: In this parallel-group, double-blind, active comparator study, 802 subjects aged ≥18 years with a diagnosis of CLBP (lower back pain ≥12 weeks duration) who required regular use of analgesics (≥4 days/wk) and had a baseline score of ≥4 on an 11-point numeric rating scale (NRS-Pain; where 0 = no pain and 10 = worst possible pain), were randomized to receive either celecoxib 200 mg bid or tramadol HCl 50 mg qid for 6 weeks. This treatment duration represents standard clinical care for patients with short-duration flare-ups. No rescue medication was allowed. Successful responders (primary end point) were defined as subjects completing 6 weeks' treatment and having ≥30% improvement from baseline to week 6 on the NRS-Pain scale. A 2-stage analysis was used to test for noninferiority (evaluable population) and superiority of celecoxib (intent-to-treat [ITT] population). Safety and tolerability were carefully assessed for both treatment strategies.

Results: Of the 802 randomized subjects, 792 subjects were treated and included in the ITT and safety populations. A significantly greater percentage of celecoxib subjects responded successfully to treatment than tramadol HCl subjects (64.1% and 55.1%, respectively; $P < 0.001$). Significantly fewer celecoxib subjects discontinued treatment due to lack of tolerability (specific adverse events [AEs] of gastrointestinal or central nervous system origin) than tramadol HCl subjects (1.0% vs 10.6%, respectively; $P < 0.0001$) (Table). Fewer AEs and serious AEs were also reported in the celecoxib group, and fewer celecoxib subjects discontinued due to any treatment-related events (3.8% vs 13.4%, respectively). Overall, a significantly higher percentage of subjects withdrew due to lack of tolerability in the tramadol HCl group (10.6%) than in the celecoxib group (1.0%; $P < 0.0001$) (Table).

Permanent Withdrawals Due to Lack of Tolerability (All Causality) (ITT)

Adverse Event	Celecoxib 200 mg bid (n = 396), n (%)	Tramadol HCl 50 mg qid (n = 396), n (%)	*P Value*[a]
Abdominal pain	0 (0.0)	0 (0.0)	-
Dyspepsia	1 (0.3)	0 (0.0)	-
Nausea	1 (0.3)	25 (6.3)	-
Vomiting	0 (0)	14 (3.5)	-
Somnolence	2 (0.5)	7 (1.8)	-
Dizziness	2 (0.5)	20 (5.1)	-
Vertigo	0 (0.0)	1 (0.3)	-
Total	4 (1.0)	42 (10.6)	<0.0001

a Based on Cochran-Mantel-Haenszel test (general association), stratified by center.

Conclusion: Celecoxib 200 mg bid was more effective than tramadol HCl 50 mg qid in the treatment of CLBP, with fewer AEs reported. However, further studies are required to evaluate the longer-term effects of treatment for this chronic medical condition.

Disclosure: J. B. O'Donnell, Pfizer Inc, 8, Pfizer Inc., 5 ; **E. F. Ekman**, Pfizer Inc., 8, Pfizer Inc., 5, Pfizer Inc., 2 ; **W. M. Spalding**, Pfizer Inc., 3 ; **P. Bhadra**, Pfizer Inc., 3 ; **D. McCabe**, Pfizer Inc., 3 ; **M. F. Berger**, Pfizer Inc. , 3 ; **L. Prevost**, Parexel PPSI, 3 .

ACR/ARHP Poster Session C

Pathogenesis, Epidemiology, and Diagnosis

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Risk Factors for Renal Lithiasis During the Treatment with Uricosuric Drugs. Fernando Perez-Ruiz, Hospital De Cruces, Barakaldo, Spain

Purpose: This study intends to find factors at baseline, prior to starting ULT with uricosurics, and during follow up that could be associated with an increased hazard risk of developing renal lithiasis.

Method: Patients with gout and no previous history of renal lithiasis or severe renal function impairment were included in a prospective cohort follow-up study when treated with uricosurics. They were encouraged to drink fluids but no alkali was prescribed. Clearance of creatinine (Ccr) and urate (Cur), and 24-hour urinary uric acid (24-h Uua) were calculated using urine 24-h collection urine samples urinary pH, along with pH,density, and abnormals. Undissociated urinary uric acid concentration (UUua) and also 24-hour undissociated urinary uric acid excretion (24-hUUuua) were calculated in each urine sample using a nomogram. Cox proportional hazard regression analysis using a forward stepwise model was used to identify those variables independently associated with lithiasis as outcome. The rate of lithiasis was compared to that of patients on allopurinol and no previous history of renal stones.

Results: 216 patients, mean age of 59±13 years (range 24-92) and 784 patient-year exposure. 206 patients with renal underexcretion of uric acid (Cur<6 ml/min) and 10 were treated with uricsurics despite normal excretion (overproducers) of uric acid due to intolerance to allopurinol. There were 21 events, 7 oxalate, and 14 uric acid or mixed uric acid-oxalate stones. When all patients were included in multivariant regression analysis, two variables showed increased risk hazard for developing lithiasis: clearance of uric acid at baseline (Risk Hazard 1.52 per ml/min increase, 95%CI 1.13-2.05) and UUua during follow-up (Risk Hazard 1.11 per mg/dL increase, 95% CI 1.06-1.15). When patients showing overproduction were excluded from analysis, only UUua during follow-up remained to be statistically significant (Risk Hazard 1.12 per mg/dL increase, 95% CI 1.08-1.16). There was an exponential increase in the cumulated incidence of lithasis when patients were stratified on UUua (Table 1). For comparison, data 330 patients on allopurinol with no previous history of lithiasis and 985 patient-yr follow up were analyzed. Patients on uricosurics who showed UUua<20 mg/dl did not show an increase in the rate of lithiasis or events per 100-pt-yr compared to that of patients on allopurinol (Table 1).

Table 1. Events (lithiasis) depending on UUua strata and patients treated with allopurinol.

	UUua < 10 mg/dL	UUua 10-19 mg/dL	UUua 20-29 mg/dL	UUua ≥30 mg/dL	UUua < 20 mg/dL	Allopurinol
Events	1/90	6/84	8/32	6/10	7/174	10/330
%	1.11	7.14	25.00	60.00	4.02	3.03
Events per 100 pt-yr	0.30	1.89	7.41	17.14	1.08	1.01

Conclusion: Clearance of uric acid at baseline may be useful to exclude patients with normal renal handling of uric who could be exposed to a higher risk of developing lithiasis during the treatment with uricosuric drugs. The concentration of UUua was found to be the only variable independently associated with an increased risk of lithiasis during follow-up.

Disclosure: F. Perez-Ruiz, Pfizer Inc, 5, ARDEA Biosciences, 5, Savient, 5, Ipsen, 5 .

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Risk of Recurrent Gout After Acute Infection and Vaccination: The Online Case-Crossover Gout Study. Yq. Zhang[1], C. Chen[1], T. Neogi[1], C. Chaisson[1], Hyon K. Choi[2] and David J. Hunter[3], [1]BUSM, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]New England Baptist Hospital, Boston, MA

Purpose: Acute infection induces a systematic inflammatory response, which may act as a precipitant of pro-inflammatory stimuli to trigger recurrent gout attacks. Similarly, vaccination could trigger pro-inflammatory stimuli and increase the risk of recurrent gout. Furthermore, acute infection and vaccination could lead to fever and dehydration, which may also trigger recurrent gout. We evaluated the risk of recurrent gout after acute infection and vaccination in the Online Case-Crossover Gout Study.

Methods: The Online Case-Crossover Gout Study is a self-controlled prospective study to assess a set of putative risk factors triggering recurrent gout attacks. Subjects who had experienced a gout attack within the past year were recruited online and were asked to provide access to medical records for verification of gout diagnosis. Subjects were asked to log onto the study website when they experienced a gout

attack. Risk factors, including acute infection and vaccination occurring each day over the two-day period prior to an acute gout attack (case-period) were assessed using an online questionnaire. The same questionnaire was used over each of the two days during an intercritical period (control-period). We examined the relation of acute infection and vaccination over the 2-day period to the risk of recurrent gout attacks using conditional logistic regression adjusting for alcohol consumption, purine intake, and diuretic use.

Results: Include in this analysis were 535 subjects who experienced recurrent gout attacks during the study period. Participants were predominantly white (89%) and male (78%), and 58% had a college education. Of the 517 medical records obtained to date, 76% fulfilled ACR criteria for a gout diagnosis. The median time between the onset of gout attack and logging on to the website was 2 days. The proportions of acute infection and vaccination were 6.4% and 1.0%, respectively, over the control-periods. The corresponding proportions were 10.1% and 2.6% over the case-periods. Acute infection and vaccination were associated with an increased risk of recurrent gout attacks, with adjusted odds ratios of 1.7 (95% CI: 1.2-2.4) and 5.3 (95% CI: 1.4-19.6), respectively

Conclusion: Acute infection and vaccination increase the risk of recurrent gout attacks among gout patients. Our findings provide support for the concept that acute infection and immunization act as precipitants of pro-inflammatory stimuli or dehydration to trigger recurrent gout attacks.

Triggers (over 2-day period)	Control-periods	Case-periods	Adjusted OR (95% CI)
Infection			
No	1233	1009	1.0 (reference)
Yes	84	113	1.7 (1.2-2.4)
Immunization*			
No	776	640	1.0 (reference)
Yes	8	17	5.3 (1.4-19.6)

* Data were collected in the late phase of the study

Disclosure: Y. Zhang, None; **C. Chen**, None; **T. Neogi**, None; **C. Chaisson**, None; **H. K. Choi**, None; **D. J. Hunter**, None.

1501

Documentation of Fewer Gout Flares After Long-Term Urate-Lowering Treatment. M. A. Becker[1], H. R. Schumacher Jr.[2], S. Chohan[1], P. MacDonald[3], B. Hunt[3] and R. L. Jackson[3], [1]University of Chicago, Chicago, IL, [2]U Penn & VA Med Ctr, Philadelphia, PA, [3]Takeda Global Research & Development Center, Inc., Deerfield, IL

Purpose: Compare efficacy, gout flare rates, and safety of 6-month treatment with febuxostat (FEB) or allopurinol (ALLO) between subjects whose gout and hyperuricemia had been successfully treated in prior clinical trials with either FEB or ALLO for 3-5 yrs vs subjects not previously so treated.

Methods: In the 6-month CONFIRMS trial, 2269 subjects with gout and hyperuricemia were randomized to receive daily FEB 40 or 80 mg or ALLO (300 or 200 mg based on creatinine clearance). A subset of 276 subjects had previously participated in the FOCUS (5 yrs) or EXCEL (3 yrs) trials, maintaining sUA <6 mg/dL for up to 5 yrs while receiving FEB 40, 80, or 120 mg, or ALLO 300 mg. Randomization was stratified by renal function and by participation or lack thereof in the prior long-term urate lowering therapy (ULT) studies. All subjects who had previous ULT washed out for 30 days and had baseline serum urate level (sUA) ≥8 mg/dL before participating in CONFIRMS. Subjects received gout flare prophylaxis with colchicine or naproxen throughout the study. Subjects received gout flare prophylaxis with colchicine or naproxen throughout the study.

Results: The demographic and co-morbid features of subjects in the prior treatment subset did not differ from those of the entire group. The proportion of subjects with prior participation who achieved sUA <6 mg/dL at the final visit in the FEB 40 mg, FEB 80 mg, and ALLO groups was 57%, 77%, and 52%, respectively vs 43%, 66%, and 41%, respectively, among subjects without prior participation ($p \leq 0.05$ for comparison of subjects with and without prior participation for each treatment group). The **figure** shows the proportion of subjects in each treatment group requiring gout flare treatment. Overall, subjects with prior participation in each treatment group had lower rates of flares

(p≤0.001) vs those without prior participation. Rates of AEs were similar among subjects with and without prior participation, with the most frequent being URIs, abnormal LFTs, musculoskeletal pain, and diarrhea.

Conclusion: The subset of subjects who had previously received 3-5 yrs of ULT achieved sUA <6 mg/dL more often and had substantially fewer reported gout flares vs subjects who had not. This demonstrates the clinical benefit of maintaining sUA <6 mg/dL over time in reducing the incidence of subsequent gout flares and supports the likelihood of long-term urate pool depletion during successful ULT.

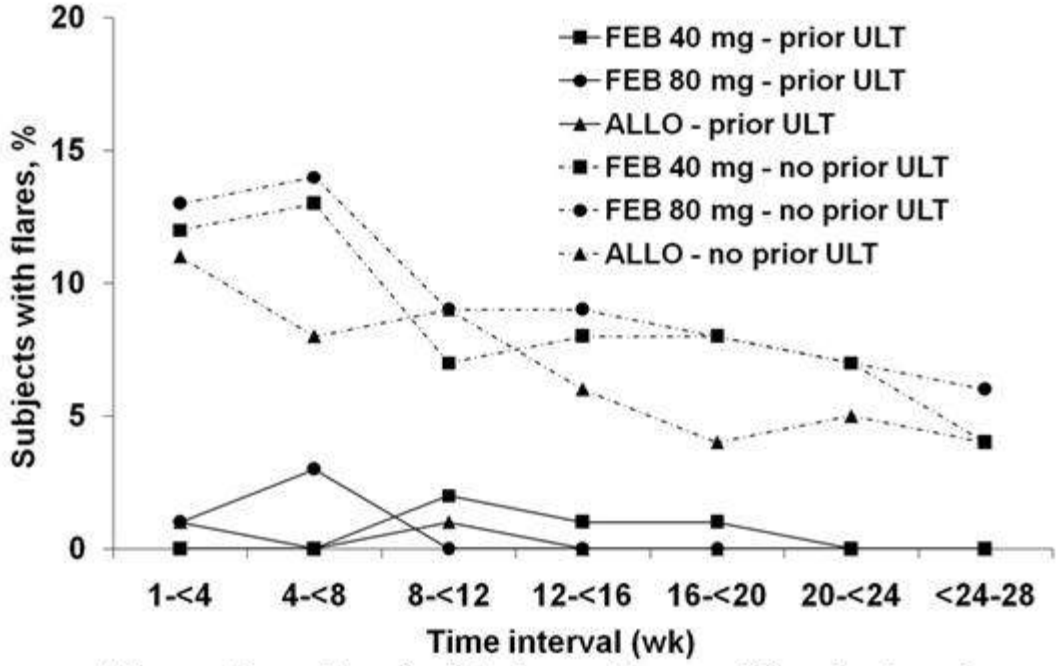

Figure. Proportion of subjects receiving gout flare treatment.

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1502

Relationship Between Serum Urate and Plasma Oxypurinol - Is There a Target Plasma Oxypurinol Concentration to Achieve Serum Urate ≤6mg/Dl. Lisa Stamp[1], J.L. O'Donnell[2], M. Zhang[3], C. Frampton[4], PT Chapman[3] and M. Barclay[3], [1]University of Otago, Dunedin, New Zealand, [2]Canterbury Health Laboratories, Christchurch, [3]Christchurch Hospital, Christchurch, New Zealand, [4]University of Otago, Christchurch, New Zealand

Purpose: Allopurinol is the most commonly used urate lowering therapy. The most feared adverse effect of allopurinol is the allopurinol hypersensitivity syndrome (AHS) which can be fatal. It has been suggested that impaired renal function, concomitant diuretic therapy and plasma oxypurinol >100µmol/L are associated with AHS. A therapeutic range of plasma oxypurinol 30-100µmol/L 6-9 hours post dose has been suggested. We wished to determine the relationship between plasma oxypurinol and serum urate (SUA) and the accuracy of the postulated therapeutic oxypurinol range.

Method: Patients with gout on stable dose allopurinol for at least one month were recruited. Allopurinol dose was gradually increased to obtain the target SUA ≤6mg/dL. Patients were seen monthly until SUA was ≤6mg/dL for 3 consecutive months. Then patients were seen 3 monthly until at least 12 months after study entry. Plasma oxypurinol at 6-9 hours post dose was determined at each visit using HPLC.

Results: 45 patients were enrolled, mean age 59.3 years (27-83), 93.3% male. Mean CrCl was 61.9ml/min (19-132) and mean SUA 7.4 mg/dL (6-10.8mg/dL). The mean allopurinol dose at baseline was 221.1mg/d (100-400mg/d) and mean plasma oxypurinol 92.3µmol/L (42.5-266.7µmol/L). 31/36 (85%) patients achieved the target SUA <6mg/dL at the 12month endpoint, mean SUA 5mg/dL (3.9-5.9mg/dL), mean plasma oxypurinol 141.8µmol/L (71.6 – 359.8µmol/L) and mean allopurinol dose 359.7 mg/d (150-600mg/d). Using mixed-effect linear modelling, allowing for individual patient effects, there was a significant relationship between allopurinol dose and plasma oxypurinol concentration ($p<0.001$). An increase of allopurinol dose by 100mg resulted in a mean increase in plasma oxypurinol of 46.8µmol/L. Additionally, mixed-effect linear modelling allowing for individual patient effects revealed a significant inverse relationship between SUA and plasma oxypurinol ($p<0.001$). A mean increase in plasma oxypurinol of 47µmol/L resulted in a 0.1mmol/L reduction in SUA. For those patients who achieved a SUA <6mg/dL, plasma oxypurinol was on average 136.8µmol/L at the first point when SUA reached the target. In comparison, plasma oxypurinol was on average 100.8µmol/L when SUA was >6mg/dL. There were no serious adverse events despite the higher plasma oxypurinol concentrations.

Conclusion: Increasing allopurinol dose results in an increase in plasma oxypurinol and a reduction in SUA. In general plasma oxypurinol, concentrations above the proposed therapeutic range were required to achieve SUA <6mg/dL. Larger studies will be required to determine the role of dose adjustment based on plasma oxypurinol concentrations.

Disclosure: L. Stamp, WYETH, 6 ; **J. L. O'Donnell**, None; **M. Zhang**, None; **C. Frampton**, None; **P. Chapman**, None; **M. Barclay**, None.

1503

Proinflammatory Effects of Octacalcium Phosphate (OCP) Crystals Are Mediated by IL-1b through NALP3 Inflammasome Activation. Borbala Pazar[1], Nathalie Busso[1], Laeticia Kolly[1], Sharmal Narayan[1], Veronique Chobaz[1], Nathalie Bagnoud[1], Hang-Korng Ea[2], Jurg Tschopp[3], Frédéric Lioté[2] and Alexander K. So[1], [1]Department of Rheumatology, CHUV, Lausanne, Switzerland, [2]INSERM UMR-S 606, Lariboisière Hospital, Paris Diderot University, Paris, France, [3]University of Lausanne, Lausanne, Switzerland

Purpose: OCP is a member of the family of basic calcium phosphate (BCP) crystals that are capable of eliciting joint and periarticular inflammation. BCP crystals have also been associated with cartilage destruction and osteoarthritis but the underlying mechanisms remain unclear. We investigated the pro-inflammatory effects of OCP in vitro and in vivo, with particular emphasis on the role of the NALP3 inflammasome.

Method: We tested the effects of OCP crystals in vitro on THP1 cells and mouse bone marrow derived macrophages (BMDM). To determine the role of the NALP3 inflammasome in OCP induced IL-1β production, BMDM from mice deficient in caspase-1, ASC and NALP3 were studied. IL-1β production was measured in the supernatants. In vivo, we tested the proinflammatory properties of OCP crystals in the mouse peritonitis model. The role of IL-1 in OCP-induced inflammation was assessed by the administration of IL1RA (anakinra) at the same time as crystal injection. Total neutrophil counts and IL-1β were measured in the peritoneal fluid.

Results: In vitro, THP1 cells stimulated with different concentrations of OCP crystals produced IL-1β in a dose-dependent manner. Release of IL-1β was maximal at 500 µg/ml (IL1 β = 2302.6 ± 46.9 pg/ml at 6h). Similarly, BMDM from wild type (WT) mice produced high concentrations of IL-1β (1123.9 ± 224.1 pg/ml) after stimulation with 500 µg/ml OCP crystals. Mouse BMDM deficient for NALP3, ASC and Caspase-1 did not produce any IL-1β after OCP crystal stimulation. In the mouse peritonitis model, injection of 1 mg of OCP crystals significantly increased total neutrophil counts (control mice: 2.6 x 104 cells, injected mice: 4.6 x 106 cells) and peritoneal exudate IL-1β levels (control mice: 2.6 ± 0.4 pg/ml, injected mice: 9.5 ± 3.2 pg/ml). The IL1 receptor antagonist, anakinra (200 µg/mouse) significantly reduced peritoneal neutrophil influx (OCP: 4.6 x 106 cells, OCP + anakinra: 1.6 x 106 cells, MSU: 4 x 106 cells, MSU + anakinra: 1.76 x 106 cells).

Conclusion: OCP crystals strongly induced IL-1β production in vitro via the NALP3 inflammasome. This was confirmed in vivo in the peritoneal inflammation model, as anakinra significantly inhibited neutrophil influx. IL-1β blockade represents an interesting and novel strategy to inhibit OCP-induced inflammation in human disease

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1504

Musculoskeletal Complications of Hereditary Hemochromatosis: A Case-Control Study. P. Richette, Sébastien Ottaviani, Eric Vicaut, Philippe Orcel and Thomas Bardin, Hopital Lariboisière, Paris, France

Purpose: Osteoporosis (OP) and an arthropathy that mimics osteoarthritis (OA) are considered as classical complications of hereditary hemochromatosis (HH), but have never been investigated in a cross-sectional study. The aim of this work was to determine whether HH is associated with an increased prevalence of OA and OP.

Method: A questionnaire designed for self-completion was obtained from 303 patients with HH and 306 age- and sex-matched unaffected controls.

Results: Mean age of patients was 60.1 ± 11.3 years and 47.4% were female. Mean ferritin level at diagnosis was 1556 ± 1623 µg/l. More HH patients than controls had been given a diagnosis of OA: 50.5% vs. 28.9% (aOR=2.52 [95% CI 1.7-3.5]). Compared with the control group, we found that HH patients had a higher crude and adjusted risks of knee and hip replacement prosthesis (aOR=4.9 [95% CI 1.0-23.1] and aOR=5.1 [95% CI 2.2-11.9], respectively). Prevalence of self-reported back pain and sciatica were also higher in HH patients (OR=3.5 [95% CI 2.5-5.0] and aOR=2.0 [95% CI 1.4-2.8], respectively).

In the crude analysis, we found that more patients than controls had been diagnosed with OP: 23.3% vs. 4.6% (P=<0.0001, OR=6.2 [95% CI 3.4-11.4]). This was associated with an increased crude risk of wrist fracture (OR=1.73 [95% CI 1.0-2.9]. The difference in OP prevalence between groups persisted after adjustment for confounding factors (aOR=4.82; 95%CI [3.35-9.91]). In the adjusted model, a non significant trend of increased prevalence of wrist or vertebral fractures was found in HH patients (aOR=1.6; 95%CI [0.9-2.9] and aOR=1.6; 95%CI [0.7-3.6], respectively). The severity of iron overload, defined by a ferritin level at diagnosis 1000 µg/l, was associated with OA (P=<0.0001) and the presence of hip prosthesis (P=0.01). OP was more frequent in HH patients with a severe iron overload (P=0.004) as were wrist (P=0.03) and vertebral fractures (P=0.04), respectively. The mean delay between the start of the joint complaints and the diagnosis of HH was 8.6 ± 8 years. One-third of patients stated that their pain worsened following phlebotomy. Joint pain was the symptom reported to prominently affect the quality of life of HH patients (57% of responders), following by asthenia (33%).

Conclusion: This first case-control study demonstrates a significant association between HH and OA, low back pain and OP. Joint involvement in patients with HH can be severe, especially when serum ferritin levels at diagnosis are increased to 1000 mg/L or more. Physicians should be better aware of HH, to achieve an earlier diagnosis.

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1505

How Successful Are Joint Aspirations in Patients with Suspected Gout? Soumya G. Rao[1], Gilda M. Clayburne[2], Janet E. Dinnella[1] and H. Ralph Schumacher Jr.[1], [1]U Penn & VA Med Ctr, Philadelphia, PA, [2]VA Medical Center, Philadelphia, PA

Purpose: Crystal proof is accepted as the gold standard for the diagnosis of gout. Synovial fluid (SF) aspiration may be difficult from some joints such as shoulders, wrists, fingers, ankles and feet. There are few reports evaluating success of joint aspirations in patients suspected of acute gout.

Method: All SF aspiration attempts by faculty or fellows at this center are recorded in detail in the electronic system. We retrospectively collected data for 1 year (Jan 2008 - Dec 2008) on any patient who underwent arthrocentesis with gout as a diagnostic consideration. If the amount of SF collected was determined to be sufficient to perform a crystal search, the arthrocentesis was considered successful. 139 patients with a clinical diagnosis of suspected acute gout were considered for this study. SF aspiration was attempted from 156 joints for analysis with compensated polarized light microscopy. Of the 139 patients, 87 had a history of gout (38 had prior positive crystal proof) and 47 patients had an initial swollen joint.

Results: Table:

	Total	Knee	MTP	Ankle	Wrist	Olecranon	MCP	Shoulder
Total attempts	156	78	25	13	11	20	8	1
Unsuccesful Aspiration	15	0	5	3	3	1	2	1
Succesful Aspiration	141	78	20	10	8	19	6	0
MSU	114	60	19	6	8	15	6	0
Other Diagnosis	28							
Septic Joint	5	3	1			1		
Rheumatoid Arthritis	1					1		
Traumatic	4	2				2		
Osteoarthritis	7	6		1				
CPPD	8	8*						
Undetermined	3			3				

*1 patient had both MSU and CPPD

90% of aspiration attempts were successful. Monosodium urate (MSU) crystals were identified in 73% of samples. Knee aspirations were most common (50%) followed by MTPs (16%). We had 100% success in knee aspirations. MTP aspirations were successful in 80% and they resulted in identification of MSU crystals in 95%. Other diagnoses were made or supported in 18% of the attempts. Interestingly 2 of the patients without crystals found were re-aspirated and were found to have positive MSU crystals in an adjacent joint. Unresolved issues were most common in the ankle joint. Some patients with previous MSU at some joint had no MSU crystals and other causes for the arthritis were found.

Conclusion: Joint aspirations even of the more difficult joints have a good chance of confirming suspected gout or supporting some important alternative diagnosis. Further evaluation of techniques for and experience with aspiration of some joints may improve results.

Disclosure: S. G. Rao, None; **G. M. Clayburne**, None; **J. E. Dinnella**, None; **H. R. Schumacher**, None.

1506

A Strong Role for the ABC-Binding Cassette G2 (ABCG2) Gene in Susceptibility to Gout in New Zealand Western Polynesian, but Not Eastern Polynesian (Mäori), Cases and Controls. Tony R. Merriman[1], Nicola Dalbeth[2], Amanda Phipps-Green[1], Marilyn Merriman[1], Ruth Topless, Peter Gow[3], Andrew Harrison[1], John Highton[1], Peter B. B. Jones[2], Lisa Stamp[1] and Jade Hollis-Moffatt[1], [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Counties Manukau District Health Board, Auckland, New Zealand

Purpose: New Zealand (NZ) Māori and Pacific Island men have the highest reported rates of gout. Genetic variation in ABC efflux transporter G2 (*ABCG2*), a renal urate transporter, is convincingly associated with gout in Caucasian, with the non-synonymous single nucleotide polymorphism (SNP) Q141K (*rs2231142*) the likely etiological variant. The aim of this study was to examine a role for *ABCG2* in susceptibility to gout in three NZ cohorts (of Māori, Pacific Island and Caucasian ancestry).

Methods: Patients that satisfied the ACR classification criteria for gout (n=55, 102 and 171, for Māori, Pacific Island and Caucasian respectively) were recruited from rheumatology outpatient clinics. The control samples were comprised of 89, 41 and 555 individuals, respectively, without arthritis. SNP *rs2231142* was genotyped using Taqman. Population stratification in the Māori and Pacific Island analyses was accounted for using genomic control markers together with STRUCTURE and STRAT software.

Results: Strong association of the minor allele of *rs2231142* with gout was observed in the Pacific Island samples (OR = 4.13, $P = 9.8 \times 10^{-6}$) but not in the Māori samples (OR = 1.59, $P = 0.25$). Similar results were evident after accounting for population structure ($P_{Maori} = 0.15$; $P_{Pacific} < 0.001$). Within the Pacific Island case samples there was a region-specific effect; 93 % of the risk allele positive individuals were Western Polynesian (Samoa, Tonga, Niue, Tokelau), compared to 58% of the risk allele negative individuals, with the remainder Eastern Polynesian (Cook Islands); $P = 2 \times 10^{-5}$. The genotype distribution in the Cook Island Māori cases (1,1 = 74%; 1,2 = 26%; 2,2 = 0%) was similar to that observed in the NZ Māori cases. Association with gout was also seen in the Caucasian samples (OR = 2.00, $P = 9.7 \times 10^{-6}$).

Cohort	Genotype (n, freq)			Minor allele (n, freq)	OR [95% CI]	$P_{allelic}$	P_{strat}
	1/1	1/2	2/2				
Māori							
Case	35 (0.686)	16 (0.314)	0 (0.000)	16 (0.157)	1.59 [0.76-3.31]	0.25	0.15
Control	64 (0.790)	17 (0.210)	0 (0.000)	17 (0.105)			
Pacific Island							
Case	33 (0.327)	43 (0.426)	25 (0.248)	93 (0.460)	4.13 [2.14-8.00]	9.8×10^{-6}	< 0.001
Control	25 (0.658)	13 (0.342)	0 (0.000)	13 (0.171)			
Caucasian							
Case	101 (0.601)	59 (0.351)	8 (0.048)	75 (0.223)	2.00 [1.47-2.73]	9.7×10^{-6}	-
Control	429 (0.763)	125 (0.222)	8 (0.014)	141 (0.125)			

Conclusion: Our data confirm a role for *ABCG2* in gout susceptibility in NZ Pacific Island and Caucasian sample sets. Unlike the situation at *SLC2A9* where the Caucasian-associated variants are considerably stronger risk factors for gout in both Māori and Pacific Island people than in Caucasian, the ABCG2 Q141K variant has a stronger effect only in Pacific Island people. The reason for this could be genetic difference between Western and Eastern Polynesian populations.

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1507

Low Glycosaminoglycan Levels in Osteoarthritic Articular Cartilage Vesicles. Kathryn Kiehn, Claudia Gohr and Ann K. Rosenthal, Medical College of Wisconsin, Milwaukee, WI

Purpose: Calcium containing crystals are commonly found in osteoarthritic joints and correlate with increased severity of cartilage degeneration. Articular cartilage vesicles (ACV) are chondrocyte derived extracellular organelles active in calcium crystal formation. Quantification of calcium uptake by ACVs is a standard model of pathologic cartilage mineralization. Paradoxically, ACVs isolated from osteoarthritic cartilage form fewer crystals than those from normal cartilage. The extracellular matrix, comprised largely of collagen and proteoglycans, dramatically affects ACV mineralization behavior in vitro. We recently showed that human ACVs contain higher levels of type II collagen than porcine ACVs, and this correlated with a reduced capacity for mineralization. Little is known about proteoglycans and their component glycosaminoglycans (GAGs) in ACV preparations. This study characterizes the GAG and proteoglycan composition of ACVs and compares ACVs derived from normal human, normal porcine and osteoarthritic human articular cartilage.

Method: Porcine cartilage from adult knee joints (n=5), human osteoarthritic cartilage from knee replacement surgery for osteoarthritis (n=5) and age matched normal human cartilage from NDRI (n=2) was obtained. ACVs were isolated by sequential enzymatic digestion followed by differential centrifugation. GAG analysis was performed using the dye binding Blyscan assay. Keratan sulfate was estimated by measuring chondroitinase ABC resistant GAGs. Western blotting was performed with antibodies against protein cores of biglycan, fibromodulin, aggrecan, and decorin.

Results:

	Normal	**Osteoarthritic**	**Porcine**
Total GAGs (ng/mg protein)	227.6 ± 29.3	108.5 ± 19.6	157.07 ± 23.8
% Keratin Sulfate	35 ± 8	74 ± 11	64 ± 4

1. All ACV fractions contain GAGs, despite enzymatic exposure to hyaluronidase and trypsin.
2. Osteoarthritic ACVs contain less sulfated GAGs ($p \leq 0.001$) and a higher percentage of keratan sulfate ($p \leq 0.02$) than normal human ACVs
3.Porcine ACVs have a GAG composition intermediate between normal and osteoarthritic human ACVs.
4. Non-quantitative Western blotting revealed similar types of proteoglycans on ACVs from osteoarthritic, normal human and porcine ACVs

Conclusion: GAGs are present in ACV preparations. Differences in quantities and types of GAGs in ACV preparations derived from osteoarthritic and normal human cartilage reflect matrix changes seen in aging and osteoarthritis. However, unlike type II collagen levels, the lower levels of GAGs on osteoarthritic ACVs are unlikely to explain their reduced capacity to mineralize in vitro. Knowledge of the residual matrix components in ACVs is crucial to understanding their mineralization behavior, as matrix components may dramatically affect crystal formation. Further characterization of ACVs will allow for new insights into the pathogenesis of cartilage mineralization and osteoarthritis.

Disclosure: K. Kiehn, None; **C. Gohr**, None; **A. K. Rosenthal**, None.

1508

Developing American College of Rheumatology and European League against Rheumatism Criteria for Definition of a Flare in Patients with Gout. Angelo L. Gaffo[1], H. R. Schumacher Jr.[2], Kenneth G. Saag[3], William J. Taylor[4], Jeroan Allison[3], Lang Chen[3], Janet E. Dinnella[2], Ryan C. Outman[3] and Jasvinder A. Singh[5], [1]Birmingham VA Medical Center, Birmingham, AL, [2]U Penn & VA Med Ctr, Philadelphia, PA, [3]UAB, Birmingham, AL, [4]University of Otago Wellington, Wellington, New Zealand, [5]VA Medical Center, Minneapolis, MN

Purpose: Various non-validated flare criteria have been used in published gout studies. Our objective is to develop criteria for definition of acute flare in patients with known gout.

Method: Following Delphi panels and cognitive mapping, possible flare criteria were identified, including report of swollen, tender, or warm joints, pain & global assessment, Health Assessment Questionnaire (HAQ), and acute phase marker levels. For greatest relevance to clinical trials utilization, we also focused on patient self-reported items and added patient self-report of a flare. Data were then cross-sectionally collected on 212 consecutive crystal-proven gout patients from 8 international clinic sites. We evaluated potential gout criteria against a gold standard of presence of a gout flare defined by an experienced investigator who examined each patient. Possible gout flare criteria rules were initially selected using multivariate logistic regression. Subsequently, an approach using the number of independent criteria and a classification tree were utilized to define the diagnostic rules.

Results: The mean age (SD) of the study sample was 56.3 (15) years, 210 (98%) were men, and gout duration was 13 ± 11 years. Fifty-four (26%) patients were having physician-diagnosed flares. Using multivariable logistic regression the presence of any warm joint [OR 3.3, 95% CI 1.1-10.4], pain at rest > 3 (scale from 0 to 10) [OR 11.7 95% CI 2.5-55.6], patient self-defined flare [OR 25.6 95% CI 5.8-113.0], and presence of any swollen joint [OR 22.2 95% CI 1.1-434.0] were more significantly associated with presence of an acute gout flare. Using the number of criteria format the greatest discriminating power was seen with ≥ 3 criteria (sensitivity 90.7%; specificity 82.1%) (Table). A classification tree identified pain at rest > 3 followed by patient self-defined flare as the rule most strongly associated with a flare (sensitivity 83.3%; specificity 90.4%). The areas under the curve for the number of criteria model and the classification tree were 0.931 and 0.873, respectively.

Conclusion: We propose criteria for a gout flare based on patient self-report items. Patient self-reported flare, overall pain at rest, warm joints, and swollen joints were the items most consistently predictive of flares. Final validation of the criteria will examine its performance among patients participating in clinical trials.

# of gout criteria required*	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy
0	100	0	25.7	NA	25.7
1 or more	100	26.3	32.0	100	45.2
2 or more	98.2	60.3	46.1	99.0	70.0
3 or more	90.7	82.1	63.6	96.2	84.3
4 or more	72.2	95.5	84.8	90.9	89.5

*Criteria examined: positive gout flare according to patient, presence of any swollen joint, presence of any warm joint, and overall pain at rest greater than 3.
PPV - Postive Predictive Value
NPV - Negative Predictive Value

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1509

The Independent Impact of Gout On Risk for Coronary Heart Disease Among Elderly Women: A Population-Based Study. Mary De Vera, M. Mushfiqur Rahman, Vidula Bhole, James Rankin, Jacek Kopec and Hyon K. Choi, Arthritis Research Centre of Canada / University of British Columbia, Vancouver, BC

Purpose: Despite the substantial prevalence of gout among aging women, little is known about associated cardiovascular risks. While it has been shown that men with gout have an increased risk of coronary heart disease, no corresponding data are available for women. Our objective was to evaluate the independent association between gout and acute myocardial infarction (AMI) requiring hospitalization among elderly women, aged ≥65 years.

Method: Using population-based administrative health data from a musculoskeletal cohort and a cohort study design, we compared incidence rates of AMI in 9,642 newly diagnosed gout patients and 48,210 controls, with no history of ischemic heart disease, matched (1:5 ratio) on age, gender, and length of medical record. Definitions of gout exposure were based on ICD-9 codes in physician claims and hospitals databases. AMI outcomes were ascertained from hospitalization data; discharge information was used to determine fatal and non-fatal outcomes. We performed Cox proportional hazards models stratified by gender to estimate the relative risk (RR) for AMI, adjusting for baseline characteristics (age, history of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease [COPD]) and time-dependent prescription medication use (non-steroidal anti-inflammatory drugs, glucocorticoids, anticoagulants, diuretics, statins, and hormone replacement therapy).

Results: The mean age for the cohort was 73.9 years and for women, 75 years. The proportion of individuals with hypertension, COPD, diabetes, and hyperlipidemia were 45%, 21%, 14%, and 11%, respectively; and for women, 50%, 21%, 13%, and 12%, respectively. Over a mean 6-year study follow-up, we identified 3,268 (778 fatal, 2,490 non-fatal) incident AMI cases, 996 among women. Women with newly diagnosed gout had 39% increased risk of AMI (95% CI, 1.20 to 1.61) and 41% of non-fatal AMI (95% CI, 1.19 to 1.67) compared with women without gout **(Table)**. These RRs were significantly larger than those among men (p values for interaction, 0.003 and 0.005, respectively).

	Women			**Men**			**Multivariate p-value for interaction by**
	N	**Crude**	**Multivariate**	**N**	**Crude**	**Multivariate**	

		RR	RR		RR	RR	gender
All AMI	996	1.67 (1.45, 1.93)	1.39 (1.20, 1.61)	2,272	1.19 (1.07, 1.32)	1.11 (0.99, 1.23)	0.003
Non-fatal AMI	735	1.71 (1.44, 2.02)	1.41 (1.19, 1.67)	1,755	1.18 (1.05, 1.33)	1.11 (0.98, 1.25)	0.005

Conclusion: These population-based data indicate that women with gout are at an increased risk for AMI, and the magnitude of excess risk is higher than men. Potential mechanisms behind these observations include gender differences in serum uric acid levels, uric acid metabolism, and female hormonal influence. These findings provide extended support for aggressive management of cardiovascular risk factors in all gout patients, and particularly among elderly women.

Disclosure: M. De Vera, None; **M. M. Rahman**, None; **V. Bhole**, None; **J. Rankin**, None; **J. Kopec**, None; **H. K. Choi**, None.

1510

Chronic Fructose Ingestion Stimulates Hepatic Purine Release and Promotes the Development of Fatty Liver. Zhongsheng Peng[1], Tuere Wilder[1], Adrienne Williams[1] and Bruce N. Cronstein[2], [1]NYU School of Medicine, New York, NY, [2]New York Univ Med Ctr, New York, NY

Purpose: Recent studies indicate that increased fructose ingestion is a risk factor for development of hyperuricemia and gout. Hyperuricemia is also more common in obese individuals and often accompanies the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). It has long been known that fructose induces ATP hydrolysis in the liver and the hydrolyzed ATP is further metabolized to uric acid in the intracellular and extracellular space (by ecto-5'nucleotidase, CD73). An intermediate in ATP hydrolysis to uric acid, adenosine, acts at one or more of four receptors (A1, A2A, A2B and A3) to effect a variety of physiologic and pharmacologic effects. Because we have recently demonstrated that A1 and A2B adenosine receptors play a critical role in the development of fatty liver due to ethanol ingestion, another risk factor for hyperuricemia (Peng, Z. J Clin Invest, 2009), we therefore determined whether adenosine and its receptors play a role in fructose-induced NAFL as well.

Method: Fatty liver was induced by feeding a high-fructose diet (protein 20%, fat 13%, fructose 60%, and complex carbohydrates 7% of total kcal) for six weeks. Mice (all on C57Bl6 background) were treated with either the selective A1 receptor antagonist DPCPX or the selective A2B receptor antagonist enprofylline for the final four weeks of the experiment. Hepatic steatosis was graded semiquantitatively and hepatic triglyceride was measured photometrically. Adenosine concentration in the supernatant of cultured hepatic slices was measured by HPLC.

Results: Livers from fructose-fed mice released significantly more adenosine than chow-fed mice (643±53 vs 91±2nM, n=6, $p<0.01$) and this increase depended, in part, on the presence of ecto-5'nucleotidase since the increase was blunted in livers of CD73KO mice (384±18 vs 26±3 nM, n=6, $p<0.01$). WT and A3KO mice developed severe hepatic steatosis after chronic fructose ingestion with obvious lipid droplets present in nearly 100% of hepatocytes in both periportal and pericentral areas, but A1KO mice and DPCPX-treated WT mice suffered only minimal fatty change (Steatosis grades: WT 3.9±0.6 or A3KO 3.7±0.4 vs A1KO 2.7±0.5 or DPCPX: 2.8±0.5, $p<0.01$, respectively). Similarly hepatic triglyceride levels increased following fructose ingestion in WT and A3KO mice (WT: from 30±3 to 131±11mg/g; A3KO from 32±2 to 138±11mg/g, n=6, $p<0.01$, respectively) but not so much in A1KO mice or mice treated with DPCPX (A1KO: from 29±3 to 76±6mg/g; DPCPX: 74±11mg/g vs untreated, n=6, $p<0.01$, respectively). Mice treated with enprofylline were similarly protected from developing hepatic steatosis as reflected by steatosis grade (2.5±0.3, n=6, $p<0.01$, vs untreated) and hepatic triglyceride content (72±8mg/g, n=6, $p<0.01$, vs untreated).

Conclusion: These results indicate that chronic fructose ingestion leads to increased release of adenine nucleotides resulting in higher uric acid levels and fatty liver.

Disclosure: Z. Peng, None; **T. Wilder**, None; **A. Williams**, None; **B. N. Cronstein**, CanfFite, 3, Cypress Bioscience, Inc. King Pharmaceutical (licensee of patents above) CanFite Biopharmaceuticals Bristol-Myers Squibb Cellzome Tap Pharmaceuticals Prometheus Laboratories Regeneron (Westat, DSMB) Sepracor Amgen Endocyte Protalex Allos, Inc. Combinator, 5, SLE Foundation, Inc., NY Arthritis Foundation, Board member Vilcek Foundation, 6, King Pharmaceuticals, 7, NIH, 2 .

1511

A Diagnostic Rule for Gout Arthritis in Primary Care without Joint Fluid Analysis. Hein Janssens[1], Jaap Fransen[2], Eloy Van de Lisdonk[1], Piet L.C.M. van Riel[2], Chris van Weel[1] and Matthijs Janssen[3], [1]Radboud University Nijmegen, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Ziekenhuis Rijnstate, Arnhem, Netherlands

Purpose: Gout is a common medical problem, with a world-wide prevalence of 1-2%. Most cases are managed and diagnosed by primary care physicians, and in a large number of patients without joint fluid analysis.We performed a study to estimate the validity of signs and symptoms for gout arthritis in primary care, and to develop a diagnostic rule for gout without the need of synovial fluid analysis.

Methods: Patients with a mono-arthritis were recruited from an open population of 330,000 Dutch inhabitants. Patients with a gout diagnosis according to family physicians (FPs) were enrolled in a diagnostic study (March 2004 through July 2007). Clinical variables, including the presence of monosodium urate (MSU) crystals in the synovial fluid of the affected joint, were collected within 24 hours of presentation to the FP. Statistical significant variables selected after univariate regression, and variables predefined by external knowledge and availability in primary care, were entered in multivariate logistic regression models to predict the presence of MSU-crystals in the synovial fluid. The diagnostic performance of the models was tested. The most appropriate model was transformed to a clinically useful diagnostic rule.

Results: There were 328 patients included. The most appropriate model contained the predefined variables ‘male gender’, ‘acute (mono-)arthritis before’, ‘onset within one day’, ‘joint redness’, ‘MTP1 involved’, ‘hypertension, or one or more cardiovascular diseases’, and ‘serum uric acid>0.35mmol/l’. This model had a ROC-area of 0.85 (95%CI 0.81-0.90). The performance did not change after transforming the regression coefficients to easy-to-use scores and was nearly equal to the statistical optimal model (ROC-area 0.87; 95%CI 0.83-0.91).The final prediction rule after transforming the shrunken regression coefficients resulted in the following clinical scores:Male gender:2,One or more previous attacks:2,Onset within one day:0.5, joint redness:1, Joint location MTP-1:2.5,Hypertension,or one or more CV diseases;1.5,Serum uric acid>0,35mmol/l:3,5.The prevalence of gout at 3 cut-off points were:≤4 points,2%;>4 and <8 points,31% and ≥8 points 80%.

Conclusion: In this study a diagnostic rule for gout was developed, that can be used validly by primary care physicians without joint fluid analysis.In addition it can be used for research purposis

Disclosure: H. Janssens, None; **J. Fransen**, Sanofi Aventis, 2 ; **E. Van de Lisdonk**, None; **P. L. C. M. van Riel**, None; **C. van Weel**, None; **M. Janssen**, None.

1512

Ultrasonography Shows Active Inflammation in Clinically Unaffected Joints in Chronic Tophaceous Gout. Ralf G. Thiele[1] and Naomi Schlesinger[2], [1]University of Rochester, Rochester, NY, [2]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Purpose: To examine whether persistent low-level inflammation is present in asymptomatic, chronic tophaceous gout. It is unclear whether there is ongoing inflammation in chronic tophaceous gout in between attacks, if joints appear unaffected, and serological markers of inflammation remain within normal limits. It is further unclear how erosions develop in gout. In contrast to rheumatoid arthritis, synovial proliferation is only moderate in gout, and bony erosions occur outside of synovial joints as well. In vitro, gouty tophi are surrounded by a corona of foreign body giant cells and an associated inflammatory response of mononuclear cells. Sonographically they are surrounded by an anechoic halo. Persistent inflammation has not been demonstrated yet in vivo.

Method: 45 ultrasound (US) studies of 34 consecutive patients (female = 13, male = 21) were included in this study. Inclusion criteria: 1. History of chronic tophaceous gout, monosodium urate crystal proven. 2. Absence of signs or symptoms of active gout (pain, redness or warmth) during visit. 3. CRP and ESR within normal limits within one week of visit. A total of 1154 images and video clips were reviewed. Examined joints included MTP (n=76); MCP (n=62); ankle (n=16); wrist (n=8); DIP (n=3); PIP (n=5); IP (n=2); knee (n=10); elbow (n=2).

All US studies were performed according to published guidelines, by a rheumatologist certified in musculoskeletal US, with >15 years of US experience (RT). MCP joints were examined from dorsal in long and short axis, first MTP joints from a dorsal, medial and plantar aspect. Tophi were defined as hypo- to hyperechoic, inhomogeneous aggregates with a “wet clumps of sugar” sonographic appearance. Synovial tissue was defined as poorly compressible hypoechoic tissue within the hyperechoic joint capsule or hyperechoic tendon sheath. Gray scale and Doppler studies were performed in all patients. Inflamed tissues were defined as displaying a pulse synchronous power Doppler or color Doppler signal. Studies were performed using 14-18 mHz linear transducers.

Results: Pulse synchronous Doppler signals associated with tophi were seen in 19/34 patients. Inflammatory changes were seen in 24/76 MTP joints; 12/62 MCP joints; 2/10 knee joints; 2/16 ankle joints; 4/8 wrist joints; 2/2 IP joints; 1/5 PIP joints; 1/2 elbow joints. Doppler signals were more often seen over the anechoic corona surrounding tophi or invading tophi than over tissue that emanates from the synovial lining of the joints. Erosions were associated with tophaceous material and not with synovial tissue. Doppler signal could occasionally be seen surrounding tophi as they invade the bone.

Conclusion: Persistent inflammatory changes were seen in more than half of asymptomatic gout patients. ESR and CRP seem to be unreliable markers of subclinical inflammatory gout. Our study suggests that tophi and their surrounding anechoic corona are associated with erosion formation in gout. In contrast to rheumatoid arthritis, synovial proliferation was limited, and invading pannus was not appreciated. Gout is frequently a chronic inflammatory arthropathy.

Disclosure: R. G. Thiele, None; **N. Schlesinger**, None.

1513

Heart Failure and Gout: An Intimate Relationship? Patricia Ninaber[1], Margareth Rolfes[1], Frank Willems[1], Lian Roovers[1], Richard Westra[1] and Matthijs Janssen[2], [1]Rijnstate Hospital, Arnhem, Netherlands, [2]Ziekenhuis Rijnstate, Arnhem, Netherlands

Purpose: Heart failure is strongly associated with gout. Known risk factors for gout are the use of diuretics, renal impairment, overweight and obesity. We analysed in an observational cross-sectional study the prevalence of gout with regard to the severity of heart failure as expressed in levels of NT-ProBNP, left ventricle ejection fraction(LVEF), and functional class.

Methods: We collected by standard questionnaires the clinical characteristics of heart failure patients, the functional class based upon the New York Heart Association (NYHA class) and related risk factors for gout. LVEF was determined using 2D echocardiography. In addition renal function, uric acid and NT-pro BNP(n<15pmol/l) were determined. NT-ProBNP samples were collected in a stable phase of heart failure.

Results: In total 157 patients(98 men, 59.women), mean age 67.9 yrs, (range 36 to 92.yrs), mean disease duration 3.7yrs (range 0.25.to 24 yrs) were included. Gout was diagnosed in 36 patients(28 men ,8 women). All except for two patients were treated with loop diuretics (98,7%) and 84.6.% had elevated serum uric acid levels. In respectively 17 out of 83 patients with NYHA class I and II (20,3%) and 21 out of 57 patients with NYHA class III and IV (36,8%) gout was diagnosed (p=0,06). In patients with gout mean NT-ProBNP was 578 pmol/l (median 548 pmol/l) compared to a mean of 300 pmol/l (median 371 pmol/l) in the group without gout (p<0,0001). Mean LVEF in patients with gout was 26% (22%-30%) compared to 30%(28%-33%) for patients without gout(p=0,11) .

Conclusion: Although almost all patients were treated with diuretics the severity of heart failure as expressed in levels of NT-ProBNP was strongly related to the presence of gout. This applies also for LVEF and functional class although not significantly. This study gives evidence that gout is associated with severe forms of heart failure

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ACR/ARHP Poster Session C

Pediatric Systemic Lupus Erythematosus, Scleroderma, Myositis, Vasculitis, Bone Diseases, Pain

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1514

Biomarkers of Juvenile Dermatomyositis (JDM) Aid in Assessing Disease Activity Over Enzymes Alone. L. Rider[1], L. Li[1], J. Chipman[1], R. Costello[2], T. O'Hanlon[1], T. Fleisher[2], G. Csako[2] and F. Miller[1], [1]NIEHS, NIH, Bethesda, MD, [2]Laboratory Medicine, Clinical Center, Bethesda, MD

Purpose: To evaluate the utility of acute phase reactants, serum muscle enzymes, lymphocyte flow cytometry and von Willebrand Factor VIII related antigen (vWF) as correlates of disease activity in juvenile dermatomyositis (JDM).

Method: Serum or plasma was measured for acute phase reactants, and muscle enzymes using commercial assays (BN-II immunoturbidimetry [Siemens], Hitachi 736 [Roche] and Synchron LX-20 [Beckman Coulter]) in 33 JDM patients (median age 11.5 yrs) and 37 age, gender and race-matched controls, after holding morning medications. Flow cytometry assessed for T, B and NK cell subsets. vWF antigen was quantified by agglutination (STA-R, Roche/Stago). Disease activity measures were assessed by physicians blinded to laboratory results.

Results: Serum levels of muscle enzymes (CK, LDH, AST, ALT, and CK-MB/CK ratio [$P < 0.004$ for all]), acute phase reactants (albumin, alpha-1-acid glycoprotein [AAG], serum amyloid A [SAA], ferritin, haptoglobin, erythrocyte sedimentation rate [ESR]), and vWF lets were increased in JDM patients compared to controls. Lymphocyte subsets (CD3% and CD8% were also increased but NK% was decreased in JDM patients ($P = 0.0001$- 0.045). Many measures correlated moderately with each other ($r_s = 0.25–0.68$, $P = 0.0001–0.046$) and only two were redundant (AST with ALT, $r_s = 0.74$). vWF, CK-MB/CK ratio, albumin, LDH, AAG, AST, ALT, ESR, hematocrit (Hct), and NK% all correlated with MD global activity ($r_s = 0.39–0.60$, $P = 0.001–0.046$). Many of these also correlated with muscle strength by manual muscle testing (MMT) as well as C reactive protein (hsCRP), CD8%, and complement components C3c and C4 ($r_s = 0.39 – 0.62$, $P = 0.001 – 0.048$). Extramuscular activity (ExMA) by the Myositis Disease Activity Assessment Tool correlated with several of these markers, but also with SAA, ferritin, C3c, hsCRP, cystatin C and IgA ($r_s = 0.41– 0.67$, $P = 0.001$- 0.049). Multivariable linear regression modeling using backwards elimination yielded a model that best predicted MD global activity and included vWF, CK-MB/CK, ALT, AST, ESR, Hct and AAG ($R^2 = 0.69$, $P = 0.004$). This was improved from a model that included only muscle enzymes (CK-MB/CK alone, $R^2 = 0.30$, $P = 0.01$). Predictors of strength included CK-MB/CK, CD8%, and albumin ($R^2 = 0.75$, $P < 0.001$), which was also improved over a model consisting of only enzymes (CK-MB/CK alone, $R^2 = 0.19$, $P = 0.042$). ExMA was highly predicted by the combination of vWF, CK-MB/CK, hsCRP, and AAG ($R^2 = 0.85$, $P < 0.001$) and not predicted by muscle enzymes in isolation ($R^2 = 0.0$).

Conclusion: An endothelial activation marker vWF, as well acute phase reactants, peripheral blood lymphocyte subsets, and muscle enzymes are good biomarkers of disease activity for JDM. In various combinations, these predict global activity, strength, and are most helpful in assessing ExMA. The addition of these biomarkers appears to improve upon the assessment of disease activity over muscle enzymes measured in isolation.

Disclosure: L. Rider, NIEHS, NIH, 2 ; **L. Li**, NIEHS, NIH, 2 ; **J. Chipman**, NIEHS, NIH, 2 ; **R. Costello**, NIH Clinical Center, 2 ; **T. O'Hanlon**, None; **T. Fleisher**, NIH Clinical Center, 2 ; **G. Csako**, NIH Clinical Center, 2 ; **F. Miller**, NIEHS, NIH, 2 .

1515

Clinical Indicators of Disease Are Not Indicative of Aspiration Risk in Newly-Diagnosed Patients with Juvenile Dermatomyositis.

Julie Fuller[1], Richard Adams[2] and Marilynn G. Punaro[2], [1]UT Southwestern Medical School, Dallas, TX, [2]Texas Scottish Rite Hospital for Children, Dallas, TX

Purpose: To evaluate in newly-diagnosed patients with juvenile dermatomyositis (JDM) the incidence and severity of dysphagia as assessed by videofluoroscopic swallow study (VFSS) and to correlate this objective data with symptoms reported, physical exam findings and Childhood Myositis Assessment Scores (CMAS).

Methods: This study is a retrospective chart review on all patients with newly-diagnosed JDM at our institution between January 1, 2000 and March 10, 2009 for whom VFSS were available for analysis. VFSS is performed routinely at our institution on all newly-diagnosed patients with JDM by a speech-language pathologist. Patients are seated in an upright position and offered a selection of foods of various textures and liquids of varying consistencies that are treated with barium liquid or paste. Videofluoroscopy during feeding is recorded and reviewed by a speech language pathologist for various swallow abnormalities, including laryngeal penetration and aspiration.

Results: 70 patients met inclusion criteria and had undergone VFSS at the time of diagnosis. The female to male ratio was 3.67:1 (55 F/15 M). 64% of the patients were white, 20% Hispanic, 14% black and 1% Indian. The median age at symptom onset was 5.5 years (range 0.5-17.6 yrs) and the median age at diagnosis was 6.0 years (range 1.7-17.8 yrs). The median age at VFSS was also 6.0 years (range 1.7-17.7 yrs).

Swallow Abnormality	**Yes**	**%**
Abnormal Oral Phase	35	50
Abnormal Pharyngeal Phase		

Delayed swallow	60	86
Pooling/stasis	51	73
Residue	66	94
Laryngeal penetration	47	67
Aspiration	22	31
Any abnormality	70	100

Aspiration rate when	**Present**	**Absent**	**p-value**
Dysphagia + dysphonia	2/3(67%)	20/67(30%)	0.2307
Dysphagia only	10/21(48%)	12/49(24%)	0.0904
Dysphonia only	2/3(67%)	20/67(30%)	0.2307
CMAS score ≤8	4/5(80%)	18/65(28%)	0.0312
Female	21/55(38%)	1/15(7%)	0.0264
Vasculitis	1/13(8%)	20/56(36%)	0.0904

Conclusion: All patients had some abnormality on VFSS; nearly a third of patients had aspiration. Clinical indicators of disease alone did not predict aspiration, which may be asymptomatic.

Disclosure: J. Fuller, None; **R. Adams**, None; **M. G. Punaro**, None.

1516

99mTechnetium-Labeled Methylene Diphosphonate Bone Scintigraphy in the Initial Assessment of Chronic Non-Bacterial Osteomyelitis of Childhood and Adolescents. H. Morbach, T. Schwarz, C. Beck, M. Stenzel, C. Dueren, M. Beer, P. Schneider and H.J. Girschick, University of Wuerzburg, Wuerzburg, Germany

Purpose: Chronic non-bacterial osteomyelitis (CNO) is an inflammatory, non-infectious disorder of the skeletal system with unknown aetiology mainly affecting the metaphyseal regions of long bones in children and adolescents. Radiological methods covering the whole body are an important tool in the diagnostic approach of CNO. Therefore we wanted to analyse the sensitivity of ^{99m}Technetium-labeled methylene diphosphonate (Tc-99m MDP) bone scintigraphy in comparison to whole-body magnetic resonance imaging (MRI) in detecting the extent of inflammatory lesions in CNO at the time of diagnosis.

Methods: Tc-99m MDP bone scintigraphy and MRI has been performed in the initial assessment of 32 patients diagnosed with CNO. Both methods were compared with regard to sensitivity by two independent radiologists.

Results: A total of 54 clinically affected body sites could be found by clinical examination in the patient group. Whereas inflammatory lesions could be detected in 53 out of 54 sites by MRI (98.1 %), Tc-99m MDP only revealed inflammatory foci in 40 out of 54 body sites (74.1 %). In 2 of the 32 patients bone scintigraphy did not reveal any suspicious lesion, whereas MRI revealed multiple lesions in these patients. In particular, the sensitivity of bone scintigraphy was inferior in the detection of symmetrical and/or metaphyseal lesions.

Conclusion: Tc-99m bone scintigraphy was less sensitive in detecting multifocal inflammatory lesions in childhood CNO, potentially due to the symmetrical and/or metaphyseal localization of inflammatory lesions in this disease. Therefore, whole body MRI techniques can be considered as the gold standard in the diagnosis of children and adolescents with CNO.

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1517

Vitamin D Levels in Children with Rheumatologic Diseases. Christina F. Pelajo, Jorge Lopez-Benitez and Laurie C. Miller, Floating Hospital for Children at Tufts Medical Center, Boston, MA

Purpose: Vitamin D deficiency has been linked to development of autoimmune diseases such as inflammatory bowel disease, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (SLE). However, literature about this subject in children is sparse. The aim of this study was to evaluate the prevalence of vitamin D deficiency among children with autoimmune diseases versus non-autoimmune conditions attending a pediatric rheumatology specialty clinic.

Method: Chart and laboratory review of all consecutive visits at a pediatric rheumatology clinic between September 2008 and May 2009 (N=184; F:M 128:56).

Results: Of these patients, 125 had autoimmune rheumatologic diseases (SLE, juvenile idiopathic arthritis [JIA], dermatomyositis, scleroderma, vasculitis) and 59 had non-autoimmune conditions (Lyme, patello-femoral syndrome, hypermobility, etc). Mean age was 12.5 years (range 1-19 years).

	Vitamin D deficiency < 20 ng/ml	Vitamin D insufficiency 20-29 ng/ml	Combined deficiency & insufficiency
Autoimmune rheumatologic diseases N =125	35 (28%)	46 (37%)	81 (65%)
Non-autoimmune conditions N N=59	11 (19%)	25 (42%)	36 (61%)

Vitamin D deficiency was found in 50% of SLE patients, 50% of dermatomyositis patients and 22% of JIA patients. Children with autoimmune diseases taking prednisone had lower levels of vitamin D than those who were not on this medication (21.5 ± 2.4 vs 26.9 ± 1.0, p=0.04). Ethnicity, body mass index and age were also risk factors for vitamin D deficiency. African-Americans and Hispanics were more likely to be vitamin D deficient than Caucasians (p<0.0001). Overweight children had lower levels of vitamin D than those with normal body mass index (p=0.01). Age correlated inversely with vitamin D levels (r=0.18, p=0.01). Notably, 59% of children taking vitamin D supplements had levels <30ng/ml. Of the 88 patients with active autoimmune disease, 24 (27%) had deficient and 30 (34%) had insufficient levels of vitamin D. However, disease activity did not correlate with vitamin D levels.

Conclusion: About 2/3 of children attending a pediatric rheumatology specialty clinic were vitamin D deficient or insufficient. Factors contributing to low vitamin D levels included age, body mass index, prednisone intake, and ethnicity. Autoimmune disease did not appear to be a specific risk factor for vitamin D deficiency.

Disclosure: C. F. Pelajo, None; **J. Lopez-Benitez**, None; **L. C. Miller**, None.

1518

Prevalent Vertebral Fractures Among Children with Rheumatic Disorders at the Time of Initiation of Glucocorticoid Therapy: Results of the Canadian STeroid-Associated Osteoporosis in the Pediatric Population (STOPP) Research Program. A. Huber[1], D. Cabral[2], B. Lang[1], A. Ni[3], P. Dent[4], J. Ellsworth[5], K. Houghton[2], C. LeBlanc[5], P. Miettunen[6], Kiem G. Oen[7], J. Roth[3], C. Saint-Cyr[8], R. Scuccimarri[9], S. Atkinson[10], J. Hay[11], B. Lentle[12], M. Matzinger[3], N. Shenouda[3], K. Siminoski[13], Leanne M. Ward[3] and Canadian STOPP Consortium, [1]IWK Health Centre, Halifax, NS, [2]BC Children's Hospital, Vancouver, BC, [3]Children's Hospital of Eastern Ontario, Ottawa, ON, [4]Hamilton Hlth Sci McMaster Div, Hamilton, ON, [5]Stollery Children's Hospital, Edmonton, AB, [6]Alberta Childrens Hospital, Calgary, AB, [7]University of Manitoba, Winnipeg, MB, [8]CHU Sainte-Justine, Montreal, QC, [9]Montreal Childrens Hospital, Montreal, QC, [10]McMaster University, Hamilton, ON, [11]Brock University, St. Catharine's, ON, [12]Vancouver Hospital and Health Sciences Centre, Vancouver, BC, [13]University of Alberta, Edmonton, AB

Purpose: Vertebral fractures have emerged as an important but under-recognized problem in children with chronic inflammatory disorders. The timing of vertebral fracture onset in relation to disease onset and glucocorticoid (GC) administration remains unknown. The aim of this study was to evaluate spine health among 134 children (89 girls) with rheumatic conditions (median age 10 years; 25th, 75th inter-quartile range 6.0 to 14.0) who were enrolled in a national bone health research program within 30 days of initiating GC therapy.

Method: Children were divided into 3 sub-groups: 1) juvenile dermatomyositis (JDM, N=30); 2) juvenile idiopathic arthritis (JIA), excluding systemic JIA (N=28); and 3) other diagnoses (systemic lupus erythematosus, systemic vasculitides, systemic JIA and other rheumatic diseases; N=76). Thoracolumbar spine radiograph and lumbar spine areal bone mineral density (LS BMD) were performed within 30 days of GC initiation. Genant semi-quantitative grading was used to assess vertebral morphometry. Clinical variables were analyzed for association with vertebral fracture and LS BMD Z-score.

Results: Thirteen vertebral fractures were noted in 9 children (7% of the cohort; 3 JDM patients, 6 with Other Diagnoses). Six patients had a single vertebral fracture and 3 patients had between 2 and 5 fractures. Fractures were clustered in the mid-thoracic (69%) and upper lumbar regions. Three vertebral fractures (23%) were moderate (Grade 2); the others were mild (Grade 1). For the entire cohort, mean (±SD) LS BMD Z-score was low (-0.6±1.22, $p<0.001$) despite a mean height Z-score that was similar to the healthy average (0.02±1.0, $p=0.8$). LS BMD was not significantly associated with vertebral fractures. Back pain was highly associated with increased odds for fracture (OR 10.6, 95% CI 2.0-54).

Conclusion: In children with rheumatic conditions, vertebral fractures are present in a significant percentage of patients prior to prolonged GC exposure. LS BMD within 30 days of GC initiation did not predict development of vertebral fractures; however, back pain was highly associated with fractures.

Disclosure: A. Huber, None; **D. Cabral**, None; **B. Lang**, None; **A. Ni**, None; **P. Dent**, None; **J. Ellsworth**, None; **K. Houghton**, None; **C. LeBlanc**, None; **P. Miettunen**, None; **K. G. Oen**, None; **J. Roth**, None; **C. Saint-Cyr**, None; **R. Scuccimarri**, None; **S. Atkinson**, None; **J. Hay**, None; **B. Lentle**, None; **M. Matzinger**, None; **N. Shenouda**, None; **K. Siminoski**, None; **L. M. Ward**, Novartis , 9 .

1519

Spinal Epidural Lipomatosis in Pediatric Patients with Chronic Autoimmune Disorders. Jana Möller, Juliane Hamel, Gabriele Hahn and Frank Pessler, Technical University Dresden Children's Hospital, 01307 Dresden, Germany

Purpose: Spinal epidural lipomatosis (SEL) is a pathological accumulation of fat in the spinal epidural space that may arise as a rare complication of corticosteroid therapy. The natural history of this entity in pediatric patients is inadequately understood. We analyzed the available cases of corticosteroid-associated SEL in pediatric patients with autoimmune disorders.

Method: Case series and literature review. Inclusion criteria: autoimmune disorder with chronic corticosteroid treatment; onset of SEL before age 16 years.

Results: Two new cases were identified, plus 11 cases published in the international literature. Patient 1 is a 14-year-old Caucasian girl with SLE who was treated with mycophenolate mofetil, hydroxychloroquine, methyl-prednisolone pulses, and oral prednisolone (2 mg/kg tapered to 0.2 mg/Kg over 6 months). At the end of the taper, she was admitted to the hospital because of vomiting, paresthesias, back pain, and incontinence to urine and stool. The anal wink reflex was absent. Spinal MRI showed no abnormalities in the spinal cord but extensive SEL abutting the entire length of the spinal cord. Patient 2 is a 10-year-old African American girl with Sjoegren syndrome involving the central nervous system. She had been treated with cyclophosphamide and high-dose corticosteroids for 6 months when she developed radicular pain

and paresthesias. MRI showed extensive SEL compressing several dorsal nerve roots. In order to minimize corticosteroid-related untoward effects, treatment with rituximab was initiated in both patients, deflazacort was given instead of prednisolone and subsequently tapered successfully, while lipomatosis-related symptoms improved. Review of all 13 cases (mean age, 11 +/- 3.3 years; table 1) showed that steroid-related spinal epidural lipomatosis occurred after a mean duration of corticosteroid treatment of 1.3 years (median, 0.7 years), but as early as after 3 months. Two patients (17 %) required surgical decompression, whereas the others responded adequately to reduction in corticosteroids.

Conclusion: SEL should be considered in pediatric patients on chronic corticosteroid therapy, who develop spinal neurological symptoms or radicular pain, even in the first months of therapy. Corticosteroid-sparing therapies and, in severe cases, surgical decompression are warranted to prevent long-term complications resulting from spinal cord compression.

Table. Characteristics of patients.

Pt.	Age (y)	Sex	Diagnosis	Duration of steroid treatment (y)	Treatment
1	6	m	JIA	1	surgical
2	16	m	Renal transplant	3	steroid reduction
3	11	m	Nephrotic syndrome	0.8	surgical
4	14	f	Nephrotic syndrome	0.4	steroid reduction
5	14	m	Nephrotic syndrome	0.8	steroid reduction
6	10	m	HSP nephritis	0.3	steroid reduction
7	8	f	IBD	6.5	steroid reduction
8	10	f	Nephrotic syndrome	0.4	steroid reduction
9	5	f	Nephrotic syndrome	1.4	steroid reduction
10	14	m	SLE	0.17	not available
11	10	m	Nephrotic syndrome	0.7	steroid reduction
12	11	f	Sjögren Syndrome	0.6	steroid reduction
13	14	f	SLE	0.5	steroid reduction

Disclosure: J. Möller, None; **J. Hamel**, None; **G. Hahn**, None; **F. Pessler**, None.

1520

Assessment for Early Cardiovascular Risk in Pediatric Rheumatic Disease. Pascal N. Tyrrell, Timothy J. Bradley, Lawrence Ng, Cameron Slorach, Sunita Sidhu, Khosrow Adeli, Joseph Beyene, Rayfel Schneider, Brian M. Feldman and Earl D. Silverman, The Hospital for Sick Children and University of Toronto, Toronto, ON

Purpose: Adults with systemic lupus erythematosus (SLE) and rheumatoid arthritis are at increased risk of premature atherosclerosis irrespective of the presence of traditional cardiovascular risk factors. The aims of this study were to determine the prevalence of early vascular markers of atherosclerosis and the role of treatment and disease activity related factors in children with SLE, systemic juvenile idiopathic arthritis (SJIA) and juvenile dermatomyositis (JDM).

Method: Subjects were enrolled into a prospective longitudinal study and assessed following the first visit. Drug therapy and disease activity were recorded. Fasting lipid and glycemic profiles were performed. Vascular assessment included carotid intima-media thickness (CIMT), flow-mediated dilatation (FMD), pulse wave velocity (PWV). These indices were converted to z-scores using normal population data from the same center. Between group comparisons were made using parametric methods.

Results: Of the 137 children tested, SLE patients were older and more predominantly female (n=88, mean age: 15.4 ±2.5, 83% female) than JDM (n=28, 13.9 ±2.3, 50% female) and SJIA patients (n=21, 13.9 ±2.4, 57% female). Most children had a relatively healthy BMI (mean 22.4 ±4.6) and normal lipid profile of total cholesterol, LDL and HDL cholesterol, and triglyceride levels except for JDM patients who had elevated triglyceride (mean z-score: 1.8 ±2.9) and total cholesterol levels (mean z-score: 1.2 ±2.4). At the time of testing, subjects had been followed for a mean of 3.1 ±3.0 years and 91% were treated with corticosteroids (mean cumulative dose/kg: 0.2 ±0.3g). The following inflammatory markers were found to differ significantly for SLE compared to JDM and SJIA: higher ESR, lower complement levels C3 and C4, and lower albumin levels. CRP was found to be significantly higher in SJIA than SLE. Vascular function measures compared with controls: CIMT was lower in SJIA only (p=0.020); FMD was no different; and PWV was higher in SLE and JDM (both p<0.001). No difference between the three disease groups was found for CIMT, FMD or PWV when adjusting for sex, age, BMI, disease duration or cumulative corticosteroid dose.

Conclusion: Vascular markers of early atherosclerosis were found in children with rheumatic diseases but differed from controls according to the underlying disease. We found different disease-specific inflammatory factors in these patients which are likely to be important in determining risk of atherosclerosis and warrant further investigation.

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Varicella Vaccine in Children and Adolescents with Systemic Lupus Erythematosus (SLE) – Immunogenicity and Safety. Cassia M. P. Barbosa[1], Maria T. Terreri[1], Claudio A. Len[2], Maria Isabel Moraes-Pinto[2], Paula Rosario[2] and Maria O. Hilário[2], [1]Universidade Federal de Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo,, Brazil

Purpose: To determine the immunogenitiy and the safety of the varicella vaccine in children and adolescents with SLE.

Methods: In a prospective, randomized and controlled study we included two groups of SLE patients (55 patients) who were randomized to be vaccinated or not and a group of healthy controls (28 individuals). The patients were excluded if they had received gammaglobulin, cyclophosphamide or metilprednisolone in the last 3 months. Other immunossupressors and corticosteroids under 20 mg/day were allowed. Leucocytes number below 700 and platelets number below 100 000 were also exclusion criteria. Each patient received single dose of the varicella vaccine (Biken® Aventis Pasteur). All patients and controls were evaluated pre vaccination and at 30-45, 180 and 360 days afterwords. At first visit they were submitted to a questionnaire, physical examination and laboratory tests, including serum antibody titres for VZV antigen (ELISA) and specific varicella zoster interferon gamma (IFN**)** production by CD4 and CD8 T cells. At days 30-45, 180 and 360, we analyzed the vaccinated groups' serological responses and the percentage of specific IFN positive CD4 and CD8 T cells. Repeated measure ANOVA was used for analysis of data evaluated more than once in time, with multiple comparisons performed by Tukey test. Level of significance was set at p<0.05.

Results: The study comprised of 28 SLE vaccinated patients (21F/7M, mean age 15.3±2.5 years; mean disease duration 4.4±2.6 years), 27 unvaccinated SLE patients (22F/5M, mean age 14.1±3.1 years; mean disease duration 4.7±2.7 years) and 28 healthy controls (21F/7M, mean age 15.0±2.5 years). The vaccinated groups (SLE and controls) showed no difference in the frequency of adverse events (p=0.797), all were mild. The serum antibody titres to VZV antigen increased in both vaccinated groups with no difference between them (p=0.227). The production of INF specific to VZV was lower in the SLE group compared to healthy controls (p= 0.001). The frequency of flares was the same in both groups of patients (4 in each group). The SLEDAI (SLE Activity Index) was similar in both groups of patients (p=0.797) in all assessments. In the follow-up period of two years there were 4 herpes zoster in the SLE unvaccinated group and zero in the vaccinated group.

Conclusion: In this controlled group, without or with low activity of SLE, the varicella vaccine was shown to be safe, without severe adverse events and with no association with disease flares. The varicella vaccine immunogenicity measured by serum antibody titres was appropriate. Immunizing SLE patients with the varicella vaccine may be a possibility to prevent herpes zoster.

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1522

Malignancy in Pediatric-Onset SLE. S. Bernatsky[1], Rosalind Ramsey-Goldman[2], K. G. Oen[3], A. Rosenberg[4], C. Gordon[5], Susan Manzi[6], Dafna Gladman[7], E. M. Ginzler[8], M. A. Petri[9], S.C. Bae[10], Murray Urowitz[7], M. A. Dooley[11], S. Edworthy[12], O. Nived[13], G. S. Alarcon[14], J. G. Hanly[15], C. Aranow[16], K. Steinsson[17], M. Zummer[12], J-L. Senecal[12], J. Pope[12], P. R. Fortin[7], A. E. Clarke[1] and SLICC, [1]MUHC, Montreal, QC, [2]Northwestern Univ., Chicago, IL, [3]Univ. Manitoba, Winnipeg, MB, [4]Royal Univ Hosp, Saskatoon, [5]Univ. Birmingham, Birmingham, United Kingdom, [6]Univ. Pittsburgh, Pittsburgh, PA, [7]TWH, Toronto, ON, [8]SUNY-Downstate, Brooklyn, NY, [9]JHU, Baltimore, MD, [10]Hosp. Rheumatic Dis., Seoul, South Korea, [11]UNC, Chapel Hill, NC, [12]CaNIOS Investigator, [13]Univ. Hospital, Lund, [14]Univ. Alabama, Birmingham, AL, [15]Dalhousie, Halifax, NS, [16]Feinstein Inst., Manhasset, NY, [17]Univ. Hospital

Purpose: Recent data have confirmed an increased cancer risk in adult-onset systemic lupus erythematosus (SLE), particularly for lymphoma. However, to date there have been no assessments specifically in pediatric-onset SLE. We examined cancer incidence in subjects with pediatric-onset SLE, comparing this to expected risk based on general population cancer rates.

Methods: We examined cancer occurrence in 2 cohorts of patients diagnosed as having pediatric-onset SLE. Cohort 1 was comprised of patients followed at 2 pediatric centres. Cohort 2 (which contained no subjects from cohort 1) was comprised of individuals with the onset of lupus before age 16, who had been followed since adulthood at non-pediatric centres. All patients were linked to regional tumor registries to determine cancer occurrence over the observation interval. The person-years of follow-up for each subject were calculated from the date first seen at the respective clinic, & the first of 3 possible events: death, invasive cancer, or end of study interval. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person-years in the cohort by the geographically matched age, sex, & calendar year-specific cancer rates, summing over all person-years.

Results: There were 77 patients in Cohort 1(81.8% female) & 488 patients in Cohort 2 (89.7% female). The average age at SLE diagnosis was similar in Cohort 1 (12.1 years, standard deviation, SD, 3.5) compared with Cohort 2 (12.9 years, SD 2.8). Cohort 1 subjects were followed from an average age of 12.1 years & contributed a total of 925 patient-years of follow-up (average 12.0 years of follow-up time, SD 8.7). Cohort 2 subjects were followed from an average age of 20.2 years (SD 8.3, median 18) and contributed a total of 4,260 patient years (average 8.7 years, SD 7.2). Within the observation interval, no invasive cancers occurred in Cohort 1 (expected number of cancer, 0.4, SIR 0.0), and 2 cancers (upper aerodigestive tract and renal adenocarcinoma) occurred in Cohort 2 (expected number of cancers 4.4, SIR 0.45). Combining both cohorts, the over-all SIR was 0.42 (95% CI 0.05, 1.50).

Conclusion: This is the first-ever report of malignancy occurrence focussed on pediatric-onset SLE. Previous literature, based primarily on adult-onset SLE, has suggested a moderate increased risk of cancers over-all, with a 3 to 4 fold increased risk of lymphoma. We were unable to demonstrate this increased risk in pediatric-onset disease. However, a larger study of longer-term cancer outcomes in this population, following all patients from the time of diagnosis onward, is in progress.

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Ten-Year Follow up of Children Systematically Treated with Cyclophosphamide for SLE. Risa Alperin[1], Anusha Ramanathan[1], Emma J. MacDermott[1], Alexa B. Adams[1] and Thomas J. A. Lehman[2], [1]Hospital for Special Surgery, New York, NY, [2]Hosp for Special Surgery, New York, NY

Purpose: To assess the 5- and 10-year outcomes of a cohort of children systematically treated with 36 months of bolus IV cyclophosphamide (IVCY) for SLE.

Method: The records of all childhood-onset SLE patients who were treated with systematic IVCY were reviewed. Laboratory parameters were compared using the Wilcoxon matched-pairs signed-ranks test pre-IVCY and at 5 and 10 years after completion of treatment (8- and 13-years follow-up). Prednisone dose and laboratory parameters were recorded at each clinic visit and BILAG and SLEDAI scores were calculated.

Results: Sixteen patients children with SLE were systematically treated with IVCY for 36 months as previously described (1). The average age at diagnosis was 12.7 years old and female:male ratio was 3:1. Mean follow up was 9.94 years (5-16 years). Mean SLEDAI pre-IVCY was 10.125 +/- 5.018, at 5-years post-completion 4.875 **+/-** 3.096 ($p<0.0061$), at 10-year post-completion 4.667 +/- 3.464 ($p<0.1094$). BILAG pre-IVCY was 9.688 +/- 6.041, at 5-year 3.063 +/- 2.932 ($p<0.0001$), at 10-year 4.000 +/- 2.872 ($p<0.0117$). Mean initial prednisone dose pre-IVCY was 42.317 +/- 42.454, at 5-year 11.614 +/- 9.486 ($p<0.0003$), at 10-year 9.444 +/- 7.156 ($p<0.0273$).

Urine protein pre-IVCY was 1.875+ +/- 1.310, at 5-year 0.8750+ +/- 1.025 ($p<0.0574$), at 10-year 0.5714+ +/- 0.7868 ($p<0.0313$). Hemoglobin pre-IVCY was 11.569 +/- 1.638, at 5-year 13.381 +/- 1.454 ($p< 0.0001$), at 10-year 13.722 +/- 1.615 ($p< 0.0078$). ESR pre-IVCY was 47.438 +/- 25.193, at 5-year 22.625 +/- 30.024 ($p< 0.0052$), at 10-year 23.444 +/- 35.200 ($p<0.0391$). C3 pre-IVCY was 69.027 +/- 26.079, at 5-year 94.394 +/- 27.386 ($p<0.0413$), at 10-year 103.22 +/- 30.462 ($p<0.1953$). CreatInine pre-IVCY was within normal range at mean 0.8063 +/- 0.1843, at 5-year 0.8267 +/- 0.2789 ($p<0.9460$), at 10-year 0.9189 +/- 0.1788 ($p<0.1563$).

Conclusion: The drug was well tolerated without major infection in patients who completed follow up. There was one death secondary to end-stage renal disease and sepsis in a patient who had been lost to follow-up and discontinued all medications for 2 years. One patient had persistent fungal skin infection. One patient contracted hepatitis A and C in association with IV drug abuse. Less than 50% of patients had minor infections with multiple infections occurring in a small number of patients. There were no malignancies reported. There were no reported instances of infertility. There were three desired pregnancies and one adoption.

These data demonstrate that consistent 36-month IVCY was associated with significant improvement of both laboratory and qualitative-outcome measures as seen in our cohort of sixteen patients. Side-effect profile was excellent with infection being the most significant occurrence. There was a dramatic decrease in corticosteroid doses and the associated side effects.

1. Intermittent intravenous cyclophosphamide therapy for lupus nephritis. Lehman et al. J Pediatrics 1989 Jun:114(6):1055-60

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1524

The Biologic Rationale for Recurrent Intravenous Methylprednisolone Pulsing for Induction of Pediatric Systemic Lupus Erythematosus. Tracey Wright[1], Marilynn G. Punaro[2], Jeanine Baisch[3], Zhaohui Xu[3] and M. Virginia Pascual[3], [1]Univ of TX Southwestern, Dallas, TX, [2]Texas Scottish Rite Hospital for Children, Dallas, TX, [3]Baylor Institute for Immunology Research, Dallas, TX

Purpose: Intravenous methylprednisolone (IVMP) is commonly used to induce remission and treat moderate to severe flares of systemic lupus erythematosus (SLE). The frequency of IVMP use varies by center according to physician preference and is not standardized. The objectives of this study were to 1) characterize an IVMP induction protocol, and 2) examine the flow cytometry and gene expression analysis that provide the justification for this therapy.

Method: Medical chart review was used to determine the clinical characteristics of 60 children and adolescents with SLE who received recurrent IVMP during the first 6 months following diagnosis. Gene expression analysis was also performed on 7 subjects who were initially IVMP naïve using the following methods. At each clinic visit, three milliliters of whole blood were collected in Tempus tubes for RNA extraction and hybridization. Microarray analyses were performed using the Illumina platform. In addition, RNA was also analyzed using NanoString technology, a novel method based on direct multiplexed measurement of gene expression.

Results: The majority of the cohort (85%) was female and 62% were Hispanic. Nephritis (83%), cytopenias (77%), arthritis (74%), and mucocutaneous manifestations (59%) were common clinical features. The median SLEDAI score was 8 (0-37). The median number of IVMP doses administered during the first 6 months of disease was 12 (1-33) with most subjects receiving 3 consecutive doses for 3 consecutive weeks. Using flow cytometry and gene expression technologies, IVMP was found to significantly decrease the plasmacytoid dendritic cells (pDC) which produce IFN α and to erase the IFN α gene signature. The IFN α gene signature was abrogated for 7-10 days and then returned. Daily oral corticosteroids did not extinguish the IFN α gene signature. IVMP also effectively spared subjects from high dose daily oral corticosteroids. By 3 and 6 months after diagnosis, 65% and 73% of subjects were on daily maintenance corticosteroids of 10 mg or less. Three cases of significant infection occurred after the first course of IVMP.

Conclusion: Frequent use of IVMP is an effective method of corticosteroid administration during induction therapy in SLE. It reduces the need for high dose daily oral corticosteroids during the lead time of steroid-sparing immunosuppressive agents and is generally well tolerated. IVMP effectively extinguished the IFN α signature which characterizes pediatric SLE and is often correlated with disease activity. The pDCs which make IFN α were also reduced. Until more targeted therapies are developed, frequent IVMP may be the best therapy during induction. Future longitudinal analysis will clarify the optimal regimen of recurrent IVMP pulsing.

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Variability of Mycophenolic Acid (MPA) Pharmacokinetics (PK) in Childhood-Onset Systemic Lupus Erythematosus (cSLE) May Be Partly Explained by UGT Genotype. A. Carmela Sagcal-Gironella[1], Tsuyoshi Fukuda[2], Kristina Wiers[1], Shareen Cox[2], Shannen Nelson[1], Marisa Klein-Gitelman[3], Alexander A. Vinks[2] and Hermine Brunner[1], [1]Cincinnati Children's Hospital Medical Center (CCHMC) Division of Rheumatology, Cincinnati, OH, [2]CCHMC Division of Clinical Pharmacology and Pediatric Pharmacology Research Unit, Cincinnati, OH, [3]Children's Memorial Hospital, Chicago, IL

Purpose: Mycophenolate mofetil (MMF) is a prodrug that is pre-systemically hydrolyzed by esterases to the biologically active moiety, mycophenolic acid (MPA). MPA is mainly metabolized by UDP-glucuronosyltransferases (UGTs) in the liver, intestine, and kidney into the inactive 7-O-glucuronide (MPAG) metabolite. Since genetic variants in UGT1A8, 1A9, and 2B7 have been proposed to explain the large variability of MPA exposure (PK) in transplant patients, the utility of pharmacogenetic (PG) testing is currently being investigated for individualizing MMF therapy. The relevance of these UGT polymorphisms to MPA PK in cSLE has not been addressed, but may be helpful in better understanding the MPA exposure-effect relationship in cSLE. In our ongoing pharmacokinetic-pharmacodynamic study, the contribution of UGT genotype in relation to MPA PK in cSLE was investigated in an exploratory fashion.

Methods: Full 9-hour pharmacokinetic profiles were obtained from cSLE patients (n=18; F:M=17:1; age 10-30 years, 43% Caucasian, 57% African-American, 81% non-Hispanic) who were on stable MMF treatment. The MPA PK parameters dose-normalized area under the curve from 0 to 9 hours ($AUC_{0\text{-}9h}$), peak concentration (Cmax), time to peak concentration (Tmax), and oral clearance (CL/F) were assessed and analyzed by non-compartmental analysis. Genomic DNA was extracted using standard procedures and genotyped for *UGT1A8*3 (830G>A)*, *UGT1A9*3 (98T>C)*, *1A9-2152T>C*, *1A9-440C>T*, *1A9-331T>C*, *1A9-275T>A* and *UGT2B7-900A>G* by TaqMan assay and direct sequencing.

Results: Large inter-patient variability in $AUC_{0\text{-}9h}$ (mean ± S.D.: 38.7 ± 19.8 mg*hr/L/gMPA, range: 14.9 - 95.4) and oral clearance (CL/F) of MPA (mean ± S.D.: 27. 9 ± 13.7 L/hr, range: 8.3 - 59.3) was observed. Patients with *UGT1A9 -440T (-331C)* or *UGT2B7 -900G* appeared to have a trend toward lower CL/F and higher MPA exposure (AUC) than the wild-type of all evaluated single nucleotide polymorphisms (SNPs). Patients with *UGT1A9 -275A* showed relatively high CL/F over a wide range. No patients with the *UGT1A9*3* genotype were found. In an exploratory fashion, wild-type and *-275A*-carriers were analyzed and showed significantly higher CL/F compared to the rest of the carriers of SNPs *1A9 -440T (-331C)* or *2B7-900G* ($p<0.05$, Mann-Whitney's U test).

Conclusion: Our preliminary data suggest that UGT1A9 and UGT2B7 polymorphisms may explain in part inter-individual differences in MPA exposure in patients with cSLE. Further studies in larger cohorts are needed to confirm the observed trends.

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Efficacy of Mycophenolate Mofetil in the Prevention and Treatment of Lupus Nephritis in Pediatric Lupus Patients. Lenore M. Buckley[1] and Krista Edelman[2], [1]Virginia Commonwealth University School of Medicine, Richmond, VA, [2]Virginia Commonwealth University School of Medicine, Riichmond, VA

Purpose: To assess the experience with mycophenolate mofetil (MMF) and hydroxychloroquine (HCQ) in the prevention and treatment of nephritis in pediatric lupus patients at one center.

Methods: Observational study of the results of treatment with MMF and HCQ in pediatric patients who presented with lupus nephritis and those who did not have nephritis at presentation but were considered to be high risk.

Results: 49 patients with childhood onset SLE (average age 14 yrs at presentation) have been followed for a mean of 6 yrs. 22 (45%) were treated for nephritis, 16 (35%) had nephritis at presentation and 6 (10%) after a mean follow up of 2 yrs . Two children were in renal failure and on dialysis when treatment was begun – one with nephritis at presentation and one who developed nephritis during follow up. Of the 16 patients who presented with nephritis, the mean serum creatinine was 1.78 mg/dl at presentation and 0.77 mg/dl at last visit. 4 children (25%) presented with an elevated creatinine (1.2-5 mg/dl, one on dialysis). All 16 were treated with MMF and HCQ and all responded to treatment with improvement in proteinurea, serum albumin, and normalization of serum creatinine. After years of good control of renal disease, 2 (13%) developed worsening renal function after a prolonged period of noncompliance. Both were subsequently treated with IV cyclophosphamide and have stable renal function but significant damage by renal biopsy (creatinine 1.8 mg/dl and 1.7 mg/dl).

Of the 33 children (67%) without nephritis at presentation, 18 (55%) were considered high risk for the development of nephritis as defined by: onset of SLE < 18 yrs, positive anti DSDNA antibody, and one other risk factor (non white race, anti RNP antibodies, age of onset of SLE< 10, or low complement levels). All received treatment with MMF and HCQ due to other SLE manifestations. Nephritis developed in 1 of the 15 (7%) and 5 of 18 (28%) of the low risk and high risk patients, respectively. Of the 5 high risk patients who developed nephritis, 5 (100%) had anti DSDNA antibodies, 5 (100%) had anti RNP antibodies, and 5 (100%) had low complement levels at presentation. All 6 patients who developed nephritis had onset of renal disease after a prolonged period of noncompliance. In this group, the initial and last creatinine was 0.58 mg/dl mg and 0.79 mg/dl respectively. Two patients have persistently elevated creatinine of 1.2 mg/dl. Fair to good compliance with treatment was seen in 0% and 50% of the high risk patients who did and did not develop nephritis, respectively.

Conclusion: MF and HCQ were effective therapies for treating nephritis and for preventing renal disease in high risk patients. All children with nephritis at presentation responded to treatment and only those high risk patients who were noncompliance with MMF and HCQ treatment developed nephritis. Progression to renal damage occurred only in those with significant nephritis risk factors and significant noncompliance. Noncompliance with oral medications is a major limitation in the successful treatment of pediatric lupus.

Disclosure: L. M. Buckley, None; **K. Edelman**, None.

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Urinary Biomarkers May Differentiate Between Children with ISN/RPS Class IV Versus Class V of Lupus Nephritis (LN). Lena Das[1], Michiko Suzuki[1], Michael Bennett[1], Kathleen A. Haines[2], Marisa Klein-Gitelman[3], Judyann C. Olson[4], Karen Onel[5], Kathleen O`Neil[6], ED. Silverman[7], Nora G. Singer[8], Lori B. Tucker[9], Michael Wyder[10], Kenneth Greis[10], Prasad Devarajan[1] and Hermine Brunner[1], [1]Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [2]Hackensack Univ Med Ctr, Hackensack, NJ, [3]Children's Memorial Hospital, Chicago, IL, [4]Med Coll of Wisconsin, Milwaukee, WI, [5]Univ of Chicago, Chicago, IL, [6]Oklahoma University Health Science Ctr, Oklahoma City, OK, [7]Hospital for Sick Children and University of Toronto, Toronto, ON, [8]University Hospitals/Case Medical Center/Rainbow Babies and Children's Hospital, Cleveland, OH, [9]BC Childrens Hospital, Vancouver, BC, [10]University of Cincinnati, Cincinnati, OH

Purpose: Biopsy-proven LN occurs in up to 75% of all children with SLE. ISN/RPS classes of LN differ in major histological features, clinical manifestations and prognosis. Our aim was to identify urinary biomarkers that can differentiate between ISN/RPS class IV and class V in children with LN.

Method: In this ongoing study, urine samples from children with LN ISN/RPS class IV (n=6) and pure class V (n=7) collected within 60 days of a kidney biopsy and those of controls with focal segmental glomerulosclerosis (n=4) were tested. Two proteomic methods were employed that reliably measure large and mid-molecular weight proteins, i.e. 2-dimensional gel electrophoresis (2-DGE) and surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), respectively. Candidate biomarker proteins were

selected if levels differed significantly when comparing class IV vs. V, class IV vs. controls, or class V vs. controls. The identity of relevant protein spots seen on 2-DGE was obtained by MALDI-TOF-MS/MS.

Results: Using 2-DGE and MALDI-TOF-MS/MS, we found human serum albumin fragments (25kDa) and α1-B glycoprotein (60kDa) significantly over-expressed in class IV vs. class V LN. For SELDI-TOF-MS/MS four different chromatographic surfaces were tested; spectra were analyzed with ProteinChip Data Manager 3.07. The resulting urinary signature of mid-molecular weight proteins that differed between groups of samples based on robust and reproducible peaks is shown in the ***Table***, with areas under the receiver operating characteristic curves > 0.7 (all $p < 0.05$).

Conclusion: We have identified two proteins and a urinary biomarker signature that appear to be significantly different between LN ISN/RPS class IV and class V. Further studies in larger patient groups, including adults with SLE, are needed to confirm our findings and to assess the diagnostic accuracy of these candidate biomarkers.

SELDI ProteinChip type of chromatographic surface #	**Class IV vs. class V ***	**Controls vs. class IV ****	**Controls vs. class V ****
Cation exchange	7807	3273 3323	
Normal phase	3266 3278	3936 4270 4478 7787 23119	23119
Hydrophobic binding	3816 3876 4247 5835 9075 9452 16673	3876 6796 16134 25835 28101	4475 4631 7634 11830 11958 13080 47905
Metal affinity	4349 4639 4702 8846	15096 15298 66411 138089 148232	7035 15096 15298

Values are MS peaks at m/z of Da; Peaks (Da) with fold change >2; ** Peaks (Da) with fold change > 10*

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Class V Nephritis in Pediatric SLE: Treatment and Long-Term Outcome. Boris Hugle[1], Earl D. Silverman[2], Pascal N. Tyrrell[1], Elizabeth Harvey[3], Diane Hebert[1] and Susanne M. Benseler[1], [1]The Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children and University of Toronto, Toronto, ON, [3]Hospital for Sick Children, Toronto, ON

Purpose: To evaluate presenting features, treatment regimens and long-term outcome of pure membranous lupus nephritis in pediatric systemic lupus erythematosus (pSLE).

Method: A single-center cohort study of consecutive patients diagnosed with pSLE at age < 18 years between January 1990 and July 2008 was performed. Data collection: demographics including ethnicity, clinical features, laboratory test results, medications and SLE disease activity (SLEDAI). Outcomes: 1) survival, 2) renal survival, 3) renal flares and time to flare, 4) proteinuria as measured by total urine protein/24 hours at last follow up and urine protein:creatinine ratio (uP:Cr) at 1 year and last follow up, 5) serum creatinine at last follow-up and 6) damage (SLICC-DI plus renal and treatment-related domains).

Results: A total of 32 of 457 consecutive pSLE patients (7.0%) had membranous lesions on first renal biopsy. Of these, 25 patients had biopsy-confirmed class V nephritis, alone or in combination with mesangial hypercellularity (WHO class Va/Vb). These were 4 boys and 21 girls with a median age at first renal biopsy of 13.8 years (4.2-18.4), mean nephritis follow-up 3.8 years (0.7-14.8). Ethnicity: Asian (52%), Black (24%), Caucasian (16%) and mixed (8%); mean SLEDAI at presentation 9.1 (0-19); proteinuria: mean urine protein at diagnosis 2.7 ± 4.6 g/24h (21/25); mean UP:CR 327.4 g/mol (21.0-2020.8 g/mol, 19/24), mean serum creatinine 54.1 µmol/l, Treatment: prednisone in 24/25 (96%), azathioprine in 8 (36%), cyclosporine in 7 (28%), ACE inhibitors in 11/25 (44%). Outcome: 1) overall survival: 100%, 2) renal survival: 100%, 3) flares: 11 renal flares in 8/25 patients (32%) (mean time to 1st flare: 18.6 months), 4) proteinuria: mean urine protein excretion 0.4 ± 0.7 g/24h (0.03-2.8 g/l, 23/24) at last follow-up and mean uP:Cr 23.5 ± 31.6 (18/25) at 1 year follow-up and 27.2 ± 33.1 (23/25) at last follow up, 5) serum creatinine 58.5 ± 13.4 µmol/l at last follow-up and 6) mean SLICC-DI 0.52 at last follow-up (0-4), 0/25 (0%) with damage as defined by the renal domains, 4/25 (16%) cataract, 2/25 (8%) diabetes, 2/25 (8%) osteoporosis.

Conclusion: The long-term outcome of pediatric patients with pure membranous lupus nephritis is excellent. No patient had persistent renal damage at last follow-up. The study suggests that the need for aggressive immunosuppression in pediatric patients with pure Class V nephritis may need to be questioned.

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Development of a Predictive Rule for Nephritis in Pediatric Lupus Patients. Lenore M. Buckley[1] and Krista Edelman[2], [1]Virginia Commonwealth University School of Medicine, Richmond, VA, [2]Virginia Commonwealth University School of Medicine, Riichmond, VA

Purpose: Approximately 20% of patients with lupus have onset in childhood and childhood onset is a risk factor for more severe disease. Children with lupus are more likely to develop renal disease, receive more immunosuppressive treatments, have higher SDI scores over time, and are more likely to receive glucocorticoid treatment and to develop associated damage such as cataracts, AVN, and psychosocial morbidity. In addition, the cost of care for lupus patients with nephritis is significantly greater than for those without nephritis. The ability to prospectively identify pediatric lupus patients with a high likelihood of developing nephritis would allow clinicians to implement early treatment to prevent progression to renal disease and the associated glucocorticoid use, hospitalizations, declines in quality of life, and time missed from school and work. Predictive rules have been used to develop estimates of the likelihood of an event over time (i.e. FRAX for 5 and 10 year risk of fracture using risk factors) which can aid clinical decision making.

Methods: We analyzed data on risk factors in an inception cohort of 49 children with SLE (mean FU 6 yrs) to develop a predictive rule for the development of nephritis.

Results: Of this cohort, 73% were African American, 14% Caucasian, and 12% of other ethnicity. 22 children (45%) had nephritis - 16 (73%) at presentation and 6 (27%) during follow up. Children with nephritis were less likely to be Caucasian (5% vs 21%) or to have good medication compliance (9% vs 33%), and more likely to have anti DSDNA antibodies (95% vs 35%), anti RNP antibodies (11% vs 3%), both anti DSDNA and anti RNP antibodies (64% vs 42%), or low complement levels (60% vs 42%) at presentation. Using combinations of risk factors (age, race, serologies, complement level, compliance, insurance, and medications), 2 pilot predictive rules were developed with different sensitivity, specificity, and positive predictive value to estimate the likelihood of nephritis in this cohort (details and statistics to be presented at the meeting).

Conclusion: Predictive rules for nephritis in pediatric lupus patients can be developed using a combination of demographic, clinical, and laboratory based risk factors. The next step is to test these models in larger and ethnically varied cohorts of children with lupus to develop a validated predictive rule. Identification of children with lupus at high risk of developing nephritis will aid in clinical decision making about early implementation of immunosuppression and other preventive modalities as well as in risk-benefit and cost-effectiveness analyses.

Disclosure: L. M. Buckley, None; **K. Edelman**, None.

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Refractory Juvenile-Onset Lupus Nephritis Treated with Rituximab. Carlos Olmos[1] and Clara Malagón[2], [1]Fundación Cardioinfantil IC, Bogotá, DC, Colombia, [2]Asociación Colombiana de Reumatología, Bogotá, DC, Colombia

Purpose: Juvenile-onset SLE is usually aggressive and associated to severe renal involvement. About 30% of patients fail the standard treatment being considered refractory, which is also frequently associated to severe side effects. Rituximab has a very good safety and efficacy profile in adults; however, its use in children with juvenile-onset SLE and renal involvement is limited and without long-term experience. Our objective is to describe the clinical response and safety of Rituximab in a group of Colombian patients with refractory juvenile lupus nephritis.

Method: This is an observational study of 12 patients, 10 female and 2 male with a mean age of 13 years with refractory juvenile lupus nephritis. Eleven patients had lupus nephritis type 4 and 1 patient type 5. Rituximab was used in 2 intravenous infusion of 1 gram each fifteen days apart. The patients have been followed for an average of 24 months.

Results: B cell depletion has occurred in all patients; clinical disease activity index measured by SLEDAI, 24-hour proteinuria, C3, C4 and anti-DNA autoantibodies improved more than 97% in 11 out of 12. Seven out of 10 patients are out of prednisone. Only 2 patients required oral antibiotics and hospital admission for sinus and pneumonic infections, respectively. Two patients have required additional courses of rituximab due to relapse. The patient with type 5 lupus nephritis did not respond besides being B cell depleted. We did no see any serious adverse events.

Conclusion: This experience supports the use of rituximab as an excellent option of treatment for patients with refractory juvenile-onset lupus nephritis, especially in type 4 nephritis. B-cell depletion was demonstrated in this group of Colombian patients.

Disclosure: C. Olmos, None; **C. Malagón**, None.

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Defining and Measuring Global Flares of Juvenile Systemic Lupus Erythematosus (JSLE). Rina Mina[1], B. Anne Eberhard[2], Emily von Scheven[3], Gloria C. Higgins[4], Sivia Lapidus[5], Jamie Eaton[1], Laura E. Schanberg[6], Karen Onel[7], Marilynn G. Punaro[8], Judyann C. Olson[9], Jun Ying[10], Marisa Klein-Gitelman[11] and Hermine Brunner[1], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Schneider Children's Hospital, New Hyde Park, NY, [3]Univ of Calif San Francisco, San Francisco, CA, [4]Nationwide Childrens Hosp, Columbus, OH, [5]AI duPont hospital for Children, Wilmington, DE, [6]Duke University Medical Center, Durham, NC, [7]Univ of Chicago, Chicago, IL, [8]Texas Scottish Rite Hospital for Children, Dallas, TX, [9]Med Coll of Wisconsin, Milwaukee, WI, [10]University of Cincinnati, Cincinnati, OH, [11]Children's Memorial Hospital, Chicago, IL

Purpose: To define global disease flares of jSLE and use a data-driven approach to derive high-quality candidate criteria for measuring jSLE flares.

Methods: Pediatric rheumatologists answered 2 Delphi questionnaires to achieve consensus on a jSLE flare definition and identify variables for its operationalization. Candidate flare criteria were generated with these variables and tested for diagnostic accuracy using prospective data from jSLE patients (n=98) who were followed every 3 months for up to 7 visits (623 visits total). Physician-rated changes in jSLE disease course (jSLE worsening yes/no) at each visit served as criterion standard.

Results: The 1st Delphi survey was sent to 299 pediatric rheumatology members of CARRA, PANLAR and PRES (53% response rate), and the 2nd one had a response rate of 84%. There was 96% consensus that "*a flare of disease is a measurable worsening of jSLE disease activity in at least one organ system, involving new or worse signs of disease that may be accompanied by new or worse SLE symptoms. Depending on the severity of the flare, more intensive therapy may be required*". Variables suggested for use in jSLE flare criteria were: physician-rated disease activity (V_1), patient well-being (V_2), protein/creatinine ratio (V_3), disease activity index score (V_4), Child Health Questionnaire physical score (V_5), anti-dsDNA antibodies (V_6), ESR, and complement levels. There were 89 episodes of clinically relevant worsening of jSLE. Candidate flare definitions based on percent change of some or all of the jSLE variables were at most 53% sensitive, despite having a high specificity (78 – 97%) with areas under the receiver operating characteristic curves (AUC) all < 0.67. The SELENA Flare Tool had a sensitivity and specificity of 56% and 81%, respectively. Using multiple logistic regression modeling, we derived several candidate flare definitions with all AUC > 0.88. The best performing was (Δ = absolute change in variable): $-2 + [\Delta V_1 - \Delta V_4 - \Delta V_6]/5 + 1.8x\Delta V_2 + [2*\Delta V_3 - \Delta V_5]/25$ where score of > 15 identifies a patient with flare with 83% sensitivity and 86% specificity.

Conclusion: Consensus has been reached on a common definition of global disease flare in jSLE and promising candidate flare criteria have been developed. Further assessment of ease-of-use and accuracy in a prospective study is needed.

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Suicidal Ideation Common in Childhood-Onset Systemic Lupus Erythematosus (cSLE); Genetic Expression and Depressive Symptoms in cSLE.

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Purpose: Interferon (IFN) alpha plays an important pathogenic role in cSLE. People receiving alpha interferon (for hepatitis C, e.g.) have been noted to have depression. The purpose of this study is to determine the frequency of depressive symptoms in cSLE, and its relationship to IFN alpha signature.

Method: 40 unselected consecutive cSLE subjects (ages 13-18) were recruited for this study at our institution. Subjects completed the Children's Depression Inventory (CDI) at routine clinic visits, minimally 3 months apart, for three consecutive visits. Blood samples for gene expression studies were obtained at each visit, total RNA was isolated, and samples were analyzed using Illumina Human Ref8 BeadChips.

Results: 34 subjects have completed 3 study visits. 86% were female, mean age was 15.3 years, mean duration of SLE was 3.7 years, and 64% were Hispanic, 19% were African American, 11% were Caucasian, and 5% were Asian. Average SLEDAI score was 6.1, 64% were taking corticosteroids, 25% were receiving high-dose "pulse" corticosteroids, 94% had renal disease, 11% had been diagnosed with a mood disorder, and an additional 5.6% had other CNS disease.

Average CDI score for first time point was 4.6 (general adolescent population = 9). 19% admitted to some degree of suicidal ideation over the previous 2 wks, while 22% had a CDI score of 12 or greater (1 std above mean). 33% were evaluated by psychology/psychiatry. Not all subjects with suicidal ideation had elevated CDI scores.

A weak correlation between CDI and SLEDAI scores was found ($R^2 = 0.12$, $p = 0.03$). No significant correlation between interferon alpha-inducible gene expression and CDI scores was found (M1.2 r = -0.04, p = 0.84, M3.4 r = -0.04, p = 0.81, M5.12 r = -0.06, p = -0.76.) Microarray analysis did identify 9 groups of transcriptionally co-regulated transcripts (modules) with unknown biological function that

correlated with CDI scores (M7.26 r = 0.35, p = 0.04, M8.10 r = 0.40, p = 0.02, M8.14 r = 0.36, p = 0.04, M8.29 r = 0.42, p = 0.01, M8.88 r = 0.36, p = 0.04, M8.97 r = 0.40, p = 0.02, M9.1 r = 0.39, p = 0.02, M9.42 r = 0.44, p = 0.01, M9.46 r = 0.43, p = 0.01.)

Conclusion: A significant fraction (19%) of children with SLE had some degree of suicidal ideation in the 2 weeks previous to our evaluation. 33% admitted symptoms prompting psychiatric evaluation. Genomic studies showed that although there was no correlation between CDI scores and individual interferon alpha signatures, expression of a series of co-regulated transcripts of unknown biological function did correlate with these scores. This study suggests that screening for depressive symptoms and suicidal ideation should be performed in children with SLE. Although preliminary, our data suggests that blood gene expression signatures might be used to monitor depression symptoms in patients with SLE.

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Further Validation of the Pediatric Automated Neuropsychological Assessment Metrics for Adolescents with Lupus. Eyal Muscal[1], Stephen L. Holliday[2], Douglas R. Bloom[1], Barry L. Myones[1] and Robin L. Brey[3], [1]Baylor College of Medicine, Houston, TX, [2]US Department of Veterans Affairs, San Antonio, TX, [3]UTHSCSA, San Antonio, TX

Purpose: To validate the computerized Pediatric-Automated Neuropsychological Assessment Metrics (Ped-ANAM) against a traditional neuropsychological battery (TNPB) in adolescents with SLE.

Method: TNPB and Ped-ANAM were administered on the same day to 22 adolescents with SLE by a tech blinded to clinical status. Z-scores were computed for each test score in TNPB (raw test scores) and Ped-ANAM (raw Throughput – correct responses/minute) based on Ms/SDs from this patient sample. These Z-scores were then averaged to produce a single summary Z score for each battery. Pearson Correlation Coefficients ($p<.05$) were computed between the two summary scores and individual test raw scores. The summary scores were also correlated with demographic/clinical variables potentially related to cognitive performance to examine differential sensitivity of Ped-ANAM and TNPB.

Results: 22 adolescents (age range 13-18; 90.9% female, 40.9% Hispanic, 31.8% African-American) without current neuropsychiatric manifestations were evaluated during a 1-year period. Summary scores for Ped-ANAM and TNPB were moderately correlated ($r=.36$, $p<.05$). Summary scores were negatively associated with a history of antihypertensive medication use for both Ped-ANAM ($r=-.43$, $p<.03$) and TNPB ($r=-.44$, $p<.03$). The Ped-ANAM summary score but not TNPB was negatively associated with blinded ratings of cerebral volume loss on MRI ($r=-.51$, $p<.01$), current prednisone dose ($r=-.60$, $p<.01$), and BMI ($r=-.37$, $p<.05$). The TNPB summary score but not Ped-ANAM was positively associated with age ($r=.76$, $p<.01$), anti-phospholipid positive history ($r=.44$, $p<.03$), and anti-ribosomal P positive history ($r=.37$, $p<.05$). Surprisingly, patients with a positive history for these two antibodies performed better on the TNPB. Neither battery summary score was significantly related to depression, cumulative prednisone dose, disease activity/damage, flares in the past year, lupus anticoagulant positivity, or anti-neuronal antibody positivity. Six of 15 (40%) TNPB raw test scores significantly correlated with the Ped-ANAM summary measure ($r=.41$-$.65$, $p<.03$-$.01$) and four of 11 (36%) Ped-ANAM raw scores correlated with the TNPB summary score ($r=.41$-$.52$, $p<.03$-$.01$).

Conclusion: Ped-ANAM and TNPB summary raw scores are moderately correlated but appear to be differentially sensitive to selected demographic and clinical measures that may modify cognitive performance in SLE. Results from this multi-ethnic cohort generally support similar conclusions from a study published by Brunner in 2007. This suggests that Ped-ANAM, which takes less time to administer and is less susceptible to practice effects than TNPB, is a promising technique for assessing cognitive performance in SLE. Replication with larger samples and normative control groups for Ped-ANAM is needed.

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Preliminary Findings of Functional Magnetic Resonance Imaging (fMRI) Assessments of Visuoconstructional Ability in Childhood-Onset Systemic Lupus Erythematosus (cSLE) Patients and Best-Friend Controls. A. Carmela Sagcal-Gironella[1], Marisa Klein-Gitelman[2], Aimee Baker[1], April German[1], Eric Anderson[3], Tresa Roebuck-Spencer[4], Dean Beebe[1], Frank Zelko[2], Darren Gitelman[5], Scott Holland[3], Mark DiFrancesco[3] and Hermine Brunner[1], [1]Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH, [2]Children's Memorial Hospital, Chicago, IL, [3]CCHMC Imaging Research Center, Cincinnati, OH, [4]National Rehabilitation Hospital, Washington, DC, [5]Northwestern University, Chicago, IL

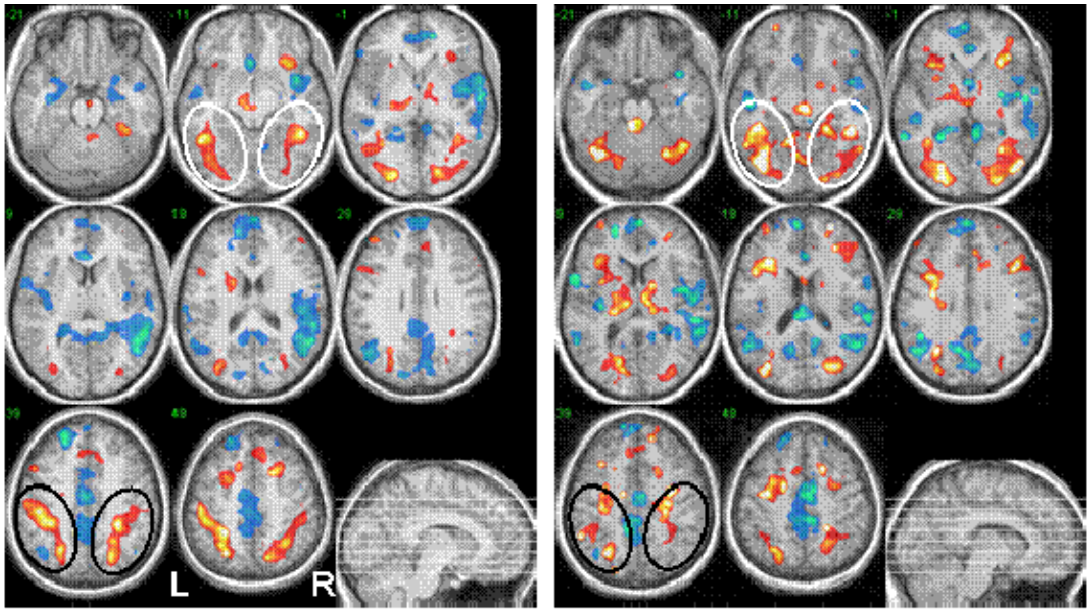
Purpose: 1) To use fMRI to identify cognitive neuronal networks involved in visuoconstructional ability (VCA) which is often impaired in cSLE. 2) To characterize both cognitive and neural differences in VCA between cSLE patients and matched best-friend controls using fMRI, the Pediatric Automated Neurological Assessment Metrics (Ped-ANAM), and formal neuropsychological (NP) testing.

Methods: 10 subjects (F:M=8:2, 40% African-American, 60% Caucasian), 5 with cSLE and 5 controls matched for age, sex, and race performed the square completion task to probe VCA during fMRI. Imaging was done on a 3T scanner with a 12-channel head coil. Functional data consisted of T2*-weighted echo-planar images acquired at TR=3 seconds with a resolution of 4x4x3 mm. A high resolution T1-weighted anatomic reference image was acquired for each subject. Group average responses were calculated ($p<0.001$ uncorrected). Other VCA assessments were: throughput scores of the matching grid, matching to sample, and spatial processing subtests of the Ped-ANAM and the Wechsler Abbreviated Scales of Intelligence block design subtest and Kaufman Assessment Battery for Children II block counting and Gestalt closure subtests in formal NP testing.

Results: Activation was seen in both dorsal ("where") and ventral ("what") visual pathways as expected for a task probing VCA. Figure 1 shows the group results for cSLE patients and controls. Both groups show activations in the two pathways, but cSLE patients appeared to activate more weakly in the dorsal pathway and more strongly in the ventral pathway compared to the controls. A negative correlation between performance on the Ped-ANAM matching grid subtest and fMRI activation in dorsal ($R^2=0.66$, $p<0.05$) and ventral ($R^2=0.63$, $p<0.05$) pathways were found across all subjects. Performance on other VCA assessments did not significantly correlate with activation patterns on fMRI, though the trend was the same.

Conclusion: In this ongoing study, cSLE patients differed in their VCA-related fMRI activation patterns from controls. Activation strength correlated with some VCA assessments across subjects. A more complete characterization of cSLE-specific fMRI activation patterns is expected as this cohort of subjects is augmented.

Figure 1: Composite activation maps for controls and cSLE subjects performing the square completion task. Color key: Red/orange= activation, Blue/green= deactivation. Black ovals indicate activation in the dorsal visual stream while the white ovals indicate activity in the ventral stream. L/R indicate the left/right orientation of the images.



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Diffusion Tensor Imaging (DTI) and Cognition in Children with SLE. Eyal Muscal[1], Elisabeth A. Wilde[1], Pavani Adapa[1], Ragini Yallampalli[1], Douglas R. Bloom[1], Barry L. Myones[1], Zili Chu[1], Robin L. Brey[2] and Jill V. Hunter[1], [1]Baylor College of Medicine, Houston, TX, [2]UTHSCSA, San Antonio, TX

Neurocognitive impairment is a prevalent feature of SLE. Disease-related white matter damage may be a mediator of these cognitive deficits.

Purpose: To assess neurocognitive functioning and white matter integrity in adolescents with SLE. We hypothesized that neurocognitive test scores would be associated with markers of tissue integrity and axonal damage on diffusion tensor imaging (DTI, an MRI tool that assesses white matter microstructure).

Method: Adolescents with SLE underwent DTI and completed neurocognitive testing. Researchers blinded to clinical status measured fractional anisotropy (FA, higher values indicate white matter tract integrity) and apparent diffusivity coefficient (ADC, higher values suggest axonal damage) metrics from DTI. Neuropsychologists blinded to clinical status assessed executive, visuo-spatial, psychomotor speed, and inter-hemispheric transfer task performance.

Results: 24 adolescents were evaluated during a 1-year period. The cohort had a female predominance (95.8%) and multi-ethnic composition (45.8% Hispanic, 33.3% African-American). Mean age at testing was 15.7 ± 1.6 years (range 13-18) and disease duration was 40.0 ± 23.0 months. Four children (16.6%) had previous severe NPSLE. Twelve subjects (50%) met a criterion of impairment (> 1.5 SD below the mean on at least 2 tests). Lowest group mean scores were on visual motor integration (VMI), verbal fluency, visual memory/spatial organization (Rey Complex Figure Test, RCFT), and inter-hemispheric transfer tests. Higher disease activity scores and number of flares within 1 year correlated significantly with lower FA and higher ADC values in corpus callosum areas, frontal white matter, and left arcuate fasciculus (range of r=0.42 to 0.71, p=<0.001-<0.05). Significant correlations between lower FA and higher ADC values in these regions and lower RCFT recall subscale scores were observed (r=0.41 to 0.52, p=0.009-0.04). Higher ADC values in right temporal and internal capsule regions were associated with lower VMI scores (r=-0.44 to -0.53, p=0.007-0.04). Lower FA and higher ADC values in posterior internal capsule and cingulate regions were associated with lower inter-hemispheric transfer subscale scores (r=0.44 to 0.59,

p=0.003-0.03). Children with prior severe NPSLE had lower median FA and higher ADC values in these regions. DTI values and neurocognitive test score differences were not significant when comparing by LAC status, history of nephritis or cumulative corticosteroid dosing.

Conclusion: We observed modest associations between white matter integrity and complex organizational task performance. This was seen even in children without prior neurological events and suggests that white matter may be an early disease target. Larger, prospective controlled studies are needed to confirm these associations and determine their value as risk predictors in children with lupus.

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Use of Cellular Text Messaging to Improve Visit Adherence in Adolescents with Childhood-Onset Systemic Lupus Erythematosus (cSLE). Tracy V. Ting[1], Deepa P. Kudalkar[2], Shannen Nelson[1], Jamie Eaton[1], Jennifer Rammel[1], Jennifer L. Huggins[1], Dennis Drotar[1] and Hermine Brunner[1], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH

Purpose: Adherence is a critical component to achieving successful outcomes in chronic illnesses like cSLE. Previous studies have indicated worse outcomes among non-adherent patients. Poor adherence to routine clinic visits is a significant problem in the management of SLE. Regular clinic appointments provide ideal opportunities for early intervention to avoid disease flares and maximize therapeutic regimens. Our aim was to improve visit adherence using cellular text messaging reminders (CTMR) and assess its impact on disease outcomes in cSLE.

Methods: An individualized CTMR was sent 7, 3, and 1 day(s) prior to each scheduled clinic appointment. Scheduling of subsequent follow-up clinic visits was also aided by CTMR as needed. Overall visit adherence was monitored prospectively over 8 months and compared to the historic visit attendance for each participant over the preceding 30 months (following standard of care [SOC]). Acceptable visit adherence was defined as attendance of ≥80% of the recommended visits as per the managing physician. Disease outcomes (SLEDAI-SLE Disease Activity Index and number of unplanned emergency room visits and hospitalizations) during the 8-month CTMR intervention period were compared to each subject's previous information during the SOC time period prior to the use of CTMR.

Results: 70 cSLE subjects (ages 13-28 years old, 93% female, 51% African American) agreed to participate by providing cell phone numbers and cellular service providers. Of the 66 participants with complete data, 64% (42/66) had poor visit adherence (<80%) during the SOC time period. Overall, the proportion of subjects with good attendance improved from 36% to 56% (p=0.04). With CTMR, 52% (22/42) of non-adherent subjects had newly acceptable visit attendance (≥ 80%). In addition to positive attendance trends, rates of visit no-shows significantly decreased (p=0.004), while self-requested visit cancellations increased (p=0.0001). No important changes in disease outcomes were observed.

Conclusion: Advances in communication technology are widely utilized by teens and young adults with cSLE. CTMR can be used as a means of improving clinic visit adherence. Important changes in disease outcomes may require longer-term CTMR intervention periods. Further studies of CTMR for both visit and medication adherence may prove highly effective and ultimately translate into improved health care utilization and better disease control in cSLE.

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Von Willebrand Factor Antigen - A Novel Biomarker of Disease Activity in Childhood CNS Vasculitis. Tania Cellucci[1], Eleanor Pullenayegum[2], Pascal N. Tyrrell[1] and Susanne M. Benseler[1], [1]The Hospital for Sick Children, Toronto, ON, [2]McMaster University, Hamilton, ON

Purpose: To characterize the presenting clinical, laboratory and imaging features of children with distinct subtypes of central nervous system (CNS) vasculitis, to determine disease activity trajectories and associated inflammatory markers, and to explore the role of the novel biomarker von Willebrand Factor antigen (vWF) levels as a marker of disease activity.

Method: A single centre cohort study of consecutive children diagnosed with primary angiitis of the CNS (cPACNS) or secondary CNS vasculitis between June 1989 and October 2008 was performed. All patients were less than 18 years of age and had to have serial vWF levels measured. Demographic, clinical, laboratory, imaging and histological data were collected. The primary outcome was disease activity as measured by physician global assessment visual analogue scale (PGA) at 3, 6, 12, 18 and 24 months. Analysis included descriptive statistics and linear mixed effects models.

Results: A total of 114 CNS vasculitis patients were identified: 102 (89%) had cPACNS, including 78 (76%) with large vessel disease (68 non-progressive, 10 progressive) and 24 (24%) with small vessel disease, and 12 (11%) had secondary CNS vasculitis. The study inception cohort consisted of 23 children: 12 (52%) were female, median age at diagnosis was 10 years (3.3, 17.8 yrs), 14 (61%) had small vessel cPACNS, 8 (35%) had large vessel cPACNS (5 progressive, 3 non-progressive) and 1 (4%) had secondary CNS vasculitis. At diagnosis: elevated CRP was seen in 26%, increased ESR in 57%, leukocytosis in 52%, high opening pressure on lumbar puncture in 85%, elevated cerebrospinal fluid (CSF) protein in 58%, CSF leukocytosis in 79%, abnormal MRI in 91%, abnormal cerebral angiogram in 33%, and vasculitis on brain biopsy in 75% patients. Disease activity decreased significantly over time (mean PGA at 3 months 4.81 (±2.52), 12 months 1.36 (±1.59) and 24 months 1.18 (±2.59); $p<0.001$) and differed significantly between cPACNS subtypes with small vessel cPACNS having persistently higher disease activity ($p=0.01$). vWF levels mirrored the course of disease activity and were significantly associated with prednisone dose ($p=0.007$) and CRP ($p=0.004$). Change in vWF levels did not predict disease activity scores over time. Linear mixed effects modeling demonstrated a trend for an association between vWF and disease activity.

Conclusion: Subtypes of childhood CNS vasculitis are distinguished by their presenting features and follow distinct disease activity trajectories. Disease activity improved significantly in all subtypes during the 24 month follow-up period. Small vessel cPACNS patient had consistently higher disease activity over time. vWF levels mirrored disease activity and therefore may be a promising novel biomarker of disease activity in childhood CNS vasculitis.

Disclosure: T. Cellucci, None; **E. Pullenayegum**, None; **P. N. Tyrrell**, None; **S. M. Benseler**, None.

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ROLE of FGF23 IN Kawasaki Disease (KD): A Possible Predictor of Subclinical Atherosclerosis. F. Falcini[1], L. Masi[2], G. Leoncini[2], F. Franceschelli[2], A. Vitale[3], S. Capannini[1], F. La Torre[3], G. Calcagno[3], M. Matucci Cerinic[4] and ML Brandi[2], [1]Department of BioMedicine, Division of Rheumatology, Transition Unit, University of Florence, Firenze, Italy, [2]Department of Internal Medicine, Metabolic Bone Disease Unit, University of Florence, Firenze, Italy, [3]Department of Paediatrics, Rheumatology Unit, University of Messina, Messina, Italy, [4]University, Firenze, Italy

Purpose: Vascular endothelial damage is a key event in KD, a systemic necrotizing vasculitis complicated by widespread long term arterial dysfunction. Endothelial damage is crucial in the process of atherogenesis as intimal lesions can become atherosclerotic plaques. KD pts seem to be at risk of early subclinical atherosclerosis. The relationship between inflammation and calcification provides evidence that inflammation is a potent initiator of vascular damage in atherosclerosis. Phosphatonins are new hormones involved in phosphate homeostasis and bone mineralization. FGF23, the master phosphatonin, acts through FGF receptor 1 present in several tissues including vasculature and heart. The *fgf23* knockout mice develop ectopic calcification, vascular and heart damage.

Aims: 1.To evaluate the serum level of intact FGF23 in KD pts. 2. To screen all patients for mutation in *FGF23* gene.

Method: 70 pts (47 M, 23 F, mean age 38.6 ± 26.65 mths) with history of KD were enrolled in the study. 14/70 had CAA. At study entry, lipid profile (total cholesterol, HDL, LDL, triglycerides) was evaluated. Forty age and sex matched healthy children acted as controls.

The serum intact FGF23 concentration was measured, using an ELISA assay (Immunotopics Inc. San Clemente, CA, USA). Genomic DNA was extracted from peripheral blood and the three *FGF23* exons, including the intron-exon boundary regions, were PCR-amplified. Purification products were analyzed on ABI Prism 100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The obtained sequences were compared to wild type reference sequence of the *FGF23* gene published on Genbank Database (NT_009759).

Results: FGF23 serum levels were higher in KD pts than in controls **(**23± 4.14 *vs*10.3±3 pg/ml; p=0.004). DNA analysis showed new intronic C insertion between -36 and -37 nucleotides close exon2, and polymorphism C>T in exon3. Interestingly, all CAA pts had FGF23 serum levels significantly higher than those without coronary disease (Mann-Whitney U test: DF: 2.5 p=0.6); 10/14 had the new C insertion and 4/14 polymorphism C>T. Conversely, C insertion was detected only in 4/56 pts without CAA and none had polymorphism C>T. CAA pts had higher cholesterol level, in particular significant LDL in comparison to those without.

Conclusion: This is the first study of serum FGF23 levels and *FGF23* gene polymorphism in pts with history of KD. Our preliminary results point to circulating FGF23 values and *FGF23* gene polymorphism as two potential predictors of early atherosclerosis in KD pts. The high amount of serum FGF23 may be in part responsible of the pathogenesis of vascular and heart damage and its complications in KD.

Disclosure: F. Falcini, None; **L. Masi**, None; **G. Leoncini**, None; **F. Franceschelli**, None; **A. Vitale**, None; **S. Capannini**, None; **F. La Torre**, None; **G. Calcagno**, None; **M. Matucci Cerinic**, None; **M. Brandi**, None.

1539

Perinatal Exposures and Kawasaki Disease in Washington State: a Population Based, Case-Control Study. Kristen N. Hayward[1], Beth A. Mueller[2], Carol A. Wallace[3] and Thomas D. Koepsell[4], [1]University of Washington & SCH, Seattle, WA, [2]Fred Hutchison Cancer Research Center, Seattle, WA, [3]Seattle Children's Hospital, Seattle, WA, [4]University of Washington, Seattle, WA

Purpose: Kawasaki Disease (KD) is an acute systemic vasculitis of childhood. It is currently the leading cause of acquired heart disease in adolescents and young adults in the United States. The etiology of KD remains unknown, but is thought to involve environmental triggers and genetic factors leading to an aberrant autoimmune-autoinflammatory response. The young age of onset of KD suggests that events in the perinatal period may be of etiologic interest. The goal of the study was to test for associations between maternal and infant perinatal exposures and KD. We hypothesized that certain perinatal infectious exposures alter infant immune development and predisposition to KD. Additionally, prenatal conditions such as preeclampsia, diabetes or maternal autoimmune disease may induce differential programming of fetal vascular responses and influence infant susceptibility to KD.

Method: A retrospective, population based, case-control, record-linkage study was performed. KD cases <10 years old occurring between 1987-2007 (N=995) were identified through Washington State Comprehensive Hospital Abstract Reporting System (CHARS) and Washington State Death Certificates via ICD9 or ICD10 codes. Cases were linked to birth certificates and birth hospitalization records. Controls were randomly selected from remaining birth records and were frequency matched to cases in a 4:1 ratio based on birth year and infant sex. Exposure information was abstracted from maternal and infant birth and hospital discharge records. Unconditional logistic regression was used to obtain adjusted odds ratio (OR) estimates and 95% confidence intervals (CI).

Results: After adjusting for infant race, sex, and year of birth, the following exposures were significantly associated with KD: maternal age ≥ 35y (OR 1.65 [1.20-2.27], p = 0.002); mother of foreign birth (OR 1.36 [1.06-1.75], p = 0.02); maternal Group B streptococcal colonization (OR 0.51 [0.26- 0.97], p=0.04); and infant hospitalization within the first 6 months of life (OR 1.42 [1.04-1.93], p = 0.03). In particular, early infancy hospitalization for bacterial illness was associated with 2.8-fold increased risk of KD in later childhood (OR 2.84 [1.6-5.1]; p < 0.0001). There was weak evidence to suggest that infant gender modifies the association between early hospitalization and KD with excess risk in males.

Conclusion: This study provides preliminary evidence of association between certain perinatal Infections and subsequent KD. The association between bacterial illness in the first 6 months of life and KD deserves additional study.

Disclosure: K. N. Hayward, Merck Pharmaceuticals, 1 ; **B. A. Mueller**, None; **C. A. Wallace**, Pfizer Inc, 2, Centocor, 2, Amgen, 2 ; **T. D. Koepsell**, None.

1540

Temporal Association in Hospitalized Cases of Influenza or Streptococcus Infection and Incident Hospitalized Cases of Henoch Schönlein Purpura. Pamela F. Weiss, Andrew J. Klink, Xianqun Luan and Chris Feudtner, Children's Hospital of Philadelphia, Philadelphia, PA

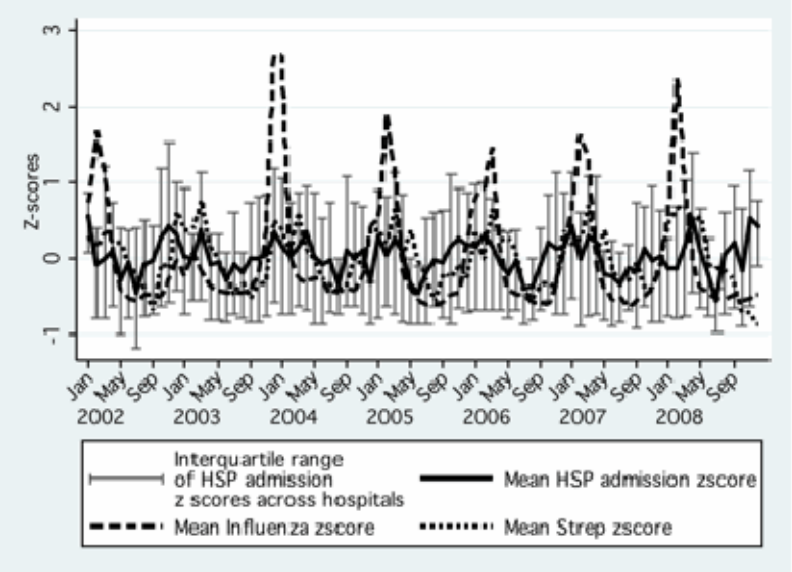
Purpose: Prior epidemiologic studies have postulated that infectious agents play a role in the pathogenesis of Henoch Schönlein purpura (HSP), as evidenced by the seasonal nature of the disease.

Methods: We conducted a retrospective cohort study of children with new onset HSP between 1 January 2002 and 31 December 2008 using administrative data from over 30 children's hospitals to determine if specific infectious exposures are associated with hospital admission. We examined the association of standardized counts of group A ß-hemolytic *Streptococcus, Staphylococcus aureus,* influenza, parainfluenza, and adenovirus with standardized counts of HSP hospital admissions using autoregressive moving average process to account for temporal autocorrelation and clustering by hospital.

Results: Among the 2,303 admissions for new-onset HSP observed over the 7-year study period, hospital admissions were most frequent September through April, but with wide variability between hospitals for each month (Figure, in which each hospital's rates are standardized as a z-score for that specific hospital). Accounting for these month-by-month differences within each hospital for rates of hospitalization due to the 5 infections and rates of HSP admissions, the rate of HSP admission in a given month increased significantly as the standardized rates of group A ß-hemolytic *Streptococcus* (estimate=0.05, 95% CI: 0.01, 0.09; p-value=0.03) or influenza (estimate=0.05, 95% CI: 0.00, 0.10; p-value=0.05) increased.

Conclusion: This is the first large multi-center cohort study to examine the association of specific infectious agents and HSP hospital admissions. Influenza and group A ß-hemolytic *Streptococcus* were both significantly associated with HSP admissions and warrant further investigation.

Figure: Monthly z-scores for admissions for influenza, *Streptococcus*, and HSP.



Disclosure: P. F. Weiss, None; **A. J. Klink**, None; **X. Luan**, None; **C. Feudtner**, None.

1541

Clinical Features of Childhood Scleroderma in An Incidence Cohort. Ariane L. Herrick[1], Holly Ennis[1], Alan J. Silman[2] and Eileen Baildam[3], [1]University of Manchester, Manchester, United Kingdom, [2]Arthritis Research Campaign, Chesterfield, [3]Royal Liverpool Children's Hospital, Liverpool, United Kingdom

Purpose: Most studies of childhood scleroderma have concentrated on well-established disease. Our aim was to describe clinical features and pattern of care in those children presenting to secondary care during a 25 month incidence study.

Method: 94 cases of childhood scleroderma (87 localised scleroderma, 7 systemic sclerosis [SSc]) were identified. Referring clinicians were asked to complete questionnaires at the time of notification and 12 months later, documenting (i) clinical features (including the site[s] of skin thickening and any extracutaneous features) (ii) serum autoantibodies (iii) current treatment and (iv) outcome at 12 months

Results: *Localised scleroderma.* The mean age when first seen was 10.4 years (± 3.7). 55 (63%) were female. 58 (67%) had linear scleroderma, 25 (29%) had non-linear morphoea and 4 (4%) had a mixed (combined) pattern. Of the 58 patients with linear scleroderma, 29 (50%) presented with lesions of the trunk and/or limbs only, 26 (45%) with face-head localisation only, and 3 (5%) with both face-head and limb involvement. Of the 87 patients with localised scleroderma, 14 (16%) had extracutaneous features, including arthritis, central nervous system, and eye involvement. Antinuclear antibody (ANA) testing was performed in 37 (43%) of patients at diagnosis and was positive in 16 (43%). Fewer than half of patients (45%) had received any treatment prior to notification, but at 12 months over half (59%) were on methotrexate. Of the 78 patients for whom 12 month follow-up data were available, 51 (65%) were improved/resolved, 14 (18%) were unchanged and 13 (17%) had deteriorated.

SSc. The mean age when first seen was 12.1 years (± 2.2). All were female. 6 (86%) had limited cutaneous SSc, 2 of whom had a dermatomyositis overlap. 6 (86%) were ANA positive. Of those tested for SSc-specific autoantibodies, 2 of 6 were anti-topiosomerase positive and 1 of 2 anticentromere positive. 6 (86%) of patients had received treatment prior to notification (5 methotrexate). 12 month outcome data were available for 6 patients: 4 were improved, 1 was unchanged and 1 deteriorated.

Conclusion: Key findings included the high prevalence (50%) of face-head involvement in those with linear disease and the high prevalence of extracutaneous disease (16%) and of ANA positivity (43%) across all localised disease. Although numbers with SSc were very small, most had limited cutaneous SSc, in contrast with larger studies in well-established disease. Over a 12 month follow-up period most patients with localised disease improved according to clinican's opinion.

Disclosure: A. L. Herrick, None; **H. Ennis**, None; **A. J. Silman**, None; **E. Baildam**, None.

1542

Assessing the Impact of Childhood Scleroderma On Physical Function and Quality of Life. EM Baildam[1], Holly Ennis[2], Ariane L. Herrick[3] and Helen L. Richards[4], [1]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]University of Manchester, Manchester, UK, United Kingdom, [4]Mercy University Hospital, Cork, Ireland

Purpose: There have been few studies of quality of life (QOL) and physical function in childhood scleroderma and these have focused predominantly on self-perception and the impact of skin lesions. Yet QOL issues are likely to be used in the future as part of a composite assessment to measure disease activity and estimate disease impact. This cross-sectional study aimed to describe QOL and physical function in childhood scleroderma in relation to their clinical and demographic profiles.

Method: Children with either localised scleroderma or systemic sclerosis (SSc) attending paediatric rheumatology clinics, together with their parents or guardians, were asked to complete a set of three validated measures: the Child Health Questionnaire (CHAQ), Child Dermatology Life Quality Index (CDLQI) and Child Health Questionnaire (CHQ-PF50). Clinical and demographic data were provided by consultant paediatric rheumatologists.

Results: 28 children and their parents/guardians participated in the study. Of the 28 children, 24 (86%) had localised scleroderma and 4 (14%) had SSc. 68% were female and the median age was 13 years (range 5-17). Median CHAQ physical function score (0-3 scale) was 0.1, indicating only moderate impairment, although 4 (14%) reported scores ≥1 (2 with localised trunk or limb lesions and 2 with SSc). Median pain VAS score (0-100 scale) was 15 indicating moderate pain with 5 (17%) reporting pain ≥ 15 (4 in children with localised trunk or limb lesions and 1 with SSc). There was a positive relationship between CHAQ scores and pain VAS scores (ρ=0.69, $p<0.00$). Median CDLQI score was 5, indicating moderate impairment in self-perception. Parental assessments on the CHQ-PF50 indicated that children with localised scleroderma had greater impairment in psychosocial domains than in physical domains, while the opposite was true for children with SSc. Lower self-esteem assessments were significantly associated with higher CHAQ function and pain scores ($p=0.04$ and $p=0.03$ respectively). Family activity was also impaired by scleroderma, with a median score of 83 (0-100, with 0 indicating greater impairment) and 13 children (46%) scoring ≤ 80.

Conclusion: Scleroderma had only a moderate impact on QOL and physical function as measured by the three validated instruments used. This is encouraging, given its potential disfiguring and debilitating nature, although a small number of children reported a greater degree of impairment.

Localised scleroderma had a more detrimental impact on psychosocial than on physical wellbeing, highlighting the importance of measuring both affective and physical outcomes.

A reduction in physical function was associated with impaired self-esteem.

Disclosure: E. Baildam, None; **H. Ennis**, None; **A. L. Herrick**, None; **H. L. Richards**, None.

1543

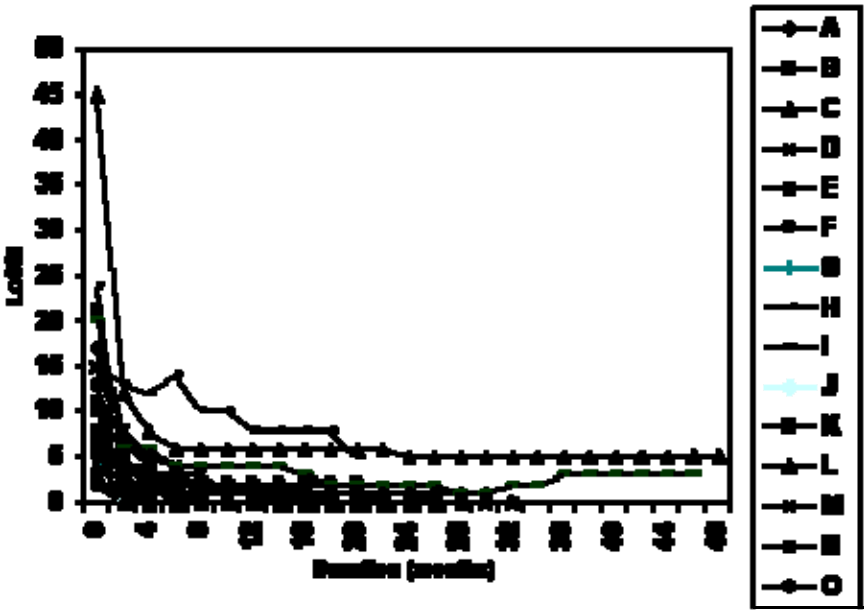
Localized Scleroderma Therapy: Do Different Regimens Matter? Amanda G. Brown[1], Kathryn S. Torok[2] and Thaschawee Arkachaisri[3], [1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]KK Women's and Children's Hospital, Singapore, Singapore

Background: Localized Scleroderma (LS) is the most common form of juvenile scleroderma. Its long-term physical and psychological impact continues to cause significant disability. Certain treatment regimens have been found to be effective in LS; however, they include small patient numbers and limited follow-up. Currently, no single treatment regimen has been established as standard of care.

Purpose: We report preliminary prospective data on the effectiveness of a single center treatment protocol in a pediatric LS cohort.

Methods: LS patients were recruited from the Scleroderma Clinic at the Children's Hospital of Pittsburgh. Patients with active disease, defined as those with erythematous lesions, and/or new lesions, or expansion of existing lesions, were started on oral prednisone 2mg/kg/day (max 60mg/day) and SC methotrexate (MTX) at 1 mg/kg/week (Max 30 mg/week). Prednisone was weaned to reach 1 mg/kg/day by the end of 6-8 weeks, and then further weaned to 0.25 mg/kg/day to complete 12 months of steroid therapy. MTX was continued for a full 24 months of SC therapy with subsequent oral therapy for 12 more months. Disease parameters evaluated were LS Skin Severity Index (LoSSI), which incorporates the following: degree of erythema, skin thickness, enlargement of existing lesions and new lesions, and physician global assessment of disease activity (PGA).

Results: 27 LS patients had serial outcome measures available to analyze. 19 were female with mean age at onset of 8.1 ± 4.1 years, mean age at first visit of 9.1 ± 3.8 years. Ten patients had linear scleroderma, 3 had *en coup de sabre*, 2 had subcutaneous morphea, 3 each had generalized or plaque morphea and 6 had mixed LS. Mean duration of follow-up was 21.6 ± 11.4 months. The change in LoSSI overtime during treatment and follow-up is demonstrated in the figure below:



All patients demonstrated a significant improvement as evidenced by a dramatic drop in the LoSSI within the first 1-2 months after therapy. PGA followed the same trend. There was no significant adverse reaction from the therapy. No patients experienced a flare during the follow-up period.

Conclusion: This single center LS treatment protocol was effective and well tolerated. Clinical outcome in LS is affected by dose and route of administration of immunosuppressive regimens. We uniformly use continuous and weaning dose of oral corticosteroids, instead of intermittent administration, along with parenteral MTX treating our LS patients without significant adverse reaction. This regimen successfully controls the acute inflammation and effectively prevents recurrence. Longer follow-up time is still needed. This regimen should be included as one of the therapy regimens for LS clinical trials.

Disclosure: A. G. Brown, None; **K. S. Torok**, None; **T. Arkachaisri**, None.

1544

The Efficacy of Imiquimod 5% Cream in Children and Adolescents with Plaque Morphea. Ronald M. Laxer[1], Paul Babyn[2], Andrea Doria[2] and Elena Pope[2], [1]The Hospital for Sick Children, Toronto, ON, [2]ON

Purpose: Therapeutic options for pediatric patients with localized plaque morphea are limited. A previous small case series suggested that Imiquimod may be useful in the infiltrative stage of morphea due to a dose dependent inhibition of human fibroblast collagen production by INF alpha and gamma, resulting in a decrease in the production of both collagen and glycosaminoglycans. Pediatric data are currently unavailable.

Objectives: 1) To evaluate the efficacy of Imiquimod in pediatric patients with localized plaque morphea, 2) To evaluate to usefulness of high frequency ultrasound in evaluation and monitoring of plaque morphea lesions.

Methods: This is an open labeled, cohort, double baseline (each 1 month in length) study, using Imiquimod 5% cream for 48 weeks, in patients of 6-18 years, with plaques of morphea less than 100 cm^2, followed in the Specialized Morphea Clinic, SickKids Hospital, Toronto. The outcome measures included 2 clinical measures: 1) an investigator and parent visual analog scale (VAS), a 100 mm scale where 0 represented no thickening and 100, “wooden-like” thickening of the skin and each 10 mm represented 10% thickening; 2) DIET (D-dyspigmentation, I-induration, E-erythema and T-telangiectasia) score, where each item can take a value of 0- none to 3-severe (maximum score of 12); and one ultrasonography score (ranging from 0-9).

Results: 9 patients participated in the study, 89% females. Their mean age was 7.83 (SD=3.79) years at onset and 8.72 (SD=3.99) years at diagnosis. Baseline data revealed a mean size of the morphea plaques of 38.87 (SD=34.44) cm^2, a mean VAS of 48.08 (SD=18.85)% and a mean DIET score of 4.38 (SD=1.2). At 48 weeks the mean VAS decreased to 20.96 (SD=10.96)%, $p<0.0001$, and the mean DIET score decreased to 2.94 (SD=1.43), $p=0.006$. The major change in the DIET score was due to changes in the induration (I), which decreased from 1.94 (SD=0.57) at baseline to 1 (SD=0.61) at 48 weeks. The ultrasonographic data is pending. The cream was well tolerated; one patient experienced ulceration that required discontinuation of the medication for 2 weeks.

Conclusion: Imiquimod 5% cream is effective in pediatric patients with plaque morphea. The benefit is more significant in the induration/infiltration. Larger prospective studies in both active and static lesions are needed.

Disclosure: R. M. Laxer, None; **P. Babyn**, None; **A. Doria**, None; **E. Pope**, None.

1545

Is the Outcome of Childhood Growing Pains Associated with Changes in the Pain Threshold? Gil Chapnick[1], Philip J. Hashkes[2], Lutfi Jaber[3], Dan Nemet[1] and Yosef Uziel[1], [1]Meir Medical center, Kfar Saba, Israel, [2]Cleveland Clinic, Cleveland, OH, [3]Child Health Center, Taibe, Israel

Purpose: We found previously that the pain threshold in growing pains (GP) is significantly lower compared to healthy controls. We examined the long-term outcome of our GP cohort and tested whether it correlates with changes in the pain threshold.

Method: We studied 35 (20 male, 15 female, mean age 13.4 ± 2.7 years) from 44 subjects in the original cohort, 5.0 ± 0.2 years after the original measurement, compared to 38 similar gender and age pain-free controls (20 males, 18 females, mean age 13.6 ± 2.7). Current GP status was assessed by parental questionnaires. Pain thresholds were measured with a Fisher-type dolorimeter applied to tender points associated with fibromyalgia.

Results: Seventeen (49%) subjects still reported pain compatible with GP. In fourteen (83%) the pain was milder and less frequent. No subjects developed other pain syndromes, including fibromyalgia. Pain thresholds of the tender points were similar in the GP group and the healthy controls (4.7 ± 1.1 kg/cm^2 in GP vs. 4.9 ± 1.1 in controls). The 17 patients with continued GP had significantly lower pain thresholds than both the control group (4.23 ± 0.72 Vs. 4.9 ± 1.1 $p<.01$) and the patients whose GP resolved (4.23 ± 0.72 Vs 5.09±1.25 $p<.01$).

Conclusion: In most subjects GP has resolved or improved after 5 years. Pain threshold remained low only in patients still suffering from GP. This finding reconfirms our hypothesis that GP may represent a variant of a noninflammatory pain syndrome in young children.

Disclosure: G. Chapnick, None; **P. J. Hashkes**, None; **L. Jaber**, None; **D. Nemet**, None; **Y. Uziel**, None.

1546

Ask Me Where It Hurts?- Developing a Standardized Approach to the Assessment of Pain in Children and Youth Presenting to Pediatric Rheumatology Providers. Jennifer N. Stinson[1], Mark Connelly[2], Elizabeth J. Chalom[3], Peter Chira[4], Laura E. Schanberg[5], Michael A. Rapoff[2], Gary Walco[6], Shirley ML. Tse[1] and Lynn R. Spiegel[1], [1]The Hospital for Sick Children, Toronto, ON, [2]University of Kansas Medical Center, Kansas City, KS, [3]St Barnabas Med Center-ACC, Livingston, NJ, [4]Stanford SOM, LPCH, Stanford, CA, [5]Duke University Medical Center, Durham, NC, [6]Seattle Children's Hospital, Seattle, WA

Purpose: To develop a Standardized Universal Pain Evaluation by Rheumatology providers for children (SUPER-KIDZ) for use at Childhood Arthritis and Rheumatology Research Alliance (CARRA) sites in North America.

Method: A 2-stage Delphi technique followed by a 2 day consensus conference (to resolve areas of disagreement and finalize items/response options) was conducted to develop consensus among CARRA members and pediatric pain experts regarding variables that should comprise pain assessment in children with rheumatic conditions. Delphi survey respondents rated importance of pain assessment domains from Ped-IMMPACT group for use in pediatric chronic pain trials (McGrath et al., 2008) in two iterative surveys.

Results: Of the 251 CARRA members, 115 (46%) and 157(63%) completed the 1st and 2nd surveys respectively. All Ped-IMMPACT domains except one (economic factors) were retained. In survey 2, poor agreement on two additional domains (lifestyle and family factors) led to their proposed exclusion. Consensus conference discussion yielded general agreement on the following domains and items for both

child self-report and parent proxy measures: Pain characteristics (current pain, average pain intensity over past 2 weeks, pain episode duration, pain frequency, pain location), associated symptoms (fatigue frequency), cognitive and emotional factors (catastrophizing, positive affect, sadness, anger, worry, stressors), and functioning (physical, social, and role). Areas agreed to be omitted from the pain assessment included: pain sensory descriptors, pain aggravating/alleviating factors, pain unpleasantness, comfort goal, global pain treatment satisfaction rating, appetite, pain self-efficacy, recent peer group changes or conflicts, and level of independence. During the consensus conference, lack of agreement over the specific questions and metrics to use for quantifying items (except for pain intensity) resulted in the assignment of workgroups to conduct further reviews of existent measures and provide recommendations thereafter.

Conclusion: A standardized approach to assessing pain that is feasible and easy to implement in clinical settings may improve pain outcomes and quality of life in children with rheumatic conditions.

Acknowledgements: This study was supported by a grant from the MayDay Fund and a meeting grant from the Institute for Musculoskeletal Health in Arthritis, Canadian Institute of Health Research. Dr. Stinson's work was supported by a CIHR Post-Doctoral Research Fellowship and Canadian Child Health Clinician Scientist Career Enhancement Award.

Disclosure: J. N. Stinson, None; **M. Connelly**, None; **E. J. Chalom**, None; **P. Chira**, None; **L. E. Schanberg**, None; **M. A. Rapoff**, None; **G. Walco**, None; **S. M. Tse**, None; **L. R. Spiegel**, None.

1547

Distal Limb Pain as Onset of Fabry Disease. Ilaria Pagnini[1], Anna Frullini[2], Franco Cecchi[2], Walter Borsini[2] and Rolando Cimaz[3], [1]Meyer Children's Hospital, Florence, Italy, [2]AOU Careggi, Florence, Italy, [3]University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy

Purpose: Fabry disease is an X-linked lysosomal storage disorder caused by α-Gal A deficiency. The onset of disease is often in childhood, and acroparesthesia (distal limb pain) are frequent early findings. These patients may not be diagnosed correctly for years.

Method: We have reviewed medical charts of 64 patients (32 M, 32 F) with Fabry disease followed in our Units, with the aim of evaluating the prevalence, characteristics, and age of onset of acroparesthesia, as well as associated signs and symptoms during the disease course. Relevant demographic and clinical data were entered into a customized database. In addition to the retrospective data analysis, we also have sent more detailed questionnaires to families in order to collect informations on acroparesthesia onset and characteristics.

Results: According to chart review, almost half of patients (30/64) presented acroparesthesia during the disease course. Acroparesthesia were more prevalent in males than in females (20M, 10F), and initially occurred in childhood or adolescence in all cases except four. Fever was present in most cases. The disease progressed involving subsequently skin (42.6%), central nervous system (49.2%), kidneys (52.4%), heart (60.6%) and gastrointestinal tract (19.7%). Mean age at diagnosis ranged from 5 to 81 years (males, 40.8; females, 47.5 years) and was only slightly earlier in patients with acroparesthesia (36.9 years, range 5-60). Diagnosis was always confirmed by low or absent α-galactosidase activity in plasma.

More detailed informations have been collected from questionnaires, up to now we received from 29/49 eligible patients (15 either deceased or refused to partecipate). Of those (18 M; 11 F), the majority (20/29, 68.9%) did present acroparesthesia during the disease course. Acroparesthesia onset occurred frequently during childhood or adolescence (median 14 years) and were severe in intensity, sometimes needing analgesic treatment. Acroparesthesia were presenting signs in more than half of the cases (15 M, 5 F), and subsequent signs occurred even years after onset (1-5 years in n=4; 5-10 years in n= 7; >10 years in n=6). In six patients acroparesthesia remained the only disease feature. Misdiagnoses before Fabry disease were: juvenile idiopathic arthritis in two cases, connective tissue disease in one, growing pains in seven, pain related to fever in one, gout in one, and anxiety disorder in one. At follow-up acroparesthesia are still present in 14/20, and their intensity is mostly mild.

Conclusion: The age of presentation of Fabry disease in our cohort was variable, but the clinical manifestations can begin in pediatric age with episodes of acroparesthesia, even isolated. Diagnostic delay is common and can be very long. Since pain is most intense in hands and feet, and is frequently associated with fever, misdiagnoses of rheumatologic conditions are common. Pediatric rheumatologists should be aware of this disorder in the differential diagnosis of limb pain.

Disclosure: I. Pagnini, None; **A. Frullini**, None; **F. Cecchi**, None; **W. Borsini**, None; **R. Cimaz**, None.

ACR/ARHP Poster Session C

Systemic Lupus Erythematosus Outcomes-Cardiac, Cognitive, and other Outcomes

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1548

Disease Activity and Levels of Anti-Apolipoprotein A1, Anti-HDL and Anti-Oxidised LDL in Patients with Systemic Lupus Erythematosus – a Prospective Study. Bethan Goulden, Ian P. Giles, Anastasia Lambrianides, Sean O'Neill, Eva Papadimitraki, David A. Isenberg and Anisur Rahman, University College London, London, England

Purpose: Patients with SLE have an increased risk of developing cardiovascular disease (CVD). Traditional risk factors do not account for all of this increased risk and inflammatory disease activity may also play a role. Inflammation may cause endothelial injury via the action of autoantibodies that interact with apoliporotein A1 (apoA1), high density lipoprotein (HDL) or oxidized low density lipoprotein (oxLDL). In a previous retrospective study we found significantly higher levels of anti-apoA1 and anti-HDL in patients with persistently active SLE disease activity than those with persistently quiescent disease. This abstract presents results of a prospective study of the same antibodies with the addition of anti-oxLDL measurements.

Method: 104 serum samples were collected from 90 different patients with SLE attending the lupus clinic at University College London Hospital. The patients were classified according to disease activity using the following definitions based on the British Isles Lupus Assessment Group Index.

Active disease - BILAG A or B score in at least one organ/system on day of sample.

Inactive disease – No BILAG A or B in any system

Persistently active disease - BILAG A or B on at least three occasions affecting at least two systems in the previous two years.

Persistently inactive disease – No BILAG A or B in any system for two years

Intemediate activity – Those who were neither persistently active nor persistently inactive by these definitions

The samples were tested by ELISA for levels of total IgG, IgG anti-apoA1, IgG anti-HDL and IgG anti-oxLDL. Values for anti-apoA1 and anti-HDL were expressed in comparison to a standard positive control used on each plate (control binding = 100AU). Values for anti-oxLDL were expressed as optical density (OD) at 405nm.

Results: The mean age of the patients was 41.1 (SD13.5) years with 93% female, 60% Caucasian and 24% Black. Of the 104 samples, 49 were from active and 55 from inactive patients. The numbers in the persistently active, intermediate activity and persistently inactive groups were 58, 24 and 20 respectively. Median anti-apoA1 was higher in active versus inactive patients (20AU vs 12AU p=0.006) and the same was true for anti-HDL (15AU vs 10AU p=0.05) but not anti-oxLDL (OD=0.12 in both groups). There was no correlation between level of any antibody and total IgG. Results for the persistently active, persistently inactive and intermediate groups are shown in the table below.

	Persistently active	Intermediate	Persistently inactive	P (Kruskall-Wallis)
Median anti-apoA1 (AU)	18	12.5	12	0.061
Median anti-HDL (AU)	12.5	15.5	8	0.062
Median anti-oxLDL (OD)	0.11	0.26	0.07	0.08

Conclusion: Raised anti-apoA1 levels were most clearly associated with both current and persistent disease activity. This agrees with our previous retrospective study and is of interest because there is a known correlation of anti-apoA1 with ischaemic heart disease in non-lupus patients. Anti-oxLDL showed no association with disease activity in this study

Disclosure: B. Goulden, None; **I. P. Giles**, None; **A. Lambrianides**, None; **S. O'Neill**, None; **E. Papadimitraki**, None; **D. A. Isenberg**, None; **A. Rahman**, None.

1549

Effects of Hydroxy-Choloroquine On Lipid Profile in Systemic Lupus Erythematosus. Rohit Aggarwal, Rachel Mikolaitis, Winston Sequeira, Joel A. Block and Meenakshi Jolly, Rush University Medical Center, Chicago, IL

Purpose: To determine the effects of Hydroxy-choloroquine (HCQ) on fasting lipid profile in patients with systemic lupus erythematosus (SLE).

Method: Data were extracted from an ongoing prospective study of quality of life in SLE. Consecutive consenting adult SLE patients were enrolled from September 2006 to April 2008. All patients were assessed prospectively using a standard protocol including demographic, clinical, and treatment variables as well as SLE Disease Activity (SLEDAI) and SLICC damage indices. These variables associated with dyslipidemia were evaluated: diabetes, hypertension, smoking, alcohol, weight, renal function, albumin and proteinuria. Fasting lipid profiles including total cholesterol (TC), High density lipid-cholesterol (HDL-C) and triglycerides (TG) were measured using standard coupled enzyme assays. Low density lipoprotein (LDL-C) was calculated using the formula LDL-C = TC – HDL – (TG/5). Abnormal values were defined as LDL-C ≥ 130 mg/dl, TC ≥ 200 mg/dl, HDL-C ≤ 40 mg/dl for men & ≤ 50 mg/dl for women; and TG ≥ 150 mg/dl. Dyslipidemia was present if at least one of the 4 components was abnormal. The background characteristics and lipid profiles of patients with and without HCQ were compared using t-tests or Mann-Whitney test for continuous variables and chi-squared tests for categorical variables.

Results: Fasting lipid profiles were available in 150 patients. Mean (± S.D) age was 44.8 (± 12.9) years and 92.8 % were females. Seventy five percent of subjects were on HCQ and 59.4 % had dyslipidemia. There were no differences between patients with or without HCQ for the following baseline variables: age, gender, ethnicity, diabetes, hypertension, smoking, alcohol, prednisone, ACE-inhibitor, protienuria, serum creatinine, SLEDAI and SLICC. In comparison to patients who were not taking HCQ, those who were treated with HCQ had a greater BMI (182.3 ± 56.2 vs. 160.7 ± 38.3, p=0.03), lower frequency of dyslipidemia (56/103, 54.3%, vs. 26/35, 74.3%, p= 0.03), fewer with abnormal TG (21/98, 21.4% vs. 15/34, 44.1 %, p =0.01), and fewer abnormal HDL-C (18/100, 18% vs. 12/32, 37.5%, p = 0.02). There were no group differences in LDL-C or TC. TG serum levels (mean ± SD) were lower in patients treated with HCQ (120.6 ±72.2) than in patients not treated (152.3 ± 75.8), p = 0.02. However, no differences were observed in serum levels of HDL-C, LDL-C or TC.

Among patients treated with prednisone, dyslipidemia (57.8 % vs. 83.3%, P = 0.039) and abnormal TG (27.7 % vs. 52.2 %, P =0.04) were less common in the HCQ group. Serum TG were highest in patients taking prednisone but not HCQ (167.2± 79.5) and lowest in patients taking HCQ but not prednisone (111.2 ± 54.2), P<0.01. Patients who were treated with both prednisone and HCQ had intermediate serum TG (128.2 ± 83.7) and were not different than patients who were only taking HCQ.

Conclusion: HCQ alone or added to prednisone therapy has beneficial effects on dyslipidemia in SLE, particularly by decreasing TG.

Disclosure: R. Aggarwal, None; **R. Mikolaitis**, None; **W. Sequeira**, None; **J. A. Block**, None; **M. Jolly**, None.

1550

Relative Importance of Remote, Recent and Cumulative Exposure to Risk Factors for Atherosclerotic Coronary Events in SLE. Mandana Nikpour, Dominique Ibañez, Dafna D. Gladman, Paula Harvey and Murray B. Urowitz, University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: SLE is strongly associated with premature coronary artery disease. Traditional risk factors as defined in the Framingham model only partly account for the increased risk of coronary events in SLE. Furthermore, many of these risk factors take a dynamic course in SLE, fluctuating over time due to changes in disease activity or treatment.

Objective: To compare ‘summary measures' of cumulative exposure with first available (‘remote') and recent values for each of total cholesterol (TC), systolic (SBP) and diastolic (DBP) blood pressure in terms of ability to estimate hazard of subsequent coronary events in SLE.

Method: Using a single centre SLE database, patients with two or more measurements of TC and BP taken before a coronary event (or last clinic visit) were included. For each patient, for each of TC, SBP and DBP, arithmetic *mean*, ‘time-adjusted' mean (*AM*) and area-under-the-

curve (*AUC*) was calculated for all serial measurements up to and including the visit before outcome. Cox and time-dependent proportional hazards regression models were used to compare summary measures with most recent and first available ('remote') measurements of each of TC, SBP and DBP in terms of ability to estimate risk of coronary event. Demographic, disease and treatment related variables were included as covariates in the models.

Results: There were over 950 patients with a mean±SD of 20±20 serial measurements of TC and BP per patient, and a mean±SD time interval between measurements of 4.2±2.3 months. Over a mean±SD follow-up of 7.0±6.7 years, among patient in the TC and BP analyses, there were 86 (71 angina, 22 MI, 2 sudden cardiac death; SCD) and 94 (75 angina, 28 MI, 2 SCD) 'first' coronary events respectively. While first available TC was not significantly predictive of coronary event, *mean* and *AM* TC were more strongly predictive (HR 2.07, p=0.003 for both mean and AM) than most recent TC (HR 1.86, p=0.001). *Mean* (HR 1.03, p=0.04) and *AM* (HR 1.03, p=0.03) DBP were significantly predictive of coronary events while first available and most recent DBP were not. Results were similar for SBP. AUC was not predictive of coronary event for either TC or BP. Other covariates in the models that were significantly predictive of coronary events were older age (HR in TC models: 1.12; HR in BP models 1.05, p<0.0001), male sex (HR 1.86, p=0.04), higher recent disease activity score (HR 1.1, p<0.0001) and recent treatment with corticosteroids (in TC models only; HR 1.87, p=0.01).

Conclusion: In contrast to the population-based Framingham model, first available ('remote') measurement of TC and BP is not significantly predictive of subsequent coronary events among patients with SLE. In SLE, summary measures of cholesterol and BP, reflecting cumulative exposure over time are better able to estimate risk of future coronary events.

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Prediction of Cardiovascular Event in Systemic Lupus Erythematosus - A 7-Year Follow up Study. Christin Bengtsson[1], Bozena Möller[2], Torgny Smedby[3], Johan Back[4] and Solbritt Rantapää Dahlqvist[5], [1]Inst of Clinical sciences, Lund, Sweden, [2]Sunderby Hospital, Luleå, Sweden, [3]Östersund Hospital, Östersund, Sweden, [4]Sundsvall sjukhus, Sundsvall, Sweden, [5]Umeå University, Umeå, Sweden

Purpose: SLE is an inflammatory multi-organ disease with the main mortality problem in atherosclerotic associated diseases. It has been shown that the mortality due to cardiovascular disease (CVD) is up to 50 times greater than in the population overall. Candidate genes and genetical loci had been revealed associated to systemic lupus erythematosus (SLE) and specific SLE manifestations.

The aim of this study was to follow up CVD event in SLE patients in the northern region of Sweden. We also wanted to study genetical, SLE specific and traditional risk factors predictive value for CVD.

Method: During one year 277 patients with SLE (≥ 4 ACR criteria) were identified and assessed using SLEDAI, SLICC/ACR, laboratory parameters, medication, smoking status and history of CVD were registered. The patients were recruited from the Departments of Rheumotology, Internal medicine, and Dermatology and all GPs in northern Sweden. The mean (±SD) age was 51.2±14.9 yrs and mean disease duration 12.5±9.7 yrs. SLEDAI was 3.5 and SLICC/ACR index was 2.4±1.3, 48.5% were ever smokers, 10.4% had angina pectoris and/or coronary artery bypass (AP/CAB), 5.9% previous myocardial infarction (MI) and 10.4% venous thrombosis (VT). The patients and 2 matched controls for each were followed up 7 years later by cross-linkage with other national health- and census-registers and the frequencies of events (CVE) e.g. AP/CAB, MI, VT/pulmonary embolism and stroke were compared with matched controls. Genetic polymorphisms of STAT1, STAT4, TRAF6, Il-10, IRF5 and TYK2 in relation to the CVE was also analysed using minisequencing.

Results: CVEs (35 vs. 20) altogether were more frequent among SLE patients compared to controls (OR= 3.97; 95%CI2.14-7.37, p<0.0001). Among the events MI (p=0.001) and VT (p=0.017) per se was significantly more common among patients compared to controls. History of previous AP, AMI, age, higher values of ACR criteria, higher SLICC and SLEDAI and presence of aCL IgG and anti-Sm antibodies at inclusion predicted significantly CVE after adjustments. Hypertension, diabetes, smoking habits, disease duration, inflammatory activity, high doses of steroids, or any of the other events did not predict subsequent CVD event. There were no association between the analyzed genetic loci and CVEs among the SLE patients.

Conclusion: Disease related factors besides some of the traditional risk factors were associated with development of CVE in SLE patients, but not treatment or any of the analysed gene polymorphisms.

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Racial Disparities in Age of CVD in SLE. Lisabeth V. Scalzi, Christopher S. Hollenbeak and Li Wang, Pennsylvania State University, Hershey, PA

Purpose: To identify if inter-racial age differences exist for cardiovascular (CVD) events and CVD mortality in systemic lupus erythematosus (SLE) patients.

Methods: Using data from the Health Care Utilization Project (HCUP) for 2003-2005, 17.6 million hospital admissions were analyzed to examine racial disparities of mean ages for in-hospital CVD events and CVD mortality in SLE patients vs non-SLE patients. HCUP is a sample of nearly 1,000 hospitals from 37 states. SLE and CVD were identified by the ICD-9 code from hospital discharge diagnoses. Mean ages for Non-SLE and SLE patients in each racial group were computed and used to calculate the difference between SLE and non-SLE (Age Δ Non SLE vs SLE) and the diference between White SLE patients and each minority SLE group (Age Δ White SLE vs minority).

Results: There were 11,099 admissions identified for CVD and 1,746 CVD mortalities in SLE. The mean ages and racial breakdown for SLE CVD events was; White, 64.5 years (yrs) (66%), Black 53.2 yrs (22%), Hispanic 55.4 yrs (8.4%), Asian 56.5 yrs (1.6%), and Other 58.1 yrs (2.1%). The mean ages and racial breakdown for in-hospital SLE CVD mortality was; White 67.4 yrs (69.8%), Black 55.5 yrs (18.9%), Hispanic 61.7 yrs (6.3%), Asian 62.7 yrs (3.4%), and Other 65.8 yrs (1.6%). SLE patients were all younger than non-SLE patients and White SLE patients were older than all minority groups for both outcomes.

The greatest age difference between SLE and non-SLE patients with CVD was in the Asian group (14.3 yrs), followed by a 13 yrs for Hispanics, 12.4 yrs for Blacks, 9.6 yrs for Others, and a 7.5 yrs for Whites (See **Table 1**). This changed when examining age differences for CVD mortality. Black SLE patients were 16.7 yrs younger, Asian SLE patients 14.1 yrs , Hispanics 12.8 yrs , Whites 11 yrs , and the Other group was 9.2 yrs younger than the race-matched non-SLE groups for CVD mortality.

Table 1: Mean Age Differences in SLE with CVD and CVD Mortality

	Whites	Blacks	Hispanics	Asians	Other
CVD					
Number of SLE Patients	7,340	2,407	936	181	235
Age Δ Non SLE vs SLE (yrs)	7.5	12.4	13	14.3	9.6
Age Δ White SLE vs minority (yrs)		11.3	9.1	8.0	6.4
CVD Mortality					
Number of SLE Patients	1004	471	171	47	53
Age Δ Non SLE vs SLE (yrs)	11	16.7	12.8	14.1	9.2
Age Δ White SLE vs minority (yrs)		14.8	12.1	11.6	13.7

We also examined the age differences between White patients and minority populations (See **Table 1**). The greatest age difference between White SLE patients and any of the minority groups was with the Black SLE patients. There was 11.7 year difference between Whites and Blacks with CVD admissions, and a 14.8 year difference for CVD mortality.

Conclusion: Age at CVD admission and CVD mortality differs between racial groups in SLE patients. The greatest age difference between SLE and non-SLE patients for CVD admission was in the Asian group (14.3 years younger than Asians without SLE) and was in the Black group for CVD mortality (16.7 years younger than Blacks without SLE). The greatest age difference between White SLE patients and a minority group was with Black patients. In the SLE population, Black patients were 11.3 years younger than Whites with CVD admissions and 14.8 years younger with CVD mortality. More detailed data analysis is warranted to examine if identifiable group characteristics may be related to these racial disparities.

Disclosure: L. V. Scalzi, NIH, 2 ; **C. S. Hollenbeak**, None; **L. Wang**, None.

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Higher Frequency of Valvular Heart Disease in Patients with Systemic Lupus Erythematosus and Jaccoud's Arthropathy.
Mittermayer Santiago[1], Stella Dourado[2], Natália Silva[3], Marina Motta[4], Lara Grimaldi[4], Vinicius Rios[5] and Verena Galvão[6], [1]Adjunct Professor at Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil, [2]Salvador, Brazil, [3]Medical Student, Salvador, Brazil, [4]Medical student, Salvador, Brazil, [5]Cardiologist at HSI, Brazil, [6]Physiotherapist, Brazil

Purpose: Jaccoud's Arthropathy (JA) was initially described as a secondary complication to rheumatic fever (RF). However, most recently described cases are associated to systemic lupus erythematosus (SLE). At least in RF, this articular complication has been observed to occur in association with valvular heart disease. The aim of this work is to investigate the presence of valvulopathy in patients with SLE and JA, when compared to lupus patients without such complication.

Methods: Patients with diagnosis of SLE based on the American College of Rheumatology criteria were enrolled in the study and divided into two groups: with or without JA and evaluated by transthoracic echocardiography.

Results: A total of 113 patients with SLE (25 with JA and 88 without JA) were assessed, of which 108 were females and five were males. Echocardiographic changes were found in 24 patients (21.2%) out of the entire population, including valvulopathy in 17 cases (15%), pulmonary hypertension in 7 cases (6.2%) and pericardial effusion in 2 cases (1.8%). In general, echocardiographic changes were more frequently seen in the JA group in comparison with the control group ($p=0.04$). Additionally, in the JA group, valvulopathy was found in 9 cases (36%) against 8 cases (9%) in the control group ($p=0.001$).

Conclusion: This study reveals for the first time the association between the presence of valvular heart disease and JA in SLE patients, suggesting that the presence of JA may be a marker of such complication. Additional studies are required for clarification of the mechanisms involved in both complications.

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Non-Calcified Coronary Plaque (NCP) in Systemic Lupus Erythematosus (SLE). Adnan Kiani[1], Jens Vogel-Claussen[1], Margaret Yew[1], Laurence Magder[2] and Michelle Petri[3], [1]Johns Hopkins University, Baltimore, MD, [2]University of MD, Baltimore, MD, [3]Johns Hopkins Univ, Baltimore, MD

Purpose: Coronary calcium (CC) is increased in SLE. Although an excellent measure of atherosclerotic burden, CC is considered to be stable. New technology can measure non-calcified plaque (NCP). We report on the first study of quantified non-calcified coronary plaque in SLE.

Method: 64 slice coronary multidetector computed tomography (MDCT) was performed in 56 patients with SLE. The MDCT scans were evaluated quantitatively by a radiologist, using dedicated software. To quantify the non-calcified plaque at each vessel

examined, we multiplied a plaque severity score (which took the values of 0-3) by a measure of the percentage of that plaque which was non-calcified. The overall non-calcified plaque score was computed as the average score from seven vessels examined.

Results: The 56 SLE pts were 88% female, 59% Caucasian, 34% African-American, 7% other; mean age 53±10 yrs. Table 1: Mean NCP score, by different variables

	Group	Mean Calcium Score	P-value	Age-adjusted p-value
Age	<45	0.15	0.30	
	45-55	0.12		
	55	0.21		
Gender	Female	0.16	0.68	0.66
	Male	0.13		
Weight	<150 lbs	0.12	0.44	0.40
	150-199	0.17		
	200+	0.20		
Body Mass Index (BMI)	<25 (n=19)	0.09	.0066	.0088
	25-29 (n=18)	0.13		
	30+ (n=19)	0.25		
Anti-ds DNA	No	0.15	0.61	0.17
	Yes	0.17		
Low C3	No	0.16	0.83	0.65
	Yes	0.15		
Low C4	No	0.17	0.72	0.96
	Yes	0.15		
Lupus anticoagulant	No	0.17	0.32	0.60
	Yes	0.13		
Prednisone	No	0.07	0.15	0.055
	Yes	0.17		
Plaquenil	No	0.14	0.88	0.91
	Yes	0.16		
Hormone Replacement	No	0.11	0.0029	0.021
	Yes	0.25		
NSAIDs	No	0.10	0.20	0.22
	Yes	0.17		

Table 2: Multivariable regression model to assess the joint association of Prednisone, HRT with NCP, controlling for age, sex, and BMI

Variable	Effect on mean NCP score (95%	P-value

	confidence Interval)	
Age (per 10 years)	.03 (-.01, .07)	.18
Male vs. Female	.02 (-.10, .15)	.70
Prednisone use	.08 (-.05, .21)	.21
Hormone Replacement	.10 (.01, .20)	.032
BMI (per 5 unit change)	.05 (.01, .08)	.0096

Conclusion: This is the first study of quantified noncalcified coronary plaque in SLE. NCP burden was more common with age > 55 and with prednisone use. Most importantly it was strongly associated with hormone replacement therapy, even after age, sex and BMI adjustment. This study strongly suggests that hormone therapy increases noncalcified plaque in SLE, and should be avoided.

Disclosure: A. Kiani, None; **J. Vogel-Claussen**, None; **M. Yew**, None; **L. Magder**, None; **M. Petri**, None.

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Cardiovascular Risk May Not Be Increased in Women with Mild Lupus. Maria J. Santos[1], Luis M. Pedro[2], Filipe Vinagre[3], Helena Canhao[4], Victor Gil[5], J. Canas da Silva[3] and Joao E. Fonseca[6], [1]Rheumatology Research Unit and Hospital Garcia de Orta, Almada, Portugal, [2]Instituto Cardiovascular de Lisboa, Lisboa, Portugal, [3]Hospital Garcia de Orta, Almada, Portugal, [4]Rheumatology Reseach Unit and Hospital Santa Maria, Lisboa, Portugal, [5]Hospital Fernando Fonseca, Amadora, [6]Rheumatology Research Unit and Hospital Santa Maria, Lisboa, Portugal

Purpose: Cardiovascular morbidity and mortality is increased in patients with Systemic Lupus Erythematosus (SLE) and accelerated atherosclerosis emerges as a major contributor. Both traditional and disease-related risk factors have been shown to contribute to premature atherosclerosis. However, it remains unclear to what extent low disease activity and the control of traditional cardiovascular (CV) risk factors might prevent cardiovascular complications. The aim of this study was to address whether women with mild lupus and well controlled CV risk factors have increased subclinical atherosclerosis.

Method: Women fulfilling criteria for SLE, with normal renal function and no previous CV events were evaluated in comparison with age-matched healthy women from the same ethnic background. Disease characteristics, presence of traditional CV risk factors, and medication were determined. An overnight fast blood sample was drawn to measure blood glucose, lipid profile, creatinine, uric acid, CRP, anti-DNA antibodies and complement levels. Bilateral ultrasound of carotid and femoral arteries assessed intima-media thickness (IMT) and the presence of atherosclerotic plaques.

Results: Twenty eight lupus women (aged 46.3 ± 12 years, 46% postmenopausal, mean disease duration 7.7±4.7 years, 35% positive for antiphospholipid antibodies, median SLEDAI 2[IQR 0-4]; median SLICC damage index 0[IQR 0-2], 46% receiving steroids (average daily dose 5.9 mg) and 78.6% receiving antimalarials) and 20 healthy women with comparable demographic characteristics were assessed. Both groups had a median of 1 [IQR 0-2] traditional CV risk factor. Patients with diabetes (7%), hypertension (32%) or hyperlipidemia (25%) were all receiving medication with a satisfactory control (Table). Atherosclerotic plaques were found in 2 patients and 2 controls. Carotid and femoral mean IMT was similar in both groups (0.7±0.2 and 0.7±0.2 mm respectively in SLE; 0.8±0.1 and 0.9±0.3 mm respectively in controls). Carotid IMT significantly increased with age (OR 1,08 per year of age; 95% CI 1,014-1,154).

	Smoker	BMI Kg/m^2	Systolic BP mmHg	Diastolic BP mmHg	Glycemia mg/dl	Cholesterol mg/dl	HDL mg/dl	LDL mg/dl
SLE (n=28)	7%	28.5 (4.8)	127 (22)	76 (10)	85 (18)	196 (43)	58 (12)	117 (41)
Control (n=20)	10%	28 (4.8)	124 (17)	70 (11)	86 (8)	217 (31)	65 (13)	137 (27)

Conclusion: The prevalence of subclinical atherosclerosis was not increased in this group of patients with mild lupus. Low disease activity as well as a good control of traditional CV risk factors might have contributed to prevent accelerated arterial disease.

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The Impact of Systemic Lupus Erythematosus On Diastolic Function:A Tissue Doppler Imaging Study in Patients without Traditional Risk Factors for Coronary Disease. Orlando Escárcega[1], Mario García Carrasco[2], Ruben Sánchez Pérez[3], Mario Jiménez Hernández[2], Claudia Mendoza Pinto[2], Pamela Munguia[2], Bernardo Briones Aguirre[2], Manuel Sandoval[2], Renan Sanchez Porras[2], Margarita Muñoz Guarneros[2], Leticia Zamudio[2] and Aurelio Lopez Colombo[4], [1]Internal Medicine: Temple University Hospital Philadelphia, PA, Philadelphia, PA, [2]Systemic Autoimmune Diseases Research Unit, HGR 36, CMN Manuel Avila Camacho, Instituto Mexicano del Seguro Social, Puebla, Mexico, [3]Fundacion de Cuore. Cardiovascular Unit, Puebla, Mexico, [4]State Research Department Instituto Mexicano del Seguro Social, Puebla, México, Puebla, Mexico

Purpose: The aim of our study was to analyze the impact of systemic lupus erythematosus on diastolic function in patients without traditional risk factors for coronary disease.

Methods: A case-control analysis was conducted. 46 women with the diagnosis of Systemic Lupus erythematosus and no previous history of smoking, hypercholesterolemia, hypertension, diabetes mellitus were included. Conventional echocardiography and tissue doppler echocardiography were performed in these patients as well as in 40 age- and sex- matched controls.

Results: 46 patients included were all female, with a mean age of 39 ± 11 years vs the control group with a mean age of 38 ± 11 years (P= 0.870). Mean age at diagnosis was 30.3 ± 9.39 years (range, 19-47). Mean time from diagnosis was 3.9 years ± 3.3 (range, 0-10). LV diastolic and systolic volumes were 53.2 vs 45.21 p=0.008 and 24.96 vs. 17.54 p=0.005 respectively, Mitral valve inflow velocities were E 66.94 vs 72.31 p=0.152, A 66.14 vs. 53.14 p = 0.012, E/A 1.01 vs. 1.36 p= 0.093. Myocardial tissue doppler velocities were e' septal at mitral annulus 8.7 vs 9.9 p=0.030, a' septal at mitral annulus 10 vs 9.8 p=0.690, e' lateral mitral annulus 9.12 vs. 11.8 p=0.001, a' lateral mitral annulus 9.9 vs 9.6 p=0.5. RV tissue doppler showed e' 9.22 vs 11.77 p=0.001, a' 10.36 vs 10.75 p=0.190.

Conclusion: Patients with systemic lupus erythematosus without traditional risk factors for coronary artery disease showed increased LV volumes and decreased velocities in tissue doppler which accounts for early diastolic dysfunction likely related to the disease itself.

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Systemic Reactive Intermediate Measures as Biomarkers of Atherosclerosis in Systemic Lupus Erythematosus. Roneka L. Ravenell[1], J. David Spence[2] and Jim C. Oates[1], [1]Medical University of South Carolina, Charleston, SC, [2]Robarts Research Institute, London, ON

Purpose: Systemic lupus erythematosus (SLE) patients have a greater incidence of cardiovascular disease (CVD) and major cardiovascular events (MCE) than the general population. Traditional risk factors for CVD are not as predictive of MCE in the SLE population. Emerging reports indicate that increased reactive intermediate (RI) production in proximity to apolipoproteins is associated with CVD in the general population. This study was designed to determine if novel serum biomarkers of RI production indicate the extent of atherosclerosis in patients with SLE.

Methods: In a pilot study, 41 subjects (93% female, 98% African-American, ages 21-65) with at least 4 ACR SLE criteria and no history of MCE were enrolled. Framingham risk factors, SLE disease activity (SLEDAI) and damage (ACR/SLICC Damage Index) scores and estimated total prednisone dose (pred) were determined. Lipid levels and SLEDAI activity markers were determined. Novel biomarkers of systemic RI production (serum protein nitrotyrosine (NTyr), ortho-Tyr (oTyr), meta-Tyr (mTyr) and chloro-Tyr (ClTyr)) were determined by high performance liquid chromatography with electrochemical detection after precipitation of serum proteins and digestion to amino

acids. These post-translational modifications of proteins (PTM) are stable indicators of reactive oxygen and reactive nitrogen stress. Carotid ultrasound measurements were performed to determine total plaque area (TPA) in both carotids. This measure is predictive of stroke, myocardial infarction, or death at five years. Univariate regressions were performed between traditional risk factors, SLEDAI, SLICC, PTM and TPA. Elevated TPA was defined as above age-adjusted values for a Canadian stroke population. These data were used to create multiple variable linear regression models. Backward regression was used to eliminate variables that did not contribute to the model. Chi square testing was performed for association between TPA and quartiles of PTM levels and Framingham risk factors. Only p values <0.05 were reported as significant.

Results: Significant associations were observed between mTyr and systolic blood pressure, SLEDAI scores, and anti-double stranded DNA antibody levels (r=0.44, 0.36, and 0.43), oTyr and waist-hip ratio (r=0.35), ClTyr and pred (r=0.36), and Ntyr and SLICC (r=0.59). TPA was associated significantly with age (r=0.44, p=0.004) in univariate models. Linear models improved upon the univariate age model by adding VLDL (r=0.46, p=0.01) and VLDL+NTyr (r=0.52, p=0.01) as independent variables with age. In chi square analysis, oTyr quartiles (but not Framingham risk factors) were associated with TPA (p=0.053).

Conclusion: This study demonstrates associations between PTM and SLE activity/damage and traditional atherosclerosis risk factors in SLE patients. PTM markers improve models with TPA as the dependent variable, and oTyr associates with increased TPA. These data suggest that interactions between lipoproteins and RI may increase the risk for CVD in SLE and are consistent with reports that RI can negatively impact cholesterol flux.

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Cardiac Magnetic Resonance Imaging Abnormalities in Patients with Systemic Lupus Erythematosus: A Preliminary Report. Hitomi Kobayashi[1], Jon T. Giles[2], Yoshiyuki Arinuma[3], Isamu Yokoe[4], Masaharu Hirano[5] and Yasuyuki Kobayashi[6], [1]Itabashi Chuo Medical Center, Itabashi-ku, Tokyo, Japan, [2]Johns Hopkins University, School of Medicine, Baltimore, MD, [3]Teikyo University, School of Medicine, Tokyo, Japan, [4]Itabashi Chuo Medical Center, Japan, [5]Tokyo Medical University, Tokyo, Japan, [6]St. Marianna University, Kanagawa, Japan

Purpose: Heart disease, including myocardial dysfunction, is a major cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE). The aim of this study was to assess and compare cardiac MRI (cMRI) findings in asymptomatic patients with SLE and explore the association of these outcomes with SLE disease characteristics.

Methods: Patients with SLE and no history and/or clinical findings of arterial hypertension, pulmonary hypertension, coronary artery disease, severe valvular heart disease, atrial fibrillation, diabetes mellitus, or echocardiographic abnormalities underwent a detailed history and physical examination, including disease activity scoring with the Systemic Lupus Disease Activity Index (SLEDAI). They underwent contrast-enhanced cMRI on a 1.5T MRI. Adenosine was used for stress perfusion to assess perfusion defects due to micro or macrovascular impairment, and delayed enhancement images were obtained for the assessment of myocardial inflammation and/or fibrosis. We evaluated the associations of cMR abnormalities with SLE disease activity and severity measures.

Results: Sixteen patients (75% female) were studied (mean age 38.7 years). The mean SLEDAI for the cohort was 4.88, with 10 participants (62.5%) falling into the low disease activity category (SLEDAI<7) and 6 participants (37.5%) falling into the high disease activity category (SLEDAI>7). Eight patients (50.0%) demonstrated a myocardial abnormality. Stress perfusion defects were seen in seven patients (43.8%),indicating microvascular impairment or myocardial ischemia. Five patients (31.2%) were found to have delayed enhancement, indicating myocardial inflammation, necrosis or fibrosis, four of whom also demonstrated a perfusion defects. Median SLEDAI was significantly higher in the group with delayed enhancement compared to the group without (4 vs. 7 units, respectively; p=0.041) and in the group with perfusion defects compared to the group without (3 vs. 8 units, respectively; p=0.001). Myocardial abnormalities were observed in all 5 patients with dsDNA antibodies vs. in 3 (27%) of those without dsDNA (p=0.026). Other SLE characteristics were not significantly associated with myocardial abnormalities.

Conclusion: Myocardial involvement, as detected by cMR, was frequent in SLE patients without known cardiac disease. Microvascular impairment and myocardial inflammation/fibrosis were both observed and, combined with their associations with SLEDAI score and dsDNA, suggest a mechanistic link between SLE activity, autoimmunity, and subclinical myocardial pathology.

Disclosure: H. Kobayashi, None; **J. T. Giles**, None; **Y. Arinuma**, None; **I. Yokoe**, None; **M. Hirano**, None; **Y. Kobayashi**, None.

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Plasma Microparticles in SLE. Michelle Petri[1], Cristina Lanata[2], Adnan Kiani[2], Jayesh Jani[3] and Thomas S. Kickler[2], [1]Johns Hopkins Univ, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins Hospital, Baltimore, MD

Purpose: Plasma microparticles (PMPs) are circulating phospholipid rich particles released from cellular membranes, including platelets, endothelial cells and white cells. These microparticles promote the generation of thrombin, which may be associated with clotting. Elevated levels have been associated with vascular dysfunction, thrombosis and inflammation.

Method: PMPs were measured in 536 SLE patients (91% female, 43% African-American, 57% Caucasian, mean age 44.8 years). 60% of SLE patients had elevated PMPs. Clinical manifestations were recorded in a cohort database. Organ damage was assessed using the SLICC/ACR Damage Index.

Results:

Factor	PMP Pos (N=319)	PMP Neg (N=203)	P-value	OR (95% CI)
African-American	48%	36%	0.0106	1.68 (1.13, 2.48)
High School Education	89%	95%	0.0273	0.44 (0.22, 0.89)
Private Insurance	78%	85%	0.0684	0.64 (0.40, 1.02)
Livedo ever	24%	35%	0.0052	0.57 (0.39, 0.84)
Arthralgia ever	96%	91%	0.0412	2.12 (1.03, 4.36)
Renal Failure	6%	2%	0.0455	2.97 (0.99, 6.90)
Leukopenia ever	46%	55%	0.0591	0.70 (0.49, 1.00)
Cholesterol ever high	47%	57%	0.0245	0.66 (0.46, 0.94)
Triglycerides ever high	15%	22%	0.0684	0.64 (0.40, 1.02)
Plaquenil use ever	91%	84%	0.0368	1.81 (1.06, 3.07)
NSAID use currently	29%	42%	0.0032	0.57 (0.39, 0.82)
Cognitive Impairment	9%	5%	0.0562	2.17 (1.00, 4.68)
Cranial Neuropathy damage	8%	15%	0.0202	0.51 (0.29, 0.90)
Proteinuria damage	7%	2%	0.0052	4.97 (1.47, 16.8)
Arthritis damage	5%	11%	0.0238	0.45 (0.23, 0.88)
Scarring Alopecia damage	6%	2%	0.0463	3.15 (1.06, 9.40)
Dermatologic Damage Score	0.05 + 0.30	0.11 + 0.33	0.0391	
Myocardial Infarction	3%	3%	0.7908	1.30 (0.44, 3.85)
Stroke	8%	6%	0.3755	1.49 (0.72, 3.10)
Hypertension	49%	50%	0.7204	0.94 (0.66, 1.33)

Deep venous thrombosis	15%	11%	0.2932	1.36 (0.80, 2.31)
Obesity	45%	39%	0.2044	1.27 (0.88, 1.81)
Smoking	38%	36%	0.7113	1.08 (0.75, 1.55)
Diabetes mellitus	6%	9%	0.2933	0.69 (0.35, 1.37)

Conclusion: PMPs are extremely frequent in SLE and more common in African-Americans. Vascular risk factors (hypertension, lipids, obesity, smoking) and thrombosis were NOT associated with PMPs. Surprisingly, since they are associated with cardiovascular risk, NSAID use may be protective against PMPs. Prospective studies are needed to determine if PMP elevation is associated with future cardiovascular disease or arterial thrombosis.

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Ability of Nonfasting and Fasting Triglycerides to Predict Coronary Artery Disease in Lupus Patients. Zahi Touma[1], Murray Urowitz[2], Dominique Ibañez[1] and Dafna Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Hypertriglyceridemia is a metabolic disorder associated with atherosclerosis. We have previously shown that there is no clinically significant difference in individual lupus patients in the levels of fasting triglycerides (FTG) and nonfasting triglycerides (NTG). We aimed to determine whether nonfasting triglycerides predict coronary artery disease (CAD) in lupus patients.

Method: Patients are followed at regular intervals (at 2-6 months) according to a standard protocol which includes: complete history and physical exam, SLE Activity Index (SLEDAI-2K), and Systemic Lupus International Collaborative Clinics Damage Index (SDI). Fasting lipid profile was measured once yearly and nonfasting was determined at all other visits. We included the entire patient cohort and all the values of TG available in our data. Time-dependent covariate survival analysis was conducted to determine the predictive ability of TG for CAD – whether fasting and nonfasting. Variables considered were: sex, age at diagnosis, age, SDI , SLEDAI-2K, smoker, glucocorticoid, antimalarial, immunosuppressive drugs, cholesterol. Variables retained for multivariate analysis were selected through the variable reduction strategy (Harell) – selecting variables which alter the parameter estimate of TG by ±10% when include in the model. Using this variable selection, age, SDI, and immunosuppressive drugs were selected to be included in the models.

Results: We identified 1289 patients since the date of the first TG available. Eighty eight percent of the patients were female. Five hundred forty one patients had elevated cholesterol level and the length of follow-up from the 1st TG to CAD/last visit was 8.82±8.19 (table 1).

Tabel1. Patients' demographics

Number of patients	1289
Number of CAD events	108 (8.1%)
Mean number of visits with TG available prior to CAD / last visit	18.8 ± 19.8
Sex F	1143 (88.7%)
Age at diagnosis (years)	30.7 ± 13.7
Age * (years)	34.9 ± 13.5
Disease Duration * (years)	4.2 ± 5.8
SDI *	0.33 ± 0.82
SLEDAI-2K *	8.81 ± 7.21

Smoker *	249 (19.7%)
Steroids *	834 (64.9%)
Antimalarial *	516 (40.2%)
Immunosuppressive *	296 (23.0%)
Elevated Cholesterol *	541 (42.1%)
Length of FU from 1st TG to CAD / last visit (years)	8.82 ± 8.19

* as of date of 1st TG available

One hundred eight patients (8.1%) developed CAD. We identified 89 events of CAD in 1137 patients in the nonfasting model and 35 events of CAD in 707 patients in the fasting model (table 2). Both nonfasting and fasting model showed ability of the variables to predict CAD; triglycerides, age and SDI while immunosuppressive drug use predicted CAD only in the nonfasting model.

Table 2. Hazard ratio for CAD in both group of analysis

	Non-fasting Model			Fasting Model		
	HR	95% CI	p	HR	95% CI	p
TG	1.80	1.10, 2.93	0.02	2.76	1.07, 7.10	0.04
Age	1.06	1.04, 1.08	<0.0001	1.06	1.03, 1.09	<0.0001
SDI	1.11	1.00, 1.23	0.06	1.18	1.00, 1.37	0.04
Immunosuppressive	2.20	1.41, 3.44	0.0005	1.27	0.61, 2.65	0.52

Conclusion: Both fasting and nonfasting TG predicted CAD in lupus patients. Nonfasting TG levels can be used in clinic to detect CAD event in lupus patients.

Disclosure: Z. Touma, None; **M. Urowitz**, None; **D. Ibañez**, None; **D. Gladman**, None.

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Systemic Lupus and Cardiac Risk Factors: A Study of Patient Record Documentation and Compliance. Christin Bengtsson[1], Anders A. Bengtsson[1], Sol-Britt Rantapää-Dahlqvist[2], Gunnar Sturfelt[1], Andreas Jönsen[1] and Ola Nived[1], [1]Inst of Clinical sciences, Lund, Sweden, [2]University Hospital, Umeå, Sweden

Purpose: Knowing that SLE patients are at greater risk for developing cardiovascular disease (CVD) and that traditional cardiac risk factors (CR) are associated with this comorbidity, we found it of importance to study patients knowledge of CR. We also wanted to analyze how we in every day clinic document information and advice about CR. Finally we were interested in compliance to received instructions about medication and improved lifestyle according to CR.

Method: This study was performed at four hospitals. All patients that fulfilled ≥4 ACR criteria, were asked to participate and fill in a cardiovascular health questionnaire (CHQ). The CHQ was blinded to the investigator that read the medical record and noted the documented CR. After this the results of the questionnaires were recorded into the same database. The CHQ is adapted from the National Health and Nutrition Examination Survey I Epidemiological Follow up Study and reveals the patients opinion of possible CR impact on developing CVD. The CHQ also asks about the patients knowledge of CR, if a physician has advised lifestyle or medication changes and if the patient has followed this advice. Compliance was based on subject´s responses, if they had followed their physicians advice.

(By permission of Dr Karen Costenbader). Kappa statistics was used to compare patients record with CHQ and to evaluate compliance.

Results: Altogether 210 out of 291 (72%) SLE patients completed the CHQ. The mean age of the patients were 55 years. High cholesterol, smoking and hypertension were known by the patients as very important risk factors and nobody considered hypertension, smoking and overweight as not important for developing CVD. The agreement between documentation and patients report was moderate for hypertension, overweight and hypercholesterolemia (kappa 0.60-0.42), for diabetes substantial (kappa 0.66) but for physical inactivity and smoking below fair (kappa 0.02, 0.05).

Patients compliance to information that they had received regarding medication and dietary changes (the latter in patients with hypercholesterolemia and diabetes) was substantial (kappa 0.58-1.0). For lifestyle changes, though, in patients with hypertension and overweight the compliance was fair to moderate (kappa 0.13-0.47).

Conclusion: All three CR fields investigated in this CHQ study (awareness, documentation and compliance), could be improved. This opens up for discussions of the best ways to accomplish this in every day clinic.

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Association of Soluble E-Selectin and Adiponectin with Carotid Plaque, Independent of Clinical Activity, in Patients with Systemic Lupus Erythematosus. Peter M. Izmirly[1], Harmony R. Reynolds[1], Tania L. Rivera[1], Mimi Y. Kim[2], PA Tunick[1], Jill P. Buyon[1] and Robert M. Clancy[1], [1]NYU School of Medicine, New York, NY, [2]AECOM, Bronx, NY

Purpose: The mechanisms underlying premature atherosclerosis in SLE are not understood. The endothelium merits focus since it provides the physiologic boundary which limits extravasation and diapedesis of inflammatory cells.

Methods: One hundred and nineteen patients with SLE, predominantly non-Caucasian, and 71 healthy controls matched for age, sex and race, underwent carotid ultrasonography and donated blood for evaluation of circulating endothelial cells (CEC), soluble endothelial protein C receptor (sEPCR) and gene polymorphism at A6936G, soluble E-selectin, and adiponectin.

Results: Carotid plaque was more prevalent among patients than controls (43% vs 17%, p=0.0002). Mean CCA IMT was greater in patients compared to controls (0.59mm±0.19 vs 0.54mm±0.11, p=0.03). Levels of CEC (19 vs 3 CECs/mL,p<0.0001) and sE-selectin (64 vs 36 ng/ml, p<0.0001) were significantly elevated in patients compared to controls. Unexpectedly, adiponectin was also significantly higher in patients compared to controls (16 ug/mL versus 11 ug/mL, p=0.0001) but no differences were seen in the levels of sEPCR or the distribution of genotype. Independent predictors of plaque status using logistic regression models included: age (p<0.0001; OR=2.1 per 10 year increase; 95% CI: 1.5-3.0), SLE status (p=0.015; OR=3.4 for SLE vs control; 95% CI: 1.3-9.1), sE-selectin (p=0.016; OR=1.2 per 10 unit increase; 95% CI: 1.0-1.4) and adiponectin (p=0.050; OR=1.5 per 10 unit increase; 95% CI: 1.0-2.4). Comparing SLE patients with and without plaque, there were no differences in cardiac CRP, complement, anti-dsDNA ab, CEC, sEPCR levels and EPCR SNP. However, sE-selectin and adiponectin levels were significantly higher in SLE with plaque compared to those without (sE-selectin 78 vs 52 ng/ml; p=0.006; adiponectin 18 vs 14 ug/ml; p=0.033). The estimated odds ratios for plaque in the final logistic regression model were: $OR_{selectin}$= 1.3 per 10 ng/ml increase (95% CI: 1.1-1.5) and $OR_{adiponectin}$=1.8 per 10 ug/ml increase (95% CI: 1.1-3.0). SELENA-SLEDAI scores were similar between groups, and the proportion of patients with SLEDAI≤ 4 did not segregate with the absence of plaque. Neither past nor current medications significantly associated with plaque. In the stable subjects (SLEDAI ≤4), age (p=0.007), sE-selectin (p=0.02) and adiponectin (p=0.02) remained associated with plaque. The prevalence of plaque was greatest in the stable patients with high sE-selectin plus high adiponectin (55%; p =0.0009) confirming the multivariable analyses. Sixty-two patients donated blood at a second visit. High sE-selectin and adiponectin were sustained in plaque patients compared to non-plaque patients (p=0.0009 and p=0.0011 respectively).

Conclusion: These results confirm that SLE patients, irrespective of race, are at increased risk for premature atherosclerosis and support the hypothesis that endothelial perturbation is contributory even in the absence of clinically measurable disease activity.

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Variability Over Time and Correlates of Total Cholesterol, Systolic and Diastolic Blood Pressure in SLE. Mandana Nikpour, Dafna D. Gladman, Dominique Ibañez, Paula Harvey and Murray B. Urowitz, University of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: Hypercholesterolemia and hypertension, two known risk factors for coronary events, are likely to take a dynamic course over time in patients with SLE, fluctuating due to changes in disease activity and treatment.

Objective: To describe and quantify variability over time of total cholesterol (TC) and blood pressure (BP) among patients with SLE and to determine their correlates.

Method: Using a single centre SLE Database, patients with two or more serial measurements of TC, systolic and diastolic blood pressure (SBP and DBP), taken simultaneously, were included in the analysis. Variability over time was described in terms of the proportion of patients whose TC and BP profile fluctuated between normal and 'elevated' (TC >5.2 mmol/L; SBP>140 mmHg *or* DBP>90 mmHg), and also in terms of within- and between-patient variance quantified using analysis of variance modelling. Generalized estimating equations (GEE) were used to determine independent correlates of each of TC, SBP and DBP, treated as continuous outcome variables.

Results: In total 1,260 patients, comprising 26,267 measurements of each of TC, SBP and DBP were included. Mean±SD number of measurements per patient was 20.8±20. The mean±SD time interval between measurements was 5.4±9.7 months. The mean±SD time interval from the start to the end of the study was 9.3±8.5 years. Over time, 64.7% of patients varied between having normal and elevated cholesterol levels, while the status of 46.4% of patients varied between normotensive and hypertensive. Using ANOVA, the between-patient percentage of total variance for each of TC, SBP and DBP was 51.8%, 48.8% and 36.1% respectively, while the *within-patient* percentage of total variance for each of TC, SBP and DBP was 48.2%, 51.2% and 63.9% respectively. Using GEE, in addition to statins and antihypertensives, independent correlates of TC & BP included age ($p=0.0005$), disease activity ($p<0.0001$) and corticosteroids ($p<0.0001$). In women, other correlates of TC and BP included disease duration ($p=0.0008$), hormone replacement therapy ($p<0.0001$) and smoking ($p=0.017$). Antimalarial use was negatively correlated with TC ($p<0.0001$). There was a strong and independent association between hypertension and hypercholesterolemia.

Conclusion: TC and BP vary markedly over time in patients with SLE, with half to two-thirds of variance over time seen *within* individuals. This variability is due not only to lipid-lowering and antihypertensive medications, but also due to disease and treatment-related factors such as disease activity, corticosteroids and antimalarials. The dynamic nature of TC and BP in SLE makes a compelling case for deriving summary measures that better capture cumulative exposure to these risk factors.

Disclosure: M. Nikpour, None; **D. D. Gladman**, None; **D. Ibañez**, None; **P. Harvey**, None; **M. B. Urowitz**, None.

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Effects of Ezetimibe Plus Pravastatin On Endothelial Dysfunction in Patients with Systemic Lupus Erythematosus (pilot study). Olga L. Vera-Lastra[1], Silvia Mendez[1] and Luis J. Jara[2], [1]MD, Mexico City, Mexico, [2]MD, Mexico

Background: Patients with systemic lupus erythematosus (SLE) have a higher risk for cardiovascular disease (CVD) not explained for the conventional risk factors. These patients have endothelial dysfunction (ED) as an early process of atherosclerosis. Treatment with statins plus ezetimibe may have a beneficial effect similar to the one seen in other groups of patients.

Purpose: To measure the effect of ezetimibe plus pravastatin after 12 months of treatment in patients with SLE on the endothelial function.

Method: An open study, before and after, which assessed the efficacy of treatment, was performed. Twenty two patients (21 women and 1 man) with diagnosis of SLE were studied, the mean age 40+/- x years. A flow-mediated vasodilatation (FMV) with doppler echocardiography of the brachial artery for the ED, basal and after 12 months of treatment with pravastatin 40 mg/day plus ezetimibe 10 mg/day was performed. In addition, a lipid profile: total cholesterol (TC), cholesterol HDL (C-HDL), cholesterol LDL (C-LDL) and serum reactive c-protein (RCP) were done.

Results: After 12 months of treatment with pravastatin and ezetimibe we found the following: improvement on the average of FMV of 10.64% IC 95% (7.58-13.58) $p<0.001$. TC decreased from 201.3+/- 58.9 mg/dl to 158.06+/-50.13 mg/dl ($p<0.01$); C-LDL from 125.78+/- 44.4 mg/dl to 78.8 +/- 32.9 mg/dL ($p<0.001$); C-HDL increased from 49.0+/- 16.8 mg/dl to 52.2+/-13.8 mg/dl ($p= 0.077$). The concentration of RCP decreased in and average of 2.11 mg/dl IC 95% (0.908-3.32) $p= 0.002$. Medications were well tolerated.

Conclusion: FMV improved significantly with treatment of ezetimibe plus pravastatin in patients with SLE, therefore decreasing ED as an initial manifestation of atherosclerosis as well as the lipid profile.

Disclosure: O. L. Vera-Lastra, None; **S. Mendez**, None; **L. J. Jara**, None.

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A Brachial-Ankle Pulse Wave Velocity Is Affected by the Level of Serum Amyloid A in Patients with Systemic Lupus Erythematosus. Masato Moriguchi, Yurika Kamiya, Tadashi Sakurai and Chihiro Terai, Jichi Medical University, Saitama Medical Center, Saitama, Japan

Purpose: Systemic lupus erythematosus (SLE) is associated with increased premature cardiovascular (CV) morbidity and mortality. For estimating CV risk, several techniques, such as electron beam CT scanning, myocardial perfusion imaging, and cervical ultrasonography were developed. However, these modalities are expensive and time-consuming methods. Pulse wave velocity (PWV) is a gold-standard measure of arterial stiffness closely associating with CV risk. Brachial-ankle PWV (baPWV) measure can be performed more easily and repeatedly and is more suitable for screening in general out-patients clinics. Using baPWV measure, we analyzed arterial stiffness of SLE patients and determined the clinical variables affecting CV risk of SLE.

Method: Seventy-six female SLE patients fulfilled ACR criteria and 54 age-matched healthy female controls were enrolled in this cross-sectional observation study. Written informed consent was obtained from every patient and control. Using form PWV/ABI, baPWV were measured in all subjects and were compared between SLE group and control. In SLE group, clinical features (age, BMI, blood pressure, duration of SLE, smoking history and SLEDAI), laboratory data (C-reactive protein, serum amyloid A, lipid profile, HbA1c, C3, C4 and serum creatinine) and treatments (dose of corticosteroid and use of immunosuppressants) were assessed simultaneously. Stepwise multiple regression analysis was performed to determine the variables affecting baPWV in SLE patients.

Results: Mean baPWV of SLE patients was significantly higher than that of healthy controls (1353±275 versus 1214±154cm/sec, $p<0.0005$). Stepwise multiple regression analysis showed that systolic blood pressure, level of serum amyloid A (SAA), and use of immunosuppressants significantly affected baPWV in patients with SLE ($\beta=0.66$; t-value=8.74; $P<0.0001$, $\beta=0.20$; t-value=2.68; $P=0.0125$, and $\beta=0.17$; t-value=2.54; $P=0.0136$, respectively). Also the multiple linear regression analysis showed that SAA levels in SLE were significantly influenced from SLEDAI score ($\beta=0.57$, t-value=5.08, $P<0.0001$).

Conclusion: This study indicated that arterial stiffness of SLE correlated with both classic CV risk factor, especially hypertension, and inflammation due to SLE per se. Not C-reactive protein but SAA may reflect active status of SLE.

Disclosure: M. Moriguchi, None; **Y. Kamiya**, None; **T. Sakurai**, None; **C. Terai**, None.

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Coronary Angiogram-Defined CAD in Systemic Lupus Erythematosus (SLE): Risk Factors and Outcomes. Mala S. Kaul[1], Emily Honeycutt[2], Linda Shaw[2], Stacy P. Ardoin[3], Sunil Rao[1] and E. William St. Clair[1], [1]Duke University Medical Center, Durham, NC, [2]Duke Clinical Research Institute, Durham, NC, [3]Ohio State University Medical Center, Columbus, OH

Purpose: Relatively little is known about the severity of coronary artery disease (CAD) on coronary angiography in patients with SLE. The objective of this study was to compare number of diseased vessels on coronary angiogram, risk factors, and outcomes between SLE patients and non-SLE controls undergoing cardiac catheterization for suspected ischemic heart disease (IHD).

Method: SLE patients (N=86) and matched controls (N=258) were identified from the Duke Databank for Cardiovascular Disease undergoing cardiac catheterization between January 1986 and October 2008 for evaluation of suspected IHD (including recent myocardial infarction, abnormal functional study, or angina). SLE diagnosis was confirmed by chart review. Controls were matched by gender and year of catheterization. Multivariable logistic regression was used to determine if SLE was associated with significant CAD (defined as >70% stenosis in at least one major vessel). Risk adjusted survival differences between the two groups were also assessed using Cox proportional hazards modeling.

Results: SLE patients (85% female) were younger than non-SLE patients (median age 49 years vs. 70 years, p<0.001), had less diabetes (14% vs. 35%, p<0.001) and hyperlipidemia (30% vs. 50%, p=0.001). Both SLE and non-SLE patients had similar rates of hypertension (70% vs.71%, p=0.892) and number of diseased vessels (Table 1). However, after adjustment for risk factors, SLE was found to significantly predict the presence of CAD (OR 2.24, 95% CI: 1.08, 4.67) (Table 2). There was a significant interaction between diabetes and SLE on the outcome of CAD such that diabetes was associated with CAD in non-SLE patients but not in SLE patients. With median follow-up duration of 4.3 years (IQR 1.9 to 8.0), after adjusting for risk factors, SLE was not significantly associated with CVD mortality (HR 1.585, 95% CI: 0.804, 3.122 p=0.184) or all-cause mortality (HR 1.683, 95% CI: 0.979, 2.892, p=0.06). However, the relationship between SLE and all-cause mortality approached statistical significance.

Conclusion: SLE is confirmed to be a significant, independent predictor of CAD identified by coronary angiography, the gold standard for assessing flow-limiting lesions in this disease. Patients with SLE have an equal severity of CAD and similar mortality rates as non-SLE controls, despite having less than half the rate of diabetes and being 20 years younger compared with controls. Diabetes was not associated with an increased risk of CAD among SLE patients.

Table 1. Number of Diseased Vessels

Diseased Vessels	SLE(%)	Control (%)
0	48	38
1	23	23
2	12	16
3	17	23

Overall p-value 0.0813

Table 2. Multivariable Logistic Regression Model for significant CAD

	p-value	Odds Ratio	95% Confidence Interval	
History of Myocardial Infarction	<0.001	7.77	4.11	14.67
Age(OR per 10 year increase, 48-75)	<0.001	2.22	1.61	3.06
Hyperlipidemia	0.014	1.89	1.14	3.15
Female	0.015	0.42	0.21	0.84
Lupus	0.031	2.24	1.08	4.67

*C-index 0.777

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Low Physical Activity Is Associated with Proinflammatory High-Density Lipoprotein and Increased Subclinical Atherosclerosis in Women with Systemic Lupus Erythematosus. Elizabeth R. Volkmann[1], Jm Grossman[2], Lori J. Sahakian[1], Brian J. Skaggs[1], John D. FitzGerald[3], Nagesh Ragavendra[3], Christina Charles-Schoeman[3], Weiling Chen[4], Alan H. Gorn[3], George A. Karpouzas[5], Michael H. Weisman[3], Daniel J. Wallace[3], Bevra H. Hahn[3] and Maureen A. McMahon[3], [1]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, [2]UCLA, LA, CA, [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, [4]UCLA, Los Angeles, CA, [5]Harbor-UCLA Medical Center, Torrance, CA

Purpose: Discovering ways to decrease cardiovascular disease in patients with Systemic Lupus Erythematosus (SLE) remains a substantial challenge in clinical practice. The present study investigates the impact of physical activity on subclinical atherosclerosis and on dysfunctional, proinflammatory high-density lipoprotein (piHDL), which may increase risk for atherosclerosis in SLE.

Method: Patients (242 women) fulfilling the ACR 1997 criteria for SLE participated in this cross-sectional study. Carotid plaque and intima-media thickness (IMT), antioxidant function of HDL, and traditional cardiac risk factors were measured. Disease activity and organ damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR), respectively. Physical activity was evaluated from self-reports by calculating the metabolic equivalent-minutes (METs) per week and by the physical function component of the Medical Outcomes Study Short Form-36 (SF-36). Data were analyzed using bivariate and multivariate regression analyses.

Results: Number of METs per week spent performing strenuous exercise was negatively correlated with IMT (r = -.30, P = 0.002) and number of plaques (r = -.30, P = 0.0001). Physical function as assessed by the SF-36 was also negatively correlated with IMT (r = .14, P = 0.03) and number of plaques (r = -.14, P = 0.04). In multivariate analyses, number of strenuous exercise METs was significantly associated with IMT (t = -2.2, P = 0.028) and number of plaques (t = -2.5, P = 0.014) when controlling for markers of SLE disease activity and damage, but not after controlling for traditional cardiac risk factors. Low physical activity, defined as < 225 total METs per week, was associated with presence of piHDL in multivariate analysis, controlling for both traditional cardiac risk factors and markers of SLE disease activity and damage, (*OR* 2.0, P = 0.03). Neither total METs per week, nor SF-36 physical function correlated with SLEDAI score, cumulative or current prednisone dose, or use of hydroxychloroquine.

Conclusion: Low physical activity is associated with increased subclinical atherosclerosis and with piHDL in patients with SLE. Increased strenuous exercise may potentially reduce the risk of atherosclerosis in SLE.

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Pro-Inflammatory High Density Lipoprotein (PiHDL) in Systemic Lupus Erythematosus. Adnan Kiani[1], Maureen A. McMahon[2], Lori J. Sahakian[2], Laurence Magder[3], B H. Hahn[2] and Michelle Petri[4], [1]Johns Hopkins University, Baltimore, MD, [2]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]University of MD, Baltimore, MD, [4]JHU, Baltimore, MD

Purpose: HDL has long been considered to be protective against coronary artery disease (CAD), due to inhibition of oxidation of LDL and promotion of cholesterol efflux. However, abnormalities in HDL composition are now recognized. Acute and chronic inflammation lead to a transformation of anti-inflammatory HDL to a pro-inflammatory form (PiHDL) which has multiple structural differences, including less apolipoprotein B and more serum amyloid A. In half of SLE patients with CAD and normal lipid profiles, PiHDL may be one of the mechanisms leading to abnormal lipid function and atherosclerosis. We looked at the association of PiHDL with subclinical measures of atherosclerosis as well as traditional and non-traditional cardiovascular risk factors.

Method: PiHDL was measured on stored sera of fifty six SLE patients at baseline and after 2 years in the Lupus Atherosclerosis Prevention Study, a clinical trial of atorvastatin vs. placebo.

Results: The patients were 89% female, 57% Caucasian, 36% African-American and 7% other ethnicity with mean age 43±10 years. Atorvastatin failed to decrease PiHDL during the 2 year trial period (Table 1).

Table 1: Change in PiHDL over the two year study based on 41 patients with both baseline and follow-up PiHDL

Baseline PiHDL	Follow-up PiHDL (mean ± SD)	Mean (±SD) change	p-value	Number (%) with increase in PiHDL	Number (%) with a decrease in PiHDL
1.66 ± 0.71	1.61 ± 0.55	-0.05 ± 0.57	0.56	22 (54%)	19 (46%)

Mean PiHDL was higher in men vs. women (2.04 vs 1.51; p=0.08), African-American vs. Caucasian (1.61 vs 1.54; p=NS), <35 years of age vs. 35-49 or 50+ (1.81 vs 1.64 vs 1.25; p=0.06 for negative trend with age), BMI>30 vs. <25 or 25-29 (1.71 vs 1.44 vs 1.54; p=NS).

Table 2 shows how subgroups defined by PiHDL correlates with measures of subclinical atherosclerosis and other risk factors for atherosclerosis.

	Low PiHDL (<1), (n=15)	Medium PiHDL (1-2), (n=26)	High PiHDL (>=2), (n=15)	P-value
Proportion (%) with coronary calcium	3/15 (20%)	12/26 (46%)	7/15 (47%)	0.20
Mean (SD) log-transformed coronary calcium score	0.53 (1.19)	1.73 (2.48)	0.83 (1.18)	0.12
Mean carotid IMT	0.60 (0.13)	0.56 (0.08)	0.54 (0.07)	0.26
Mean carotid Plaque Score	1.53 (0.83)	2.31 (2.13)	1.20 (0.77)	0.08

The proportion with coronary calcium was higher in those with medium or high PiHDL, but not statistically significant.

Conclusion: Atorvastatin failed to reduce PiHDL levels during the 2 year trial period. In contrast to previous studies, PiHDL was not associated with measures of subclinical atherosclerosis, but CAC was higher in those with moderate to high PiHDL. However, this study was limited by the use of stored samples which may have lost PiHDL activity.

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Genetically Determined Mannose-Binding Lectin Deficiency Is Associated with Subclinical Atherosclerosis in Patients with Pediatric-Onset Systemic Lupus Erythematosus. Jing-Long Huang, Chang Gung Memorial Hospital, Kueishan, Tayoyuan, Taiwan

Purpose: Mannose-binding lectin (MBL) is an innate immune protein. The aim of this study was to determine whether genetically determined MBL deficiency is associated with subclinical atherosclerosis in pediatric-onset systemic lupus erythematosus (SLE).

Methods: Between 2002 and 2009, forty-five patients with pediatric-onset SLE and 38 normal controls were recruited. In patients with SLE, prospectively longitudinal carotid ultrasonography was performed to assess subclinical atherosclerosis. MBL2 gene mutations were determined by polymerase chain reaction method and sequence analysis to identify genotypes of MBL. Functional MBL plasma concentrations were detected using enzyme-linked immunosorbent assay. Subclinical atherosclerosis was defined as intima-media thickness (IMT) of carotid artery greater than +1 standard deviation of normal controls. Associations between clinical and laboratory variables and MBL genotypes were determined by simple regression analysis, Mann-Whitney and chi-square tests.

Results: The high, medium and low MBL expression genotype groups were associated with MBL plasma concentrations (3610±6396 ng/ml vs. 580±474 ng/ml vs. undetectable, $P < 0.01$). The patients with subclinical atherosclerosis and thickening of IMT had lower MBL plasma concentrations on diagnosis of SLE than others (983±808 ng/ml vs. 3560±6716 ng/ml , $P = 0.034$ and 936±958 ng/ml vs. 2504±4834 ng/ml, $P = 0.03$, respectively). The high MBL expression genotype was associated with less subclinical atherosclerosis compared to the medium MBL expression genotype (30.8% vs. 62.5%, $P = 0.04$).

Conclusion: High MBL expression genotype was a protective factor to subclinical progression of atherosclerosis in patients with pediatric-onset SLE. Low MBL level at diagnosis of SLE was a risk factor to the subclincal atherosclerosis.

Disclosure: J. L. Huang, None.

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Evidence for Antimalarial Beneficial Effect in Cardiac Arrhythmic Events in a Large Systemic Lupus Erythematosus (SLE) Cohort. Ricardo A. Teixeira[1], Eduardo F. Borba[2], Eloisa Bonfa[2], Anísio Pedrosa[1], Silvana Nishioka[1] and Martino Martinelli Filho[1], [1]Incor, Faculdade de Medicina da USP, São Paulo, Brazil, [2]Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil

Purpose: There are no prevalence studies of arrhythmias and conduction disturbances in a large SLE population determining the influence of disease factors and long-term antimalarial use.

Method: Three-hundred seventeen consecutive SLE patients (ACR criteria) age>18 y were evaluated by resting-ECG and 24-hour *Holter* monitoring (n=142, randomly selected) for arrhythmia, conduction disturbances, heart rate variability, and repolarization parameters. Data were obtained in an ongoing electronic database protocol which consists of an extensive clinical/ laboratorial/treatment evaluation.

Results: The majority was female (91%) with medians of age and disease duration of 40.25 years and 11.36 years, respectively. Renal involvement was observed in 26.2% and hypertension in 18.9%. Antimalarial therapy (minimum of 6 months) was observed in 69% with a mean duration of 8.47 ± 6.74 years. Resting-ECG abnormalities were detected in 66 patients (20.8%): long QT in 14.2%; RightBBB in 1.9%; LeftBBB in 0.6%; 1st degree AV-block in 1.6%; sinus bradycardia in 1.3%; sinus tachycardia in 1.3%, and supraventricular tachycardia in 0.3%. Prolonged PR interval was associated with less chloroquine use (p=0.01), shorter chloroquine treatment duration (1.00±2.45 vs. 6.10±6.88 years, p=0.018) and older age (54.17±7.33 vs. 42.26±13.25 years, p=0.029). Holter monitoring events were observed in 121 patients (85.2%): HR<50bpm in 31.6%; pauses>2.0s in 2.8%; atrial tachyarrhythmia in 18.3%; atrial isolated ectopies in 63.4%, ventricular ectopies in 45.7%, and ventricular tachycardia in 2.8%. Tachyarrhythmias were associated with shorter chloroquine treatment duration (7.05±7.99 vs. 3.63±5.02 years, p=0.043) with a trend to less use of chloroquine (p=0.054), and older age (40.19±11.54 vs. 52.50±12.02 years, p<0.001). Clinical and laboratorial variables such as renal and cardiac insufficiency, hypertension, and anti-La/SS-B were not associated with conduction abnormalities (p>0.05), except for anti-Ro/SS-A with an association with supraventricular arrhythmia (p=0.042). Logistic regression model revealed that predictors for supraventricular tachyarrhythmia (AT/AF) were age (p<0.001; OR=1.100; IC95%=1.050-1.154) and shorter antimalarial use (p=0.035; OR=0.921; IC95%=0.853-0.994).

Conclusion: Antimalarials seem to have a protective role in the unexpected high rate of cardiac arrhythmias and conduction disturbances observed in SLE. Further studies are necessary to determine if this anti-arrythmogenic effect is due to the disease control or a direct effect of the drug.

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Smokers, Suffering by SLE, Have Higher Platelet Agregability Than the Non-Smokers. Low-Dose Aspirin Therapy Abrogates This Difference. Petr Bradna[1], Jaroslav Maly[1], Tomas Soukup[1], Miroslav Pecka[1], Vaclav Blaha[2], Jan Toms[1] and Zbynek Hrncir[1], [1]University Hospital and Charles University Faculty of Medicine, Hradec Kralove, Czech Republic, [2]University of Defence, Faculty of Medicine, Hradec Kralove, Czech Republic

Purpose: Both systemic lupus erythematosus (SLE) and smoking are prothrombotic situations with increased risk of atherogenesis. Aim of study was to elucidate, if smoking affects aggregation of blood platelets

Method: Study group consists of 63 patients, fulfilling ACR criteria of SLE. 46 were non-smokers, current smokers were 17 patients. 55 percents of the group were treated by low dose (100 mg QD) aspirin. We examined presence of antiphospholipid antibodies, morphological parameters of platelets, aggregation capability by aggregometry after epinephrine and ADP and by PFA-100 equipment.

Statistical analysis was performed by T-test and two-way ANOVA.test.

Results: Smoking SLE patients, not treated by aspirin, had significantly higher agregability of platelets than non-smokers (p=0, 02). Aspirin (100 mg QD) aligned the differences between smokers and non-smokers. Effect of aspirin was more displayed in patients with larger platelets (p<0, 01).

Patients with antiphospholipid antibodies demonstrated improved effect of aspirin on PFA-100 closing time. .

Conclusion: Smoking SLE patients displayed higher promptness to platelet aggregation than non-smokers.This feature with prothrombotic and proatherogenic potential could be antagonized by aspirin therapy. SLE patients, smokers, which are not able to stop smoking, should be treated by low-dose aspirin.

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Acute Transverse Myelitis and Antiphospholipid Antibodies in Lupus-No Evidence for Anticoagulation. Christina G. Katsiari[1], Irene Giavri[1], Dimos D. Mitsikostas[2], Konstantina G. Yiannopoulou[3] and Peter P. Sfikakis[1], [1]First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]Department of Neurology, Athens Naval and Veterans Hospital, Athens, Greece, [3]Neurology Service Laikon Hospital, Athens, Greece

Purpose: Current views suggest that the prothrombotic properties of antiphospholipid antibodies (aPL) have a role in the development of acute transverse myelitis (ATM) in patients with systemic lupus erythematosus (SLE). Although, trials assessing the role of aPL in SLE-associated ATM have not been possible to conduct due to the rarity of this condition, empiric anticoagulation is included in these patients' treatment. We performed a systemic review of the literature to explore, 1) the clinical and prognostic value of the presence of aPL antibodies in patients with lupus myelitis and 2) the effectiveness of anticoagulation.

Method: We systematically searched Medline using the terms: myelitis, myelopathy and lupus. Publications presenting cases of lupus myelitis that provided data on aPL antibodies were obtained. Selection of myelitis cases was based on the proposed diagnostic criteria of acute transverse myelitis: we included only cases where magnetic resonance imaging was performed 1) to exclude other pathologies and 2) to confirm myelitis. In cases where MRI was normal, we searched for other evidence of spinal cord inflammation as confirmed by pleocytosis and abnormal IgG index in cerebrospinal fluid (CSF). Demographic data as well as data on presentation, treatment and outcome were extracted from the literature. Neurological impairment was measured using the Expanded Disability Status Scale (EDSS, score range: 0 – 10). Statistical analysis was performed using the Mann-Whitney and the Fisher's exact tests.

Results: We report on a total of 67 patients (age range:15-58 years, 89% women, 66% with continuous involvement of ≥3 spinal segments, referred also as longitudinal ATM). Thirty-six patients (54%) were aPL-positive and did not differ in respect to demographic characteristics, clinical and laboratory SLE manifestations from aPL-negative patients. The presence of aPL did not predict the involvement of the thoracic part of the spine, which has been postulated to reflect a predominantly thrombosis-induced injury. The presence of aPL antibodies did not correlate with relapsing ATM, additional lupus CNS manifestations or worse clinical outcome. An unfavourable outcome could be predicted by paralysis and abnormal CSF findings at presentation (p=0.04 and 0.02, respectively), irrespective of the presence of aPL. While all patients received major immunosuppressive regiments, severe neurological impairment (EDSS score >7) was found primarily in aPL-negative patients (p=0.03). Anticoagulation was more frequently applied in aPL-positive patients (p=0.04), but any additional therapeutic effect was not evident.

Conclusion: Detection of circulating aPL appears unreliable to suggest a thrombotic cause and inadequate to support the therapeutic use of anticoagulation. Creation of a registry for ATM in SLE patients is needed to obtain more definite answers on the role of aPL in this condition.

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Cognitive Dysfunction in Patients with SLE: A Controlled Study. Marc A. Antonchak[1], Mahnaz Saoudian[1], Amber Khan[1], Tara Adhikari[1], Hermine Brunner[2] and Michael E. Luggen[1], [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Cincinnati Children's Hosp, Cincinnati, OH

Purpose: Cognitive dysfunction (CD) has been reported to occur frequently in SLE. But, almost all estimates of prevalence have utilized normal healthy individuals as controls. Chronic rheumatic diseases cause pain, fatigue, and depression which may all affect cognitive function. In order to determine the extent to which CD in SLE is caused by SLE per se, we have performed a case-control study of a community based population of patients with SLE and compared them to patients with rheumatoid arthritis.

Methods: A random subsample of SLE patients referred by community-based primary care physicians was examined. Controls consisted of RA patients who were matched for age, sex, and race. Cognitive function was assessed by the Automated Neuropsychological Assessment Metrics (ANAM), a validated, computerized, cognitive testing battery. Baseline demographic information, disease activity and damage, and treatment variables were ascertained. The primary outcome measure was the total throughput score (total number of correct responses/time).

Descriptive statistics and their distributions were determined. Final results were compared using Wilcoxon rank-sum test and Fischer's exact test. Correlates of CD were ascertained and independent factors identified by multiple linear regression.

Results: In this ongoing study, 96 lupus patients were randomly selected and 31 of them have been evaluated to date. Patients with SLE were significantly more depressed (Beck Depression Index score:16 vs. 8, $p<0.0001$), had lower quality of life (SF-36 mental component score [MCS]): 43.6 vs. 50.4, $p=0.009$), and had lower family incomes ($p=0.0154$) than the RA patients. Education, family income, fatigue, depression, pain, and SF36 physical component score and MCS were all found to correlate moderately with the ANAM performance as measured by the mean total throughput score. Independent risk factors of poorer performance included: low MCS, low educational level, and high pain scores. The total throughput scores of SLE patients were not statistically significantly different (with a power of 80% to detect a 20% difference) from those of patients with RA, even when adjustments were made for the above covariates.

Conclusion: Surprisingly, our results demonstrate no significant differences in cognitive function between community-based patients with SLE and their well matched RA controls. This would suggest that the CD observed in some patients with SLE may be due more to the effects of chronic disease than SLE per se.

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Assessment of Cognitive Function in Systemic Lupus Erythematosus, Rheumatoid Arthritis and Multiple Sclerosis Using Computerized Neuropsychological Tests. J. G. Hanly, Antonina Omisade, Li Su, Vernon Farewell, Tina Linehan and John D. Fisk, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS

Purpose: Computerized neuropsychological testing may facilitate screening by non-experts for cognitive impairment in SLE. The Automated Neuropsychological Assessment Metrics (ANAM) is a computerized test battery that takes 45 minutes to administer. We used ANAM to evaluate the cognitive performance of SLE patients compared to patients with rheumatoid arthritis (RA), multiple sclerosis (MS) and healthy controls.

Methods: Ambulatory patients with SLE (68), RA (33), and MS (20), with mild to moderate disease activity and severity, were compared to 29 healthy controls matched to SLE and MS patients for gender, age (±5 years) and education (±3 years). ANAM measures reaction time and accuracy in Simple Reaction Time (SRT), learning and recall using code substitution subtests (CDS and CDD), working memory using the Mathematical Processing (MTH) and the Sternberg Memory Scanning (ST6) subtests, sustained attention using a Continuous Performance subtest (CPT), visual-spatial processing using the Matching Grids (MSG) subtest, and short-term visual memory using the Match to Sample subtest (MSP). Efficiency of performance on each subtest was examined by "throughput"(TP) (number of correct responses per minute) and "inverse efficiency" (IE) (response speed/proportion of correct responses). Group differences were determined using O'Brien's generalized least squares test and all results were adjusted for age and education.

Results: Overall group differences were found for both IE ($p=0.01$) and TP ($p<0.01$). Control subjects were the most efficient while MS patients were least efficient. MS patients also demonstrated less efficient performance in comparison to both SLE ($p=0.01$) and RA ($p<0.01$) patients who did not differ from each other. To examine for differences in the frequency of overall "impairment", patients' IE scores on each subtest as well as the SRT subtest scores were converted to Z scores, based on the normal subjects' performances on each ANAM subtest. $Z \geq -1.5$ was considered to represent "impairment" in IE on any given subtest. Sixty-one percent of RA patients and 50% of SLE patients were impaired on at least one ANAM subtest compared to 75% of MS patients. Only 9% of RA patients and 11% of SLE patients were impaired in $\geq 4/7$ ANAM subtests, whereas 20% of MS patients were impaired to this extent. Performance on specific ANAM subtests indicated that MS patients were most often impaired on SRT, CDD and MTH subtests; SLE patients were most often impaired on SRT, CDS and CDD subtests; RA patients were most often impaired on SRT, CDS, MTH and ST6 subtests.

Conclusion: ANAM is sensitive to cognitive impairment in patients with neurologic disease, such as MS. Patients with SLE and RA had comparable performance on ANAM subtests. Slowing on SRT was common for all patient groups. While computerized testing may be sensitive to cognitive impairment in SLE, our results emphasize the lack of specificity of such deficits in many SLE patients and the role of chronic disease in the etiology.

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Prevalence and Types of Cognitive Impairment in Young Women with Systemic Lupus Erythematosus (SLE). Simone Appenzeller[1], Bruce Pike[2], Gabriel Leonard[2], Martin Veilleux[2] and A. E. Clarke[3], [1]State University of Campinas, Campinas, Brazil, [2]McGill University, Montreal, QC, [3]MUHC, Montreal, QC

Purpose: To determine prevalence and types of cognitive impairment in young women with SLE.

Method: We screened consecutive female SLE patients followed in a longitudinal cohort between 2007/2008. We excluded patients with any clinical factors associated with cerebral atrophy or vasculopathy [i.e., age ≥ 50 years, hypertension (BP >140/90 on 2 occasions or 1 occasion with concomitant antihypertensive medications), renal insufficiency (creatinine > 200mmol/dl on 1 occasion), transient ischemic attack or stroke, scleroderma features, diabetes, drug abuse or malignancy, or not educated primarily in English or French]. Healthy age matched women were selected as controls. SLE patients were assessed for disease activity [SLE Disease Activity Index (SLEDAI)] and damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)]. All subjects underwent a standardized neuropsychological evaluation to screen for possible impairment in the following cognitive domains: simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed and executive functions. The individual test results were converted into standard scores, which were compared to the normative data of the controls. Subjects with a total score in any of the 8 domains ≤2 SD below the normative value were considered impaired. Cognitive dysfunction was considered mild if there were deficits in <3 domains, moderate if deficits in 3-4 domains, and severe if deficits in ≥5 domains.

Results: One hundred and twenty seven patients < 50 years were screened, 52 fulfilled the inclusion criteria, and data are currently available on 27 (mean age 34.08, SD 8.85). Ten controls (mean age 33, SD 8.3) matched for years of education participated. Mean SLE duration was 8.1 years (SD 7.0), with a mean SLEDAI of 4.8 (SD 4.5) and mean non central nervous system SDI of 0.9 (SD 1.2). Cognitive impairment was identified in 21 (77.8%) SLE patients, mild in 8, moderate in 9, and severe in 4. Memory was impaired in 14 of 21 patients, executive functions and psychomotor speed in 11, simple attention in 9, complex attention in 6, language in 5, reasoning/problem solving in 3, and visuospatial processing in 3. Spontaneous complaints of cognitive impairment were mentioned by only 2 patients. None of the controls had any cognitive impairment. SLE patients with cognitive impairment had similar age distribution (mean difference 0.24; 95%CI of difference -4.83, 5.32), disease duration (mean difference 1.26; 95%CI -5.17, 7.70), disease activity (mean difference in SLEDAI 1.4; 95%CI -0.56, 1.31) and non central nervous system SDI scores (mean difference SDI=0.37; 95%CI -1.88,4.69) as SLE patients without cognitive impairment.

Conclusion: Cognitive impairment was frequently observed in young SLE patients and most patients did not have spontaneous complaints. The most frequently impaired domains were memory, executive functions and psychomotor speed. This study suggests that SLE patients should be routinely screened for cognitive dysfunction.

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Cognitive Dysfunction in Patients with SLE: A Prospective Study. Marc A. Antonchak[1], Mahnaz Saoudian[1], Amber Khan[1], Tara Adhikari[1], Hermine Brunner[2] and Michael E. Luggen[1], [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Cincinnati Child Hospital Medical Center (CCHMC) Division of Rheumatology, Cincinnati, OH

Purpose: Cognitive dysfunction (CD) has been reported to occur frequently in SLE. It is unclear, however, it this CD is transient, persistent, or progressive. Published reports have estimated persistence or progression in anywhere from 17% to 93% of patients. These widely divergent results may be due in part to the definition of CD employed and the lack of assessment of pre-morbid cognitive function. The later can result in misclassification with both false positive (pts with low native intelligence who score low) and false negative determinations (pts with high native intelligence who now fall within the “normal” range). Chronic rheumatic diseases cause pain, fatigue, and depression which may affect cognitive function. All studies to date have employed normal healthy individuals as controls. Definitions of CD relative to this

population will identify some pts whose major problems are depression, pain, or fatigue, which may improve, and some who have structural CNS disease, which may not.

Methods: A random subsample of SLE patients referred by community-based primary care physicians was examined at baseline and after 6 months. Cognitive function was assessed by the ANAM (Automated Neuropyschologic Assessment Metrics), a validated, computerized, cognitive testing battery, utilizing as the primary outcome measure the total throughput score (TTS=total number of correct responses/time). Disease activity, damage, and treatment variables were ascertained at baseline and at 6 mos. Premorbid intelligence was estimated by the Peabody Picture Vocabulary Test (PPVT) which correlates with other measures of native intelligence and is minimally affected by moderate CNS disease. Abnormality was defined as having scores 2 SD below the mean of an age and sex matched RA control population. The results were compared using paired t-tests or Wilcoxon sign rank test

Results: Ninety-six SLE patients were randomly selected. Twenty-nine have been evaluated to date on at least two occasions. Comparisons of baseline scores with scores at 6 months showed no significant differences in 6 of the 10 ANAM subtests but statistically significant improvement in 4 subtests and in the TTS (by ~8%, P=0.0007). The median PPVT standardized score was 99.0 (IQR: 93.5, 111.0). The PPVT did not appear to be correlated with TTS at baseline or 6 mos. At baseline, 5/29 (17.2%) patients had abnormal TTS. Three of the 5 pts remained impaired at 6 mos and 2 improved.

Conclusion: Using RA controls, 17.2% of a community based SLE cohort had CD. Most of these had persistent deficits. However, most SLE pts had normal cognitive function which remained stable or improved over 6 mos. Adjustment for premorbid intelligence did not appear to influence results in this sample. This study suggests that, in a community based population, significant CD is uncommon.

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Benign Intracranial Hypertension Is a Significant Cause of Intractable Headache in Lupus Patients with Normal Cerebrospinal Fluid Composition. Ji-Min Kim, Chang-Hun Lee, Su-Jin Moon, Ho-Sung Yoon, Kwi-Young Kang, Seung-Ki Kwok, Ji-Hyeon Ju, Kyung-Su Park, Sung-Hwan Park and Ho-Youn Kim, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

Purpose: Headache is a common symptom described by patients with systemic lupus erythematosus (SLE). Headache can be a neuropsychiatric manifestation of SLE as well as a symptom of central nervous system infections such as septic meningitis. We evaluated the etiologies of intractable headache in lupus patients who underwent cerebrospinal fluid (CSF) study.

Method: We conducted a retrospective medical record review of 1034 patients who were diagnosed of SLE in the rheumatology department of Seoul St. Mary’s Hospital between June 1996 and May 2009. We identified 24 (2.3%, mean age 27.6±9.2 years) patients who underwent CSF studies because of their intractable headache. The clinical characteristics, laboratory data, findings of brain imaging, and prognosis of these patients were analyzed.

Results: Of the 24 patients, septic meningitis was identified in 7 (29.2%) patients, aseptic meningitis in 8 (33.3%), and normal CSF composition in 9 (37.5%). Of the 9 patients with normal biochemical and cytological CSF findings, 4 (44.4%) patients were identified to have benign intracranial hypertension. The other 5 patients with normal CSF composition and normal CSF opening pressure included 2 with migraine, 2 with acute confusional state, and 1 with seizure disorder. Patients were divided into 4 groups; those with septic meningitis, aseptic meningitis, benign intracranial hypertension, and normal CSF composition and pressure. Although there were no significant differences in clinical manifestations, findings of brain imaging, and prognosis among the 4 groups, patients with benign intracranial hypertension had significantly high SLE disease activity index (SLEDAI) score compared to other groups ($p<0.001$). Serum albumin level was significantly lower in the benign intracranial hypertension group than the septic meningitis group ($p<0.005$) and the aseptic meningitis group ($p<0.05$). Serum levels of C3 were also lower in the benign intracranial hypertension group than the septic meningitis group ($p<0.05$) and the aseptic meningitis group ($p<0.05$).

Conclusion: Although benign intracranial hypertension has been reported to be a rare cause of headache in patients with SLE, our data suggest that it does account for a significant portion of headache in lupus patients with normal CSF composition. Measurement of CSF opening pressure in addition to serum levels of albumin and C3 and SLEDAI score is thought to be useful in evaluating intractable headache in lupus patients and lowering CSF opening pressure and controlling SLE disease activity seems to be helpful in those patients.

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1578

Thalamic Volumes Predict Cognitive Impairment Evaluated by Speed Processing Tasks in Systemic Lupus Erythematosus. Simone Appenzeller[1], Bruce Pike[2], Leticia Rittner[1], Gabriel Leonard[2], Martin Veilleux[2] and A. E. Clarke[3], [1]State University of Campinas, Campinas, Brazil, [2]McGill University, Montreal, QC, [3]MUHC, Montreal, QC

Purpose: To evaluate the relationship between thalamic volumes and speed processing tasks in systemic lupus erythematosus (SLE).

Method: We screened consecutive female SLE patients followed in a longitudinal cohort between 2007/2008. We excluded patients with any clinical factors associated with cerebral atrophy or vasculopathy [i.e., age ≥ 50 years, hypertension (BP >140/90 on 2 occasions or 1 occasion with concomitant antihypertensive medications), renal insufficiency (creatinine > 200mmol/dl on 1 occasion), transient ischemic attack or stroke, scleroderma features, diabetes, drug abuse, or malignancy] or not educated primarily in English or French. Healthy age-matched women were selected as controls. Speed information processing was assessed with the stroop, trail making, finger tapping, and digital symbol tests and raw data and z-scores were used for analysis. Magnetic resonance imaging (MRI) was performed on a Siemens 3 Tessla scanner and volumetric T1 1mm thick slices were used for automatic segmentation of the thalamus. Atrophy of the thalamus was defined as a volume smaller than 2 SD of the control mean. The thalamic volumes and cognitive testing were compared between groups using the t-test. The pearson correlation was used to determine the correlation between individual cognitive tests and thalamic volumes.

Results: One hundred and twenty seven patients < 50 years were screened, 52 fulfilled the inclusion criteria, and data are currently available on 27 (mean age 34.08, SD 8.85). Ten controls (mean age 33, SD 8.3) participated. We observed significantly smaller right (mean volume 6413.48mm3; SD 664.78) and left (mean volume 6380.85mm3; SD 680.99) thalamic volumes in SLE patients when compared to controls [mean right volume 7006.82mm3; SD 523.00 (mean difference -593.33; 95% CI -118.85, -1067.83) and mean left volume 7019.42mm3; SD 495.37 (mean difference -638.56; 95%CI -158.76, -1118.37)]. Bilateral thalamic atrophy was identified in 6 patients and unilateral left in 2 patients. Speed information processing was similar between groups, except for finger tapping, in which SLE patients had significantly poorer results (mean difference -38.02; 95%CI -32.45; -43.56). Right thalamic volumes correlated directly with the stroop test (pearson correlation (PR) 0.55; p 0.0001), trail making test (PR 0.487; p 0.02), digital symbol test (PR 0.35; p 0.044), and finger tapping test (PR 0.44; p 0.006). Left thalamic volumes correlated directly with the stroop test (PR 0.56; p 0.001), trail making test (PR 0.55; p 0.005), and finger tapping test (PR 0.460; p 0.04).

Conclusion: We observed significantly smaller thalamic volumes in SLE patients when compared to healthy age and sex matched controls; speed information processing was similar with the exception of finger tapping which was poorer in SLE patients. Performance of speed processing tasks correlated directly with thalamic volumes. Correlation between structural volumes and specific cognitive testing can help identify underlying structural central nervous system pathology and explain cognitive impairment in visually normal appearing MRIs.

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Diagnostic Reliability of Magnetic Resonance Imaging for Central Nervous System Syndromes in Systemic Lupus Erythematosus: A Prospective Cohort Study. Yasuhiro Katsumata[1], Masayoshi Harigai[2], Yasushi Kawaguchi[1], Makoto Soejima[1], Kae Takagi[1], Takahisa Gono[1], Yuko Ota[1], Katsuji Nishimura[1], Hisashi Yamanaka[1] and Masako Hara[1], [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Medical and Dental University, Tokyo, Japan

Purpose: Magnetic resonance imaging (MRI) is often used in the diagnosis of central nervous system (CNS) syndrome in systemic lupus erythematosus (SLE). However, previous studies of MRI as a diagnostic tool for CNS syndromes in SLE contained several limitations such as study design, number of enrolled patients, and definition of CNS syndromes. We overcame these problems and statistically evaluated the diagnostic values of abnormal MRI signals and their chronological changes in CNS syndromes of SLE.

Method: We prospectively studied 191 patients with SLE, comparing those with (n = 57) and without (n = 134) CNS syndrome. CNS syndromes were characterized using the American College of Rheumatology case definitions.

Results: Any abnormal MRI signals were more frequently observed in subjects in the CNS group (n = 25) than in the non-CNS group (n = 32) [relative risk (RR), 1.7; 95% confidence interval (CI), 1.1-2.7; $p = 0.016$] and the positive and negative predictive values for the diagnosis of CNS syndrome were 42% and 76%, respectively. Significant differences were also found when the CNS group with neurologic disorders (n = 17; RR, 2.3; CI, 1.3-4.1; $p = 0.007$) and the CNS group with psychiatric disorders (n = 16; RR, 1.9; CI, 1.1-3.4; $p = 0.038$) were separately compared with the non-CNS group. Large abnormal MRI signals ($ø \geq 10$ mm) were seen only in the CNS group (n = 7; RR, 3.7; CI, 2.9-4.7; $p = 0.0002$), whereas small abnormal MRI signals ($ø < 10$ mm) were seen in both groups with no statistical difference. Large signals always decreased in size or resolved completely in the subjects where CNS syndromes were ameliorated by treatment, but were unchanged in the subjects where CNS syndromes did not improve; this difference was statistically significant ($p = 0.029$). Chronological changes in small signals did not correspond with clinical outcome ($p = 1.000$).

Conclusion: MRI alone does not have sufficient predictive value for a diagnosis of CNS lupus, although abnormal MRI signals showed statistical associations with CNS syndrome. A large MRI signal is, however, useful as a diagnostic and surrogate marker for CNS lupus, although it is less common.

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1580

The Prevalence of Neuropsychiatric Syndromes in SLE: A Meta-Analysis. Avraham Unterman[1], Johannes ES Nolte[1], Mona Boaz[2], Maya Abady[3], Yehuda Shoenfeld[1] and Gisele Zandman-Goddard[2], [1]Sheba Medical Center, Ramat Gan, Israel, [2]Wolfson Medical Center, Holon, Israel, [3]Edgecliff Physiotherapy Sports & Spinal Centre, Sydney, Australia

Purpose: To assess the prevalence of the 19 neuropsychiatric (NP) syndromes in systemic lupus erythematosus (SLE) patients, as defined by the 1999 Ad Hoc committee of the American College of Rheumatology (ACR), by performing a meta-analysis of relevant publications.

Methods: A literature search from April 1999 to May 2008 was performed to identify studies investigating NP syndromes in patients with definite SLE, applying the 1999 ACR case definitions and having a sample size of at least 30 patients. Excluded were studies that did not relate to all 19 NPSLE syndromes, presented duplicate data, or were irrelevant.

Results: Seventeen of 112 identified studies matched the inclusion criteria, reporting on a total of 5057 SLE patients, including 1439 NPSLE patients, with 2709 NPSLE syndromes. In a sub-analysis of the 10 higher quality prospective and elicited studies (2049 patients) using the random-effects model, NPSLE prevalence was found to be 56.3%, and the most frequent NP syndromes were headache (28.3%), mood disorders (20.7%), cognitive dysfunction (19.7%), seizures (9.9%), and cerebrovascular disease (8.0%), though significant between-study heterogeneity was present ($p<0.05$). Autonomic disorder and Guillain-Barré syndrome carried a prevalence of less than 0.1%. No case of plexopathy was reported.

Conclusion: Neuropsychiatric syndromes were found to exist in more than half of SLE patients. The most prevalent manifestations were headache, mood disorders, cognitive dysfunction, seizures and cerebrovascular disease. Some NP syndromes were found to be rare and their association with SLE is questionable, necessitating reconsideration of their inclusion in the ACR criteria.

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1581

Cardiovascular Disease, Cognitive Functioning, and Depression in SLE: A Study Using Diffusion Tensor Brain Imaging. L. J. Julian, P.P. Katz, L. Trupin, L.A. Criswell, E.H. Yelin, D. Wofsy and R. Henry, UCSF, San Francisco, CA

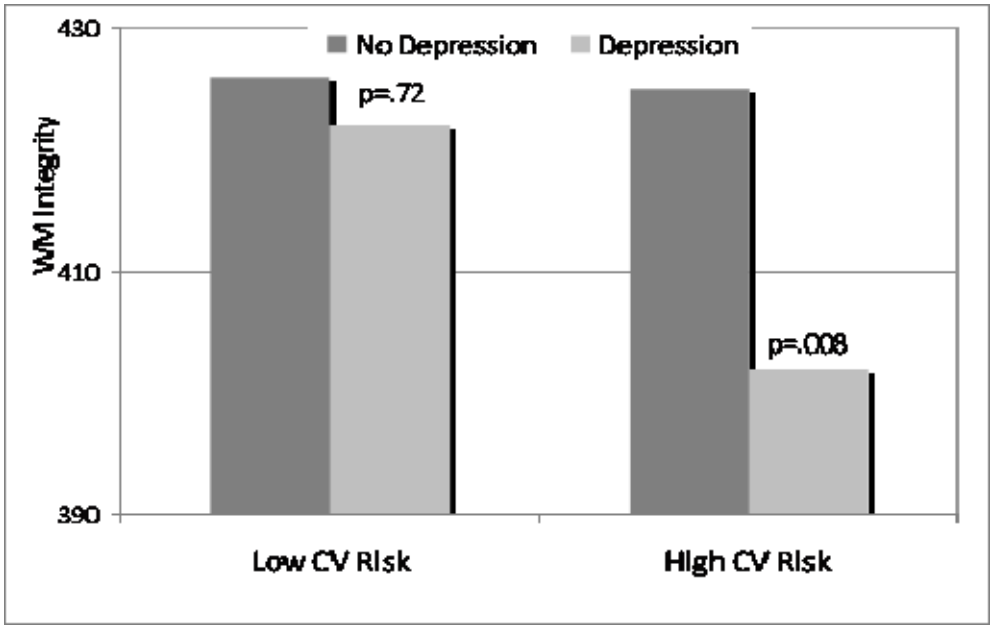
Purpose: Cognitive dysfunction and depression are common in SLE; yet the causal mechanisms of these neuropsychiatric syndromes are unclear. The purpose of this study is to evaluate the associations of depression, cognitive function and white matter integrity. To study white matter abnormalities we used an improved neuroimaging technique, diffusion tensor imaging (DTI) which identifies microstructural changes in normal appearing white matter (NAWM). Additionally, the relationships among DTI, cognitive function, and depression were evaluated with a particular focus on cardiovascular (CV) disease as a potential risk factor for WM brain abnormalities.

Methods: Participants included 41 patients with diagnostically confirmed SLE and no history of other neurological syndrome who underwent a neuropsychological and psychiatric evaluation, and brain MRI. Cognitive measures included tests of learning and memory, executive functioning, and motor speed. MRI procedures were conducted on 3Tesla MRI (GE Medical Systems Milwaukee, WI). The primary DTI index in this study is fractional anisotropy (FA) of whole brain WM with lower values indicative of poorer WM structural integrity. Patients were also categorized as having high cardiovascular risk if they had ≥ 2 traditional CV risk factors including: history of CV event, hypertension, hypercholesterolemia, family history, current or past smoking, obesity, or diabetes. Pearson or Spearman correlation coefficients were calculated to estimate associations among variables. Group comparisons were conducted using t-tests.

Results: Mean age of participants was 48±9 years, 70% had at least a high school education, and they were well represented across racial/ethnic groups. Average disease duration was 15.5±7.2 years. Reduced FA (reduced white matter integrity) was associated with increased CV risk ($r=-.46$, $p<.01$), and with reduced cognitive performance on measures of simple and complex sequencing, episodic memory, and working memory among patients with and without increased risk for cardiovascular disease (all $p<.05$). Depression was strongly associated with reduced FA among participants with increased CV risk (See Figure 1).

Conclusion: Alterations in WM structural integrity are associated with increased CV risk, depression, and poorer performance on measures of cognitive functioning. DTI can identify microstructural alterations in WM and may be a useful technique to study brain changes in SLE. The relationships with traditional CV risk factors provide some preliminary evidence in support of a vascular etiology for cognitive impairment and depression in SLE.

Figure 1. Depression and WM integrity among SLE patients stratified by CV risk



Disclosure: L. J. Julian, None; **P. P. Katz**, Bristol-Myers Squibb, 2 ; **L. Trupin**, None; **L. A. Criswell**, None; **E. H. Yelin**, None; **D. Wofsy**, None; **R. Henry**, None.

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Decreased Live Births in Women with SLE. E. Vinet[1], A. E. Clarke[1], C. Gordon[2], M.B. Urowitz[3], C. A. Pineau[1], D. A. Isenberg[4], A. Rahman[4], D. J. Wallace[5], G. S. Alarcon[6], I. N. Bruce[7], M. A. Petri[8], M. A. Dooley[9], C. Aranow[10], Ronald F. van Vollenhoven[11], SLICC and S. Bernatsky[1], [1]MUHC, Montreal, QC, [2]Medical School, Birmingham, United Kingdom, [3]TWH, Toronto, ON, [4]U College of London, London, United Kingdom, [5]Cedars-Sinai Medical Center/UCLA, West Hollywood, CA, [6]U of Alabama, Birmingham, AL, [7]Manchester Royal Infirmary, Manchester, [8]JHU, Baltimore, MD, [9]U of NC at Chapel Hill, Chapel Hill, NC, [10]The Feinstein Institute, Manhasset, NY, [11]Karolinska Univ Hosp, Stockholm, Sweden

Purpose: Multiple disease-related factors may limit the number of children borne to women with SLE. Though well-designed studies are lacking, there is a general notion that live births are not decreased in SLE, compared to healthy women. We calculated live births in women with SLE, and compared this with general population rates.

Methods: We studied women with SLE from a subset of centers participating in the SLICC Registry for Atherosclerosis inception cohort study. Women diagnosed with SLE before age 50 were included. We determined the number of children borne as of the last follow-up visit, and summed the years from the age of 15 up to the age of 50, or oldest age attained if the subject was aged < 49. We applied age- and country-specific general population birth rates, as well as relevant calendar-period rates, to these years to determine the expected number of live births for the period. We then calculated the standardized incidence ratio (SIR) of observed to expected live births. We also performed a multivariate analysis with the SIR as the dependent variable to explore potential predictors of live births, such as marital status, drugs(immunomodulators, prednisone, ASA, anticoagulants), antiphospholipid antibodies, disease activity & damage.

Results: 339 women with SLE were studied. Mean age at diagnosis was 35.3 years (standard deviation, SD, 13.3) & mean disease duration at the last visit was 2.7 years (SD 2.0). Most (43%) women were from the US, 27% from Canada, 27% from the UK, and 3% from Sweden. The majority of women (61%) were white, 19% were black, 10% were Asian and 5% were Hispanic. Most (42%) were currently married or living common-law.

Overall, the number of live births over the interval (313) was substantially below that which would be expected (479) (SIR 0.65; 95% CI 0.58, 0.73). In sensitivity analyses, we used race-specific general population birth rates, with similar results (SIR 0.65; 95% CI 0.58, 0.72). In multivariate analyses, being married or living common-law (SIR 2.07; 95% CI 1.58, 2.69) and current use of aspirin (SIR 1.36; 95% CI 1.02, 1.80) were associated with increased live births. There were trends for fewer live births in women exposed to cyclophosphamide (SIR 0.82; 95% CI 0.53, 1.27) and in those with high disease activity (SLEDAI $\geq$ 5) (SIR 0.76; 95% CI 0.54, 1.07). We did not definitively establish a decrease in live births independently attributable to positive antiphospholipid antibodies (SIR 0.98: 95% CI 0.73, 1.32) or disease damage (SLICC score $\geq$ 2) (SIR 1.02: 95% CI 0.70, 1.48), when drug exposures & clinical characteristics were adjusted for.

Conclusion: Women with SLE have fewer live births compared with the general population. Marital status & current ASA use were the most important predictors of live births (relative to the general population) in our sample.

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Lupus Activity Does Not Correlate with Estradiol During Pregnancy. Megan E. B. Clowse and Martin Tochacek, Duke University, Durham, NC

Purpose: Estradiol is considered a strong promoter of systemic lupus erythematosis (SLE) disease activity based on animal and epidemiologic studies. Estradiol levels rise 100-fold during pregnancy, suggesting that lupus activity might increase during this period. We investigated in women with SLE the association between estradiol, disease activity, and inflammatory markers during pregnancy.

Method: Consecutive pregnant women with rheumatologic disease were enrolled in the Duke Autoimmunity in Pregnancy Registry. Women were seen as soon as pregnancy was diagnosed, at mid-pregnancy between 22 and 26 weeks gestation, and post-partum. At most visits, we measured serum levels of estradiol, C reactive protein (CRP), C3, C4, and anti-dsDNA antibodies, and the erythrocyte sedimentation rate (ESR) as well as determined the SLE Pregnancy Disease Activity Index (SLEPDAI) and physician's global assessment (PGA). We correlated levels of estradiol and SLE activity at 3 separate time points to diminish the confounding effect of gestational age: 1st trimester, mid-pregnancy between 22-26weeks gestation, and post-partum. No pregnant women had multiple visits within the pre-specified time frames.

Results: The study included 29 pregnancies with a total of 91 visits. As expected, estradiol increased over the course of pregnancy and fell dramatically postpartum (correlation 0.8, $p<0.001$). There was marked inter-patient variability in estradiol levels at the mid-pregnancy visit. SLE activity did not correlate with estradiol level at any of the 3 time points (see table). In addition, mean levels of disease activity were similar at each of the time points. Levels of C3 and C4, anti-dsDNA antibody, and CRP did not correlate with estradiol levels. The ESR

was higher during pregnancy than post-partum (mid-pregnancy mean 48 vs post-pregnancy mean 17, p=0.01), but it did not correlate with estradiol at any time point.

Figure: distribution of estradiol levels by gestational age.

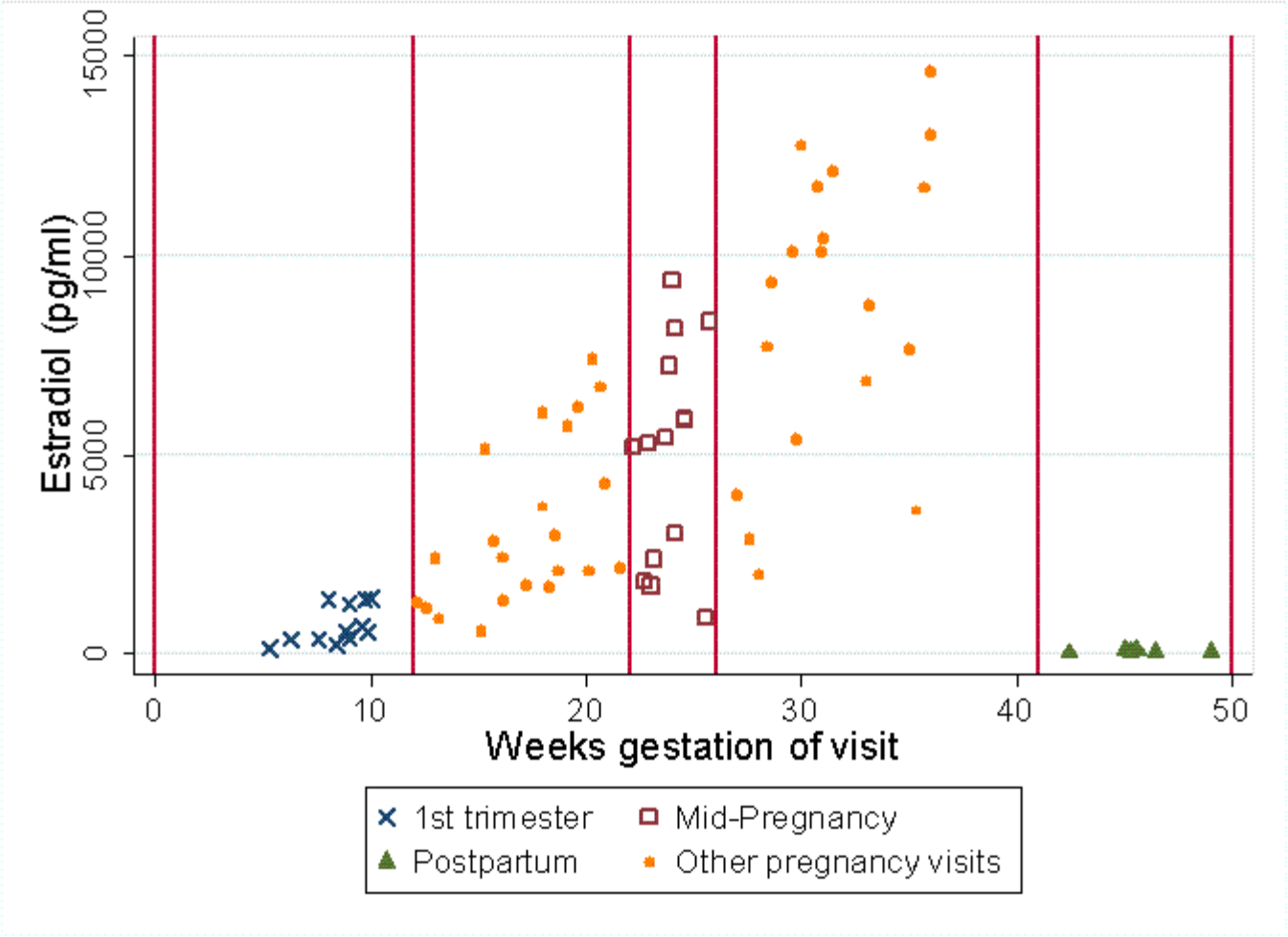

Table: SLE activity correlated with estradiol at 3 time points during and following pregnancy.

		1st trimester N=12	Mid-pregnancy N=14	Postpartum N=6
Estradiol	*Mean pg/ml (range)*	726 pg/ml (139-1389)	5056 pg/ml (906-9385)	41 pg/ml (10-81)

SLEPDAI *Mean (range)* Correlation with estradiol *(p-value)*	3.0 (0-10) 0.2 (p=0.6)	3.9 (0-10) -0.4 (p=0.2)	3.0 (0-5) 0.4 (p=0.4)
PGA *Mean (range)* Correlation with estradiol *(p-value)*	0.4 (0-1) 0.4 (p=0.2)	0.4 (0-1) -0.005 (p=0.9)	0.4 (0-1) 0.7 (p=0.1)

Conclusion: Although estradiol induces SLE activity in some murine models, it was not associated with disease activity in this cohort of pregnant women. The results of this study do not support the hypothesis that increasing levels of estradiol during pregnancy trigger SLE flares.

Disclosure: M. E. B. Clowse, None; **M. Tochacek**, None.

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Standardized Follow up of 54 Pregnancies IN 42 PATIENTS with Systemic Lupus Erythematosus. A. Theulin[1], M. Ardizzone[2], Jf Kleinmann[1], Christelle Sordet[1], Jacques-Eric Gottenberg[1] and J. Sibilia[1], [1]University Hospital of Strasbourg, Strasbourg, France, [2]Centre Hospitalier de Mulhouse, Mulhouse, France

Purpose: The prognosis of lupus pregnancies is not well known. We therefore investigated this issue in one of the national reference centers for auto-immune diseases.

Method: We performed a monocenter retrospective study of lupus pregnancies followed in a tertiary reference center between 1998 and 2008. All our patients had SLE according to the ACR criteria. Each patient was followed up using a standardized follow up, including clinical, biologic and fetal echocardiography procedure when needed (patients with anti-SSA/SSB antibody).

Results: Among the 425 patients with SLE followed in this reference center, 54 pregnancies occurred in 42 mothers. Twenty four patients had anti-Ro/SS-A, and 6 had anti-SSA and anti-SSB antibodies.

- Demographical data of mothers : Mothers age was 29.7 +/- 4.9 years, the mean SLE duration was 3.4 +/- 2.6 years and the mean number of immunosuppressor was 1.3 +/- 0.7. Ten pregnancies occurred in 7 women followed for lupus nephropathy.

At onset of pregnancy, patients were treated with low dose of corticosteroids (41 patients, 75%), mean dose was 11 +/- 8.8 mg per day, hydroxychloroquine (27 patients, 49%), azathioprine (3 patients, 5%), aspirin (37 cases, 67%). Combined treatment with aspirin and heparin was given in 4 patients with APS.

- Follow up of lupus flares during pregnancies : twenty four (44%) lupus flares were observed, 15 (27%) during pregnancy and 9 (16%) during post-partum. These flares were mild, mainly represented by arthralgia or arthritis (19 patients), and cutaneous involvement (8 patients). Among the patients with lupus nephropathy, an increasing proteinuria and transient alteration of renal function were observed in 3 patients (30%). No death and no APS-related thrombotic events occurred.

- Fetal outcome : Two (3,6%) fetal loss occurred in a patient with APS and another associated with a congenital heart block in a patient with anti-Ro/SSA auto-antibody. Thirteen (24%) preterm deliveries, and 9 (16 %) neonates with low birth weight were observed. No case of fetal deformity was observed, especially under hydroxychloroquine.

Conclusion: These data of 54 lupus pregnancies confirm that the maternal and fetal risk deserves a protocolized follow-up of these pregnancies, which allows a quite good maternal and fetal prognosis.

Disclosure: A. Theulin, None; **M. Ardizzone**, None; **J. Kleinmann**, None; **C. Sordet**, None; **J. E. Gottenberg**, None; **J. Sibilia**, None.

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Sex Hormones and Gender Influences the Function of Regulatory T Cells in SLE Patients. Ram P. Singh, Ravi Dinesh, Antonio La Cava and B H. Hahn, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: The goal of the present study was to determine the effect of gender and sex hormones on the quantity and function of regulatory T cells.

Method: Immunophenotyping was performed by flow cytometry and mRNA gene expression studies were performed by real time PCR. Protein expression was analyzed by intracellular staining and Western blot analysis. The *in vitro* effect of sex hormones b-estradiol (60pg/ml), b-estradiol inhibitor (10-20ng/ml), and androgen (10-50ng/ml) were studied by culturing cells for 72 hours followed by FACS/Western blot analyses. Apoptosis was measured by Annexin V and 7AAD staining.

Results: 1- The numbers of $CD4^+$ and $CD8^+$ regulatory T cells are decreased in healthy females compared to healthy males.

2- Both $CD4+CD25^{hi}$ and $CD8+CD25^{hi}$ subsets of healthy males had 3-4-fold higher Foxp3 mRNA compared to healthy females.

3- Foxp3 expression was higher in healthy male PBMCs than in healthy females PBMCs with and without stimulation with recombinant TGFb.

4- Stimulation of PBMCs with b-estradiol (30pg/ml) decreases Foxp3 expression in healthy females but not in age matched healthy males. At higher doses (60, 150pg/ml) estrogen has little effect on PBMCs from either sex.

5- Immunophenotyping of PBMCs from SLE patients (n~40) indicated significantly

reduced numbers of $CD4^+CD25^{hi}$ $Foxp3^+$ T cells and $CD8^+Foxp3^+$ T cells when compared to healthy matched controls (n ~20) and autoimmune disease control RA patients (n~30).

6- The in vitro proliferative potential of $CD4^+$ and $CD8^+$ T regulatory cells were defective in SLE patients compared to healthy controls ($p<0.001$).

7- Estrogen decreases Foxp3 mRNA and protein expression in $CD4^+CD25^-$ T cells from both female and male SLE patients ($p<0.05$).

8- An inhibitor of b-estradiol (ERa) increased apoptosis in male SLE patients only.

Conclusion: These data suggest that the numbers of regulatory T cells are decreased in healthy females compared to healthy males. Women may be more susceptible to SLE than men due to estrogen deregulation of the T regulatory compartment. These findings may have possible implications in understanding the regulation of disease in relation to gender bias in SLE patients.

Disclosure: R. P. Singh, None; **R. Dinesh**, None; **A. La Cava**, None; **B. H. Hahn**, None.

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Longitudinal Evaluation of Idiotypic and Anti-Idiotypic Response to the Major Epitope of La/SSB Autoantigen in Mothers Enrolled in the PITCH (Preventive IVIG Therapy for Congenital Heart Block) Study. Jg. Routsias[1], Nikolaos Kyriakidis[1], Carolina Llanos[2], Robert M. Clancy[2], Jill Buyon[2] and Athanasios G. Tzioufas[1], [1]School of Medicine, National University of Athens, Athens, Greece, [2]NYU School of Medicine, New York, NY

Neonatal lupus (NL) affects children of mothers with anti-Ro/SSA and anti-La/SSB autoantibodies. NL can cause permanent and life-threatening damage to the fetal heart, most commonly congenital heart block (CHB). Previous studies have shown that anti-idiotypic antibodies to autoantibodies against La/SSB are found in sera of mothers with healthy children, suggesting that anti-idiotypic antibodies may protect the fetus by blocking the pathogenic maternal autoantibodies.

Purpose: To investigate the effect of IVIg on the idiotype (id)-antiidiotype (anti-id) network in pregnant women with anti-Ro/SSA and anti-La/SSB antibodies who had a previous history of a child with CHB (high risk pregnancies).

Method: The interaction of IVIg with the synthetic peptides was investigated by direct ELISA assays as well as inhibition experiments. Ten mothers who previously gave birth to a child with CHB were treated during a subsequent pregnancy with IVIG using a protocol in the Preventive IVIG Therapy for Congenital Heart Block (PITCH) Study. All individuals exhibited ELISA reactivity against epitope 349-364 of La/SSB in their initial samples. Sequential sera were drawn from all mothers during pregnancy (before each IVIg infusion at 12, 15, 18, 21, 25 and 28, 34, delivery), and evaluated for antibodies against the epitope 349-364 (pep) of La/SSB (idiotypic), as well as its complementary

epitope (cpep) and anti-349-364 Fab_2 fragments (both anti-idiotypic). Anti-349-364 reactivity was also evaluated after removal of anti-Id antibodies.

Results: IVIg contains low affinity antibodies, most probably polyreactive antibodies, binding to both pep and cpep. The reactivity of anti-cpep (anti-id) antibodies appeared to be higher, compared to anti-pep antibodies. A partial inhibition of idiotype-antiidiotype binding (30%), was observed after IVIg treatment of purified antibodies. Following dosing of IVIg the maternal antibody titres to the major epitope of La/SSB decreased by 20% to 50% in four patients, remained stable in five and increased in one by 30%. In contrast, there was a substantial increase of anti-Id reactivity in all patients, ranging from 20% to 250%. After removal of anti-Id antibodies the Id reactivity was increased (up to 300%) in all patients. None of the children developed any conduction abnormality.

Conclusion: This study supports the novel finding that IVIg administration decreases autoantibody titres and enhances the anti-idiotypic antibody response in pregnant women with anti-Ro/SSA and anti-La/SSB antibodies.

Disclosure: J. Routsias, None; **N. Kyriakidis**, None; **C. Llanos**, SLE Foundation Inc., NY., 2 ; **R. M. Clancy**, None; **J. Buyon**, Alliance for Lupus Research, 2 ; **A. G. Tzioufas**, None.

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Fetal and Maternal Outcomes with Mycophenolate Mofetil (MMF) Exposure During First Trimester of Pregnancy in Patients with Systemic Lupus Erythematosus. Elizabeth C. Ortiz, Karina D. Torralba, Christine M. Evelyn and Francisco P. Quismorio Jr., University of Southern California-Los Angeles County Medical Center, Los Angeles, CA

Purpose: The US Food and Drug Administration has recently changed the pregnancy category of mycophenolate mofetil (MMF) to Category D (positive evidence of fetal risk) based on postmarketing data. MMF use during the first trimester may increase the risk of pregnancy loss and congenital malformations. The objective of the study is to establish the outcomes of SLE patients exposed to MMF during their first trimester of pregnancy.

Methods: Retrospective chart review of 700 SLE patients followed during 2006-2009 was done to identify patients who were on MMF during their first trimester of pregnancy. The patient population was primarily Hispanic, low income and without private health insurance. Obstetric and drug histories were noted, focusing on cumulative MMF dose at the time of conception, gestational age at the time of discovery, contraceptive use and outcome of pregnancy.

Results: Five SLE patients were exposed to MMF during their first trimester. The mean duration of disease was 6.2 years (3-10yrs). MMF was prescribed for nephritis (3 cases), hemolytic anemia (1) and thrombocytopenia (1). Three patients had anticardiolipin antibodies. At the time of discovery of the pregnancy, mean SLEDAI score was 2.4 (0-10); mean age of gestation was 28 days (21-37 days). Mean cumulative dose from conception to birth/fetal loss was 49g (28-103g); mean daily dose was 1.5g; maximum MMF dose from time of start of medication was 4,000g. Other medications used at the time of conception were hydroxychloroquine (4 patients), prednisone (5), alendronate (3) and benazepril (1). Three patients used barrier methods for contraception while two patients were not using contraception of any kind. All had received physician counseling regarding use of contraception prior to and while on MMF. Three patients delivered healthy babies; 2 reached full-term, 1 required emergent caesarian section for pre-eclampsia at 32 weeks. One patient who elected to terminate the pregnancy experienced fetal demise at 6.5 weeks and subsequently had passage of products with misoprostol. One patient had spontaneous abortion at 22 weeks; this patient had ongoing nephritis. There were no reported fetal malformations. No changes in SLEDAI were noted during duration of all pregnancies.

Conclusion: MMF exposure during first trimester of pregnancy in our cohort of SLE patients was associated with pregnancy loss in 40% of patients which is similar to that reported in the National Transplantation Pregnancy Registry (45%). No fetal malformations were observed, however number of live births was small. Our study emphasizes the need for better patient education and counseling, and closer monitoring for use of effective contraception while on MMF and other teratogenic medications.

Disclosure: E. C. Ortiz, None; **K. D. Torralba**, None; **C. M. Evelyn**, None; **F. P. Quismorio**, None.

1588

Pregnancy Outcome in SLE Patients Before and After Diagnosis. Regina Fare, Esther Rodriguez-Almaraz, Patricia E. Carreira, Isabel Mateo and María Galindo, Hospital 12 de Octubre, Madrid, Spain

Purpose: To analyze predictive factors for pregnancy outcome in a large group of SLE patients.

Methods: Ever pregnant SLE patients followed in the rheumatology department of a University Hospital between 1977-2008 were included. Demographic (age, time from onset and diagnosis, cardiovascular risk factors, follow up and death), clinical (SLE activity, obstetric history), treatment and pregnancies outcome data were obtained from previous databases, obstetric charts or phone questionnaires. Outcome complications included: pregnancy loss, preterm delivery, intrauterine growth retardation (IUGR), preeclampsia/eclampsia, or fetal death. Chi-square test was used to analyze associations between categorical variables and univariate and multivariate logistic regression to analyze risk factors for pregnancy outcome.

Results: We included 177 SLE patients who presented 406 pregnancies, 280 and 126 previous and after SLE diagnosis, respectively. Mean age at SLE diagnosis was 32 years (range 6-69) and mean age at pregnancy was 28 years (range 16-45). From 406 pregnancies, 307 (76%) were alive newborns, 9 (2%) IUGR and 83 (21%) preterm delivery. There were only 3 cases of neonatal lupus (3 skin and 2 hematological involvement) all in mothers with anti-Ro antibodies. There were 3 perinatal deaths but none related to SLE. Among pregnancies developing after SLE diagnosis, 52,4% presented at least one complication (30,2% miscarriage); 22,7% ended in caesarea, and 28% and 22% developed SLE flares during pregnancy and postpartum, respectively. Most of these SLE flares were mild (skin and joints). Outcome complications were more frequent in pregnancies occurring after than before SLE diagnosis: pregnancy losses (p=0,04), IUGR (p=0,003), hypertension (p=0,002), and caesarea (p=0,001). In univariate analysis, risk factors for poor outcome were previous renal involvement (p=0.04), and pregnancy less 6 months after SLE flare (p=0.02). Factors associated with good outcome were antimalarials treatment (p=0.05) and carefull monitoring in high risk pregnacy clinic (p=0.01). Previous proliferative nephritis was a risk factor for preclampsia (p=0.003). Haemolytic anemia was a risk factor for preterm delivery (p=0.003), and for preeclampsia (p=0.01). Raynaud phenomenon was a risk factor for preterm delivery (p=0.02). APS diagnosis was a risk factor for miscarriages (p=0,03), specially in 2nd trimester (p=0.01), IUGR (p=0.05) and preclampsia (p=0.03). Becoming pregnant less than 6 months after the last SLE flare was a risk factor for preclampsia (p=0.05). Treatment with steroids did not exert any protective or worsening effect for pregnancy outcome. In the multivariate analysis, renal involvement (p=0.001), and previous SLE flare (p=0.004) persisted as risk factors for poor outcome, and careful monitoring as a good prognosis factor (p=0.03).

Conclusion: Pregnancy in SLE patients should not be considered as an unacceptable high risk condition for mother and newborns. Nevertheless, the existence of previous renal involvement, haemolytic anemia or APS confer a higher risk for pregnancy complications. Pregnancy must be planned at least 6 months after last SLE flare and must be careful monitored in specialized high risk pregnancy clinics.

Disclosure: R. Fare, None; **E. Rodriguez-Almaraz**, None; **P. E. Carreira**, None; **I. Mateo**, None; **M. Galindo**, None.

1589

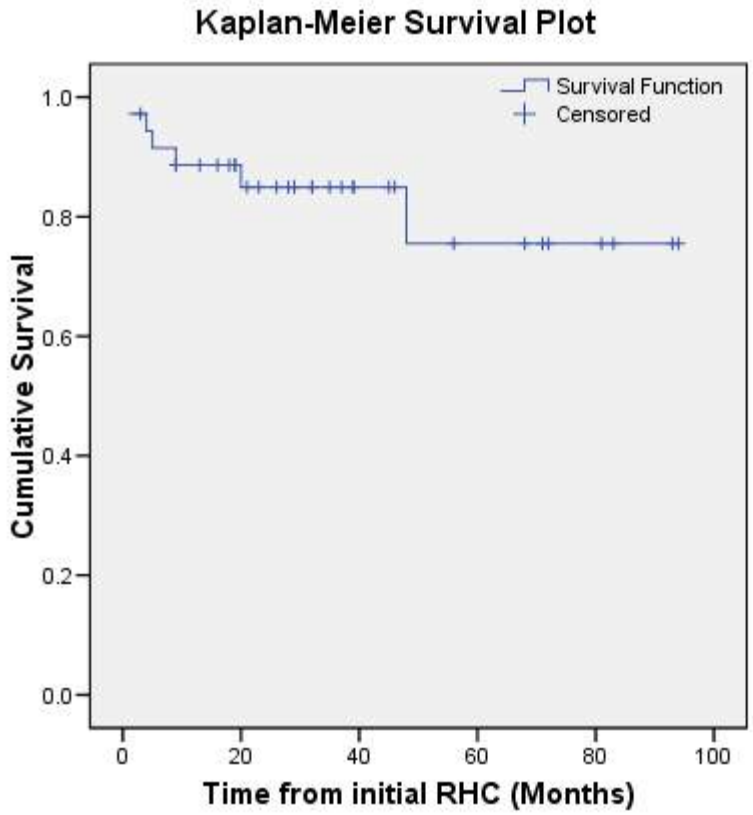
Pulmonary Hypertension in Systemic Lupus Erythematosus – A Retrospective Analysis. Rhodri Martin[1], Richard W. Lee[2], John G. Coghlan[3] and David P. D'Cruz[4], [1]Lupus Research Unit, Rayne Institute, St Thomas' Hospital, London, United Kingdom, [2]Lupus Research Unit, St Thomas' Hospital, London, United Kingdom, [3]Royal Free Hospital, London, United Kingdom, [4]St Thomas Hosptial, London

Purpose: Pulmonary hypertension (PH) is less well described in systemic lupus erythematosus (SLE) than in other connective tissue disorders such as scleroderma. National Pulmonary Hypertension Service (NPHS) guidelines state that patients should be assessed in a NPHS centre with right heart catheterisation (RHC) as the gold standard investigation.

We define burden and severity of PH in a cohort of patients with SLE referred to the NPHS.

Methods: RHC Pulmonary arterial pressures (PAP) and key clinical features were audited.

Results: RHC data was obtained for 47 patients with SLE referred between 2001 and 2008. Ten patients had lupus overlap syndromes (e.g. with scleroderma) or mixed connective tissue disease. Forty-three patients (91%) were Female with mean age 49 years (24 to 80 years). PH (PAP >25mmHg) was confirmed in 32 patients. Five others were labelled as "post-capillary" PH. Mean RHC data included (mmHg): Mean-PAP 39 (22-66); systolic-PAP 63 (32-115); diastolic-PAP 24 (11-40); wedge pressure 11 (1-25). Mean mixed venous oxygen saturations were 64% (42-82%). Eleven (23%) patients had pulmonary fibrosis. NYHA grades were: I (1); II (5); III (21); IV (8). Six deaths (16%) were recorded over 34 months mean follow up.



Conclusion: Although PH is rare in SLE, our cohort of patients suffered considerable morbidity with grade III or IV disease in 83%. Mortality rates compared favourably to those reported for Scleroderma.

Disclosure: R. Martin, None; **R. W. Lee**, None; **J. G. Coghlan**, None; **D. P. D'Cruz**, Actelion Pharmaceuticals UK, 2 .

1590

Alveolar Hemorrhage in Systemic Lupus Erythematosus: Demographic, Serologic and Clinical Associations. Aikaterini Thanou-Stavraki, Joanne Tesiram, John B. Harley and Judith A. James, Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Alveolar hemorrhage (AH) is an uncommon but oftentimes deadly severe manifestation of systemic lupus erythematosus (SLE). However, serologic and clinical predictors of SLE patients at increased risk of developing AH are not clear. Limited data from small case series suggest a link between AH and renal disease. This study uses a well-characterized, large, multi-ethnic, cross-sectional SLE cohort (n=2,448) to examine demographic, clinical and serologic associations with AH.

Method: De-identified, electronic records of the SLE database were searched for patients with AH. Each case was matched with 4 SLE affected controls for age, sex, ethnicity and race, as well as compared to the entire remaining collection. Demographic, serologic and clinical characteristics were gathered from among 1,900 datapoints for each AH positive and AH negative SLE patient. Chi-square, McNemar's test and paired t-test were used for data analysis.

Results: Among 2,448 SLE patients screened, 13 cases of well-documented AH were identified (10 females and 3 males). African race was more prevalent in AH patients than controls (23% vs. 8%, p=0.035). Patients with AH were younger at SLE diagnosis compared to controls [mean age at diagnosis 29.9 vs. 33.7 years (mean age difference 3.8 years, 95% CI 0.98-6.67, p=0.009)]. Of the ACR classification criteria for SLE, lupus nephritis as defined by presence of cellular casts was associated with AH (OR 4.75, 95% CI 1.58-19.19, p=0.003); however, no association of AH with proteinuria was found (p=0.4). Even in this small cohort, AH was significantly associated with the presence of

vasculitis at other sites (OR 3.25, 95% CI 1.00-13.68, p=0.05). Although no significant relation with clinically manifest antiphospholipid (aPL) syndrome was shown (p=0.55), aPL antibodies were more common in patients with AH (OR 3.17 with 95% CI 1.22-9.69, p=0.016). On the contrary, anti-Sm was significantly more prevalent in patients without AH in this cohort (OR <0.01 with 95% CI 0.00-0.69, p=0.023). The prevalence of other auto-antibodies, including anti-dsDNA, anti-Ro, anti-La and anti-nRNP, did not differ significantly in patients with and without AH.

Conclusion: Clinical association of AH with vasculitis at other sites, as well as with the presence of cellular casts, suggests a possible common autoimmune pathway that leads to multicentric, microvascular involvement in the lung, glomerulus and other organs. Association of AH with aPL antibodies supports a presumed pathogenic mechanism that leads to AH through formation of miscovascular thrombi, with or without pulmonary capillaritis. Replication and expansion of these findings in additional longitudinal cohorts of SLE patients is warranted, as well as expanded evaluation of potential serologic predictors of this oftentimes severe clinical manifestation.

Disclosure: A. Thanou-Stavraki, None; **J. Tesiram**, None; **J. B. Harley**, None; **J. A. James**, None.

1591

Pleurisy in a Large SLE Cohort. Roshan Dhawale[1] and Michelle A. Petri[2], [1]University of Pittsburgh, Pittsburgh, PA, [2]Johns Hopkins University, Baltimore, MD

Background: Pleurisy is one of the ACR criteria for systemic lupus erythematosus (SLE) and one of the more frequent manifestations of the disease. Little is known however, about the serological status, associated clinical features and damage accrual in patients with pleurisy.

Purpose: To compare demographics, serologies and clinical features in patients with and without pleurisy.

Methods: A well-defined cohort of 1708 SLE patients was followed longitudinally for 20 years. Patients were included if they met 1997 ACR criteria for definite SLE. Clinical features, serologic data and damage accrual (SLICC/ACR) were recorded at the time of entry into the cohort and were updated at subsequent visits. Using SELENA-SLEDAI, pleurisy was diagnosed when any of the following were present: typical pleuritic chest pain; pleural rub; and clinical/radiological evidence of pleural effusion. Analyses were performed using student t-test.

Results: SLE patients with pleurisy were found to have a younger age of onset (27.4 vs 29.6 years) and were more likely to have had fever [(OR) 1.72 (95% CI 1.35, 2.22)], lymphadenopathy [OR 1.48 (1.15, 1.94)], pericarditis [OR 3.66 (2.81, 4.77)], arthralgias [OR 3.66 (2.81, 4.77)] and arthritis [OR 1.97 (1.33, 2.91)]. They were associated with presence of anti-Smith [OR 1.52 (1.11, 2.08)], anti-dsDNA [OR 1.53 (1.18, 1.98)] and aCL [OR1.67 (1.3, 2.15)], which was highly significant. Patients with pleurisy were also more likely to develop pulmonary fibrosis (p<0.0001) and pulmonary hypertension (p=0.0013).

Table 1: Comparison of patients with and without pleurisy

Factor	**Pleurisy (n=305)**	**No Pleurisy (n = 1403)**	**P-value**	**Odds Ratio OR (95% CI)**
Demographics:				
Female Gender	96%	92%	0.0213	1.95 (1.08, 3.51)
Age at onset	27.4 +/- 11.7	29.6 +/- 12.7	0.0056	
Age at diagnosis	30.4 +/- 12.1	33.0 +/- 12.9	0.0015	
Clinical features:				
Fever	51%	38%	<0.0001	1.73 (1.35, 2.22)
Lymphadenopathy	37%	28%	0.0029	1.49 (1.15, 1.94)
Raynauds	60%	49%	0.0006	1.56 (1.21, 2.01)
Vasculitis	21%	14%	0.0052	1.58 (1.15, 2.16)

Arthralgias	98%	92%	0.0002	3.66 (1.69, 7.93)
Arthritis	84%	73%	<0.0001	1.97 (1.41, 2.74)
Myositis	13%	7%	0.0011	1.97 (1.33, 2.91)
Pericarditis	44%	17%	<0.0001	3.66 (2.81, 4.77)
Cardiac Murmur	59%	45%	<0.0001	1.74 (1.36, 2.24)
Serologies :				
Lupus anticoagulant	31%	25%	0.0425	1.33 (1.01, 1.75)
Anticardiolipin Ab	58%	45%	<0.0001	1.67 (1.30, 2.15)
Low C3	62%	53%	0.0023	1.49 (1.15, 1.92)
Low C4	57%	46%	0.0006	1.56 (1.21, 2.00)
Anti-dsDNA	66%	56%	0.0014	1.53 (1.18, 1.98)
Anti-Smith	21%	15%	0.0114	1.52 (1.11, 2.08)
Anti-RNP	33%	24%	0.0016	1.57 (1.19, 2.06)
Damage:				
Pulmonary Fibrosis	14%	6%	<0.0001	2.72 (1.84, 4.04)
Pulmonary Hypertension	12%	7%	0.0013	1.98 (1.33, 2.95)

Conclusion: Pleurisy is a common, but important, manifestation of SLE. Pleurisy is associated with the presence of anti-Smith and anti-dsDNA. These patients are more likely to develop pulmonary fibrosis and pulmonary artery hypertension. Pleurisy can serve as an important predictor of pulmonary damage and these patients should be monitored periodically over time to assess for complications.

Disclosure: R. Dhawale, None; **M. A. Petri**, None.

1592

Medication Use in Systemic Lupus(SLE). S. Bernatsky[1], C. Peschken[2], Murray Urowitz[3], Dafna D. Gladman[3], A. E. Clarke[1], J. Pope[4], P. R. Fortin[3], C. A. Pineau[1], M. Zummer[5], C.D. Smith[5], H. Arbillaga[5], M. Hudson[6] and Canadian Network for Improved Outcomes in Systemic Lupus, [1]MUHC, Montreal, QC, [2]University of Manitoba, Winnipeg, [3]Toronto Western Hospital, Toronto, ON, [4]St Joseph Health Care, London, ON, [5]CaNIOS, [6]McGill University, Montreal, QC

Purpose: To evaluate factors affecting therapeutic approaches used in clinical practice for the management of SLE, in a multi-centre cohort. A priori, factors of potential interest include patient age, race/ethnicity, disease duration, lupus activity, and accumulated damage.

Methods: We combined data from 10 clinical adult SLE cohort registries in Canada. We used multivariate generalized estimating equation methods to model dichotomized outcomes, running separate regressions where the outcome was current exposure of the patient to specific medications. Potential predictors of medication use included demographic (age at baseline, sex, residence, race/ethnicity) and clinical factors (disease-duration, time-dependent damage index scores and adjusted mean SLE Disease Activity Index (2K) scores. The models also adjusted for clustering of subjects by centre.

Results: Higher disease activity and damage scores were each independent predictors of exposure to non-steroid immunosuppressive agents, and for exposure to prednisone. This was not definitely demonstrated for anti-malarial agents. Older age at diagnosis was independently and inversely associated with exposure to any of the agents studied (immunosuppressive agents, prednisone, and anti-malarial agents). An

additional independent predictor of prednisone exposure was black race/ethnicity (adjusted rate ratio, RR 1.46, 95% confidence interval, CI 1.18, 1.81). For immunosuppressive exposure, an additional independent predictor was race/ethnicity, with greater exposure among Asians (RR 1.39, 95% CI 1.02, 1.89) and persons identifying themselves as First Nations/Inuit (2.09, 95% CI 1.43, 3.04), compared to whites. All of these findings were reproduced when adjustment for disease activity was limited to renal involvement.

Conclusion: Ours is the first portrayal of determinants of clinical practice patterns in SLE, and offers interesting real-world insights. Further work, including efforts to elucidate how differing clinical approaches may influence outcome, is ongoing.

Disclosure: S. Bernatsky, None; **C. Peschken**, None; **M. Urowitz**, None; **D. D. Gladman**, None; **A. E. Clarke**, None; **J. Pope**, None; **P. R. Fortin**, President, 6 ; **C. A. Pineau**, None; **M. Zummer**, None; **C. D. Smith**, None; **H. Arbillaga**, None; **M. Hudson**, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis - Human Etiology And Pathogenesis II

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1633

DNA Microarray Analysis Revealed Abnormal Networks of Immune Response Molecules in Bone Marrow Cells From Patients with Rheumatoid Arthritis. Hooi-Ming Lee[1], Hidehiko Sugino[1], Yasuo Adachi[2], Takahiro Ochi[3] and Norihiro Nishimoto[2], [1]Osaka University, Osaka, Japan, [2]Wakayama Medical University, Osaka, Japan, [3]Osaka Police Hospital, Osaka, Japan

Purpose: To investigate the abnormal functional networks of differentially expressed genes in bone marrow (BM) cells compared between rheumatoid arthritis (RA) and osteoarthritis (OA).

Method: Gene expression profiles (GEPs) in BM cells from 9 RA patients and 10 OA patients were obtained by using DNA microarray. Up- and down-regulated genes were identified by comparing between the GEPs of RA and those of OA. Bioinformatics analysis was performed using Expression Analysis Systemic Explorer (EASE) 2.0 based on gene ontology (GO) followed by network pathway analysis with Ingenuity Pathways Analysis (IPA) 7.5.

Results: 764 up-regulated and 1910 down-regulated genes were identified in RA compared to OA. GO term of "Biological Process" in EASE analysis revealed that up-regulated genes were most significantly classified into "Response to Biotic Stimulus" category (61 genes), which included functional category of "Immune Response" (57 genes). Abnormalities in "Cell Organization and Biogenesis", and "Signal Transduction" were also identified; down-regulated genes were dominantly classified into "Cell Proliferation" (139 genes), "Regulation of Cell Cycle" (64 genes), and "DNA Replication and Chromosome Cycle" (52 genes). Most of the genes in these 3 functional categories were overlapped with each other. Relationships among the 61 up-regulated genes in "Response to Biotic Stimulus" and the 139 down-regulated genes in "Cell Proliferation" were further analyzed by using IPA. There were 4 networks represented by the 61 up-regulated genes. The first network that with interferon (IFN) alpha, IFN beta, and MHC class I (family) *etc.* at the center included 5 IFN-inducible molecules, a cluster of human leukocyte antigen (HLA), i.e. HLA-E, HLA-F, HLA-G, and tapasin (TAP) *etc*. This network was relevant to antigen presentation, cell-mediated immune response, and humoral immune response. The remaining 3 networks were also related to cell-mediated immune response. Meanwhile, there were 7 networks constructed by the 139 down-regulated genes. The functions of the top 3 networks were related to cell cycle and DNA replication, recombination, and repair. E2F transcription factors, several cyclins and cyclin-dependent kinase played central roles in these networks. Down-regulation of these molecules was considered due to Methotrexate (MTX) effect as this repression was not significant in the patients without MTX treatment.

Conclusion: Abnormal functional networks of "Immune Response" were identified in BM cells of RA compared to OA. Overexpression of the genes that take part in antigen presentation pathway and IFN signaling was suggested contributed to pathogenesis of RA. Our results also suggested that the main therapeutic effect of MTX is demonstrated by repressing cell cycle and DNA replication genes in BM cells.

Disclosure: H. M. Lee, None; **H. Sugino**, None; **Y. Adachi**, None; **T. Ochi**, None; **N. Nishimoto**, None.

1634

Expansion of Immature Plasmacytoid and Myeloid Dendritic Cells within CD34+ Cells of the Bone Marrow in Rheumatoid Arthritis. Shunsei Hirohata[1], Tetsuya Tomita[2] and Hideki Yoshikawa[2], [1]Kitasato Univ School of Med, Kanagawa, Japan, [2]Osaka University Graduate School of Medicine, Suita Osaka, Japan

Purpose: We previously showed that bone marrow CD34+ cells from rheumatoid arthritis (RA) patients have abnormal capacities to respond to tumor necrosis factor-alpha (TNF-α) and to differentiate into fibroblast-like cells producing MMP-1, resembling type B synoviocyte. In addition, we have recently demonstrated that bone marrow plasmacytoid dendritic cells (pDC) from RA patients as well as those from osteoarthritis (OA) patients have prominent capacities to differentiate into type B synoviocyte-like cells under the influences of TNF-α. Since depletion of BDCA2-positive cells from bome marrow CD34+ cells diminished their capacities to differentiate into type B synoviocyte-like cells, it is possible that CD34+ cells expressing BDCA2 might be expanded in RA bone marrow compared with OA bone marrow. The current studies were therefore undertaken to explore in detail the phenotypic characteristics of bone marrow CD34+ cells from RA patients and OA patients.

Method: Bone marrow samples were obtained from 25 patients with RA (1 male and 24 females: mean age 60.8 years), who satisfied the ACR 1987 revised criteria for RA and gave informed consent, during joint operation via aspiration from the iliac crest. As a control, bone marrow samples were similarly obtained from 22 patients with osteoarthritis (OA) (4 males and 18 females: mean age 70.7 years). The capacity of pDC and mDC purified from bone marrow mononuclear cells by positive selection with magnetic beads to produce MMP-1 upon stimulation with TNF-α was evaluated by ELISA. The expression of BDCA2 (pDC marker), and BDCA3 (mDC marker) by CD34+ cells were examined by 2-color analysis on flow cytometry.

Results: Both bone marrow pDC and mDC from RA patients differentiated into type B synoviocyte-like cells producing MMP-1 upon stimulation with TNF-α as effectively as those from OA patients. There were no significant differences in percentages of CD34+ cells within bone marrow mononuclear cells between RA and OA. However, RA bone marrow mononuclear cells contained higher percentages of BDCA2+ CD34+ cells and BDCA3+ CD34+ cells than OA bone marrow mononuclear cells. Accordingly, percentages of cells expressing BDCA2 or BDCA3 within RA bone marrow CD34+ cells were significantly higher than those within OA bone marrow CD34+ cells. The numbers of BDCA2+ CD34+ cells were significantly correlated with those of BDCA3+ CD34+ cells in RA bone marrow, but not in OA bone marrow.

Conclusion: These results indicate that the enhanced capacity of RA bone marrow CD34+ cells to differentiate into type B synoviocyte-like cells is accounted for the expansion of cells expressing DC markers BDCA2 and BDCA3. Moreover, the data suggest that enhanced differentiation of pDC and mDC from bone marrow CD34+ cells might be involved in the pathogenesis of RA through providing precursors of type B synoviocytes.

Disclosure: S. Hirohata, None; **T. Tomita**, None; **H. Yoshikawa**, None.

1635

Histone Deacetylase Inhibitors SAHA and MS-275 Induced Growth Arrest, Suppressed NF-κB Activation, Down-Regulated the Secretions of Nitric Oxide, IL-6, IL-18, VEGF and MMPs in Rheumatoid Arthritis Synovial Fibroblast-Like Cells. Qiu-Yi Choo[1], Paul C. Ho[1], Yoshiya Tanaka[2] and Hai-Shu Lin[1], [1]National University of Singapore, Singapore, Singapore, [2]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Purpose: Histone deacetylase inhibitors SAHA and MS-275 exhibited potent anti-rheumatic efficacy in rodent models for rheumatoid arthritis (RA). However, their mechanisms of actions remain elusive. This study aimed to investigate their anti-rheumatic mechanisms.

Method: The anti-rheumatic mechanisms of SAHA and MS-275 were studied in E11 cells, a cell line established from rheumatoid arthritis synovial fibroblasts (RASFs).

Results: MS-275 and SAHA inhibited E11 proliferation at low nM levels (IC_{50}s<100 nM). Such anti-proliferative activities were independent of cytotoxicity but associated with cell cycle arrest at G_0/G_1 phase and the induction of cyclin dependent kinase inhibitor p21. MS-275 and SAHA also suppressed LPS-induced NF-kB p65 nuclear translocation. As a probable consequence, the secretions of nitric oxide (NO), IL-6, IL-18, VEGF, MMP-2 and MMP-9 from E11 cells were down-regulated.

Conclusion: Histone deacetylase inhibitors MS-275 and SAHA displayed therapeutic potential for RA. Anti-rheumatic mechanisms include RASFs proliferation blockade, pro-inflammatory cytokine and NO secretion suppression as well as angiogenesis and matrix metalloproteinase production down-regulation. These activities might be mediated through p21 induction and the inactivation of NF-kB.

Table 1. IC_{50} values (nM) of MS-275 and SAHA in E11 cells

Inhibition	MS-275	SAHA
Cell proliferation	65	44
NF-kB activation	<100	<100
NO production	<1	<1
IL-6 secretion	121	5311
IL-18 secretion	<1	<1
VEGF secretion	5	62

Disclosure: Q. Y. Choo, None; **P. C. Ho**, None; **Y. Tanaka**, None; **H. S. Lin**, None.

1636

Expression and Function of Novel Phosphoinositide 3-Kinases (PI3K) Isoform in Fibroblast-Like Synoviocytes. Beatrix Bartok[1], David L. Boyle[1], Christian Rommel[2], Sanna Rosengren[1] and Gary S. Firestein[1], [1]UCSD School of Medicine, La Jolla, CA, [2]Intellikine, La Jolla, CA

Purpose: Class I phosphoinositide 3-kinases (PI3K) regulate diverse cellular functions such as cell survival, proliferation, migration and glucose metabolism. Of the four PI3K isoforms (α, β, γ, δ), α and β are ubiquitously expressed. γ and δ, however, are mainly expressed in leukocytes and therefore could be important targets for inflammatory disease. This hypothesis is supported by the observation that genetic deletion or selective inhibition of PI3K γ or δ decrease inflammation in several pre-clinical models. To explore the biology of these two kinases in rheumatoid arthritis (RA), we assessed their expression, regulation and function in cultured fibroblast-like synoviocytes (FLS).

Method: Quantitative real-time PCR (qPCR) was used to determine relative expression of the PI3K isoforms in cultured FLS after IL-1 (2ng/ml), TNF (50 ng/ml) or LPS (1ng/ml) stimulation. PDGF (1ng/ml) induced Akt phosphorylation was detected using Western blot analysis. To evaluate PI3Kδ–mediated Akt phosphorylation in RA FLS in response to PDGF we used a novel, selective PI3K δ inhibitor INK007 with 30 fold selectivity over γ (IC50= 0.2 nM for δ; 6 nM for γ, and > 5000nM for α and β). FLS proliferation in response to PDGF was measured using the MTT assay on day 0, 2, and 4.

Results: RNA transcripts for PI3K α, β, δ were constitutively expressed in cultured FLS cell. Relative PI3K δ mRNA expression was increased 4-6 fold in response to IL-1, TNF or LPS stimulation, peaked after 24 hr (n= 3, $p< 0.05$) and decreased to baseline by 48 hr. There was no effect of PDGF or TGFβ on PI3K δ expression. PI3K α and β mRNA levels were only marginally increased by the TNF or IL-1 (1-2 fold increase). Western blot analysis showed that PI3K δ protein was also increased by pro-inflammatory cytokines. Of interest, PI3Kγ mRNA was not detected in resting FLS or after exposure to cytokines or LPS. Akt activation, especially after PDGF exposure, is responsible for many PI3K effects on cellular function. Akt phosphorylation in FLS was already detected within 5 min of stimulation with PDGF. To determine if PI3K δ contributes to Akt activation, FLS were preincubation with the selective PI3K δ inhibitor INK007 and then stimulated with PDGF. INK007 decreased P-Akt levels by 70% compared with PDGF alone. To evaluate the functional relevance of PI3K δ-mediated Akt activation, we assessed the effect of PI3K δ inhibition on FLS proliferation in vitro. INK007 decreased FLS proliferation in response to PDGF. The concentration dependent inhibitory effect was evident within 2 days in culture. By day 4, PDGF-stimulated cell growth was decreased 20% by 0.3 μM and 50% by 3 μM (n=2 separate experiments).

Conclusion: This is the first demonstration that PI3K δ is expressed and inducible in fibroblasts. Because it regulates Akt phosphorylation and cell growth, PI3K δ could contribute to synoviocyte hyperplasia in RA. In contrast, the γ isoform was not expressed in FLS. Selective inhibition of this PI3K δ could be useful in RA by suppressing synoviocyte function.

Disclosure: B. Bartok, None; **D. L. Boyle**, Intellikine, 2 ; **C. Rommel**, Intellikine, 3 ; **S. Rosengren**, None; **G. S. Firestein**, Intellikine, 9, Intellikine, 2 .

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SPACIA1, A Novel Gene Involved in Proliferation of Synoviocytes in Arthritis. Tomoo Sato[1], Ryoji Fujii[1], Koji Konomi[2], Naoko Yagishita[1], Hiroyuki Aono[2], Yoshihisa Yamano[1], Moroe Beppu[1], Kusuki Nishioka[3] and Toshihiro Nakajima[4], [1]St. Marianna University School of Medicine, Kanagawa, Japan, [2]Santen Pharmaceutical Co. Ltd., Nara, Japan, [3]St Marianna University, Kawasaki Kanagawa, [4]Choju Medical Institute, Fukushimura Hospital, Misato Marine Hospital, St. Marianna University, Kanagawa

Purpose: Synovial proliferation is an important aspect of Rheumatoid arthritis (RA), however its mechanism is still unclear and no effective target for synovial proliferation has been isolated. Here we show a novel gene involved in proliferation of synoviocytes in arthritis

Methods: To find the molecules related synovial proliferation, we perform transcriptome analysis using model mice of collagen-induced arthritis (CIA). The effects of candidate molecules on proliferation of synovial fibroblasts were confirmed by using siRNA. In regard to one of the candidate molecules, synoviocytes-proliferation associated in CIA 1 (SPACIA1), we analyzed expression in RA and osteoarthritis synoviocytes with or without synovitis. The effects of SPACIA1 overexpression on CIA were assessed by using its transgenic mice.

Results: We identified a novel gene involved in the proliferation of synoviocytes in arthritis from the candidate molecules and named SPACIA1. SPACIA1 knock down by its siRNA reduced proliferation in RA synovial fibroblasts. SPACIA1 was up-regulated in multilayered synovial lining cells in RA and OA. SPACIA1 transgenic mice showed fast onset and exacerbated of collagen-induced arthritis, compared with wild type mice.

Conclusion: SPACIA1 could be associate synovial proliferation and might be related synovitis. Overexpression of SPACIA1 led to exacerbation of collagen-induced arthritis. These findings indicate the importance of SPACIA1 in synovial proliferation in RA. SPACIA1 might be a potential therapeutic target for synovial proliferation in RA.

Disclosure: T. Sato, None; **R. Fujii**, None; **K. Konomi**, Santen Pharmaceutical Co. Ltd., 3 ; **N. Yagishita**, None; **H. Aono**, Santen Pharmaceutical Co. Ltd., 3 ; **Y. Yamano**, None; **M. Beppu**, None; **K. Nishioka**, None; **T. Nakajima**, None.

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Secretory Phospholipase A_2 Group IIA Binds to Integrin αvβ3 and Induces Proinflammatory Signaling. Jun Saegusa[1], Masaaki Fujita[1], Shino Tanaka[1], Akio Morinobu[1], Seiji Kawano[1], Yoshikazu Takada[2] and Shunichi Kumagai[1], [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]University of California, Davis, Sacramento, CA

Purpose: Secretory phospholipase A_2 group IIA (sPLA$_2$-IIA) was first isolated and purified from synovial fluid from patients with rheumatoid arthritis (RA). Increased levels of sPLA$_2$-IIA are detected in the serum and synovial fluid of patients with RA. In addition to being an acute phase reactant, sPLA$_2$-IIA is considered to play an important role in the pathogenesis of inflammatory diseases by activating immune cells. It has been demonstrated that intraarticular administration of sPLA$_2$-IIA in the rabbit led to the development of arthritis. Notably some biological effects associated with sPLA$_2$-IIA are independent of its catalytic function. Therefore It has been proposed that sPLA$_2$-IIA action is mediated through interaction with specific receptors. However sPLA$_2$-IIA receptors in human have not been established. Integrins are a family of cell adhesion receptors that recognize extra cellular matrix ligands and cell surface ligands. Integrins transduce signals to the cell upon ligand binding. In this study, we investigated whether sPLA$_2$-IIA binds to integrins and transduces proinflammatory signals.

Method: The binding of sPLA$_2$-IIA to integrins was studied by ELISA-type binding assays, adhesion assays, flow cytometry and surface plasmon resonance. Amino acid residues in sPLA$_2$-IIA that are critical for integrin binding were investigated by docking simulation and mutagenesis. Several mutations were introduced within the predicted interface of sPLA$_2$-IIA with integrin, and integrin-binding defective sPLA$_2$-IIA mutants were generated. Catalytically inactive mutant of sPLA$_2$-IIA were also generated by mutating His-47 to Gln (H47Q) as a control.

Results: sPLA$_2$-IIA specifically bound to integrin αvβ3 at a high affinity ($K_D = 2\times10^{-7}$ M). We identified amino acid residues in sPLA$_2$-IIA (Arg-74 and Arg-100) that are critical for integrin binding. The R74E and R100E mutations in sPLA$_2$-IIA significantly reduced the binding to integrin αvβ3, while the H47Q mutation did not. Interestingly, wild-type and the catalytically inactive H47Q mutant of sPLA$_2$-IIA induced

cell proliferation and MAPK activation in monocytic cells in a dose-dependent manner, but the integrin binding-defective mutants did not. This indicates that integrin binding is required, but catalytic activity is not required, for $sPLA_2$-IIA-induced proliferative signaling.

Conclusion: Integrin αvβ3 may serve as a receptor for $sPLA_2$-IIA and mediate pro-inflammatory action of $sPLA_2$-IIA in a manner independent of its catalytic activity. Integrin-$sPLA_2$-IIA interaction may be a novel therapeutic target for RA and other inflammatory disorders.

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Expression of Synoviolin in the Synovium of Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Osteoarthritis in Relationship to the Response to TNF Blockade. Ruth Klaasen, Desiree Pots, Carla A. Wijbrandts, Danielle M. Gerlag and Paul P. Tak, Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: The E3 ubiquitin ligase synoviolin functions as an anti-apoptotic factor and its expression is associated with the development of arthritis in mice (1). It has been suggested that increased levels of synoviolin in peripheral blood are related to non-response to infliximab treatment in patients with rheumatoid arthritis (RA) (2). We investigated the expression of synoviolin in the synovium of patients with active RA compared to psoriatic arthritis (PsA) and osteoarthritis (OA), and its relationship to response to tumor necrosis factor (TNF) blockade in RA and PsA.

Methods: Synovial tissue samples were obtained from 54 active RA and 21 active PsA patients on stable methotrexate therapy before start of TNF blockade (infliximab and adalimumab, respectively); 11 inflammatory OA patients served as disease controls. In 5 of these RA patients serial synovial tissue samples were obtained 28 days after start of anti-TNF treatment. Synoviolin expression was detected by immunohistochemistry and evaluated by digital image analysis. Double immunofluorescence was performed to detect co-expression of synoviolin with CD3, CD55 and CD68. Clinical response was defined as a decrease in DAS28 $\geq$ 1.2 after 16 weeks of therapy.

Results: Expression of synoviolin was higher in RA patients compared to PsA (median and interquartile range, IQR), respectively 89187 (23066-170625) integrated optical density (IOD)/mm^2 and 37740 (7325-101802) IOD/mm^2 (P = 0.039). The expression in the OA group tended to be lower compared to both groups (median 27809, IQR 3956-267125 IOD/mm^2 (N.S.). In the intimal lining layer synoviolin was expressed by both CD68+ intimal macrophages (50-60%) and CD55+ fibroblast-like synoviocytes (40-50%). In the synovial sublining synoviolin was mainly expressed by CD68+ macrophages (80%), but also by CD3+ T cells (<10%). Clinical response to anti-TNF therapy was observed in 29/54 (54%) RA and in 14/21 (67%) PsA patients. Of interest, there was not relationship between synoviolin expression at baseline and the clinical response to TNF blockade in either group. Twenty-eight days after infliximab therapy there was persistent synoviolin overexpression in 4 of the 5 patients.

Conclusion: Synoviolin is overexpressed in the synovium of RA patients, and is expressed by macrophages, fibroblast-like synoviocytes and T cells. Synoviolin expression at baseline is not related to the clinical response to anti-TNF therapy. Persistent synoviolin expression after anti-TNF therapy may contribute to autonomous disease progression and could represent an additional therapeutic target.

References:
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Toh ml et al Arth Rheum 2006 Jul;54(7):2109-18

Disclosure: R. Klaasen, None; **D. Pots**, None; **C. A. Wijbrandts**, None; **D. M. Gerlag**, None; **P. P. Tak**, None.

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Effect of FTY720 On Bone Remodeling in Rheumatoid Arthritis. Chieri Kanda[1], Tsuyoshi Iwasaki[2], Sachi Tsunemi[1], Sachie Kitano[1], Harunori Takeshita[2] and Hajime Sano[1], [1]Hyogo College of Medicine, Nishinomiya, Japan, [2]Hyogo University of Health Sciences, Kobe, Japan

Purpose: Bone remodeling is controlled by bone formation by osteoblasts and bone resorption by osteoclasts. The pathogenesis of bone destructive disorders such as rheumatoid arthritis (RA) and osteoporosis is caused by an uncoupling of bone remodeling. Sphingosine 1-phosphate (S1P) is one of the cell-derived lysophospholipid growth factors that signal diverse cellular functions such as proliferation, angiogenesis, and inflammation. We previously demonstrated that S1P signaling induced proliferation and prostaglandin productions by synovial cells from RA patients (Arthritis Rheum 54;2006). The present study we investigated the role of S1P signaling for bone remodeling using murine myoid cell line which differentiate into osteoblasts, human $CD4^+$ T cells, and B cells.

Method: Bone morphogenetic protein (BMP)-induced osteoblastogenesis was examined using murine myoid cell line C2C12. Osteoblast generations were examined by the expression of alkaline phosphatase (ALP) in the cells and productions of osteocalucin by the cells. RANKL expressions on C2C12 cells and human B cells were examined by RT-PCR analysis.

Results: Both S1P and S1P antagonist, FTY720, enhanced BMP-induced expression of ALP in C2C12 cells and osteocalucin production by these cells. These enhancing effects were stronger in the FTY720 treatment than in the S1P treatment. RANKL expressions on C2C12 cells were increased by the S1P treatment but were not increased by the FTY720 treatment. RANKL expressions on human B cells were also increased by either the S1P or the FTY720 treatment. These augmenting effects were stronger in the S1P treatment than in the FTY720 treatment.

Conclusion: These results indicate that although S1P signaling induces osteogenesis by the enhancement of BMP-induced osteoblast generation, it may also have an adverse effect on bone remodeling by the enhancement of RANKL expression on osteoblasts and B cells in synivial tissues. In contrast to S1P, FTY720 may enhance osteogenesis without affecting RANKL expressions on osteoblasts and B cells in synovial tissues. FTY720 may therefore be able to control bone remodeling in RA.

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The Role of Sphingosine 1-Phosphate/S1P1 Signaling in the Osteoclastogenesis of Rheumatoid Arthritis. Masayasu Kitano[1], Harunori Takeshita[2], Sachi Tsunemi[1], Chieri Kanda[1], Masahiro Sekiguchi[1], Naoto Azuma[1], Tsuyoshi Iwasaki[2] and Hajime Sano[1], [1]Hyogo College of Medicine, Nishinomiya, Japan, [2]Hyogo University of Health Sciences, Kobe, Japan

Purpose: Sphingosine 1-phosphate (S1P) via the S1P receptor signaling elicits diverse cellular responses such as cell proliferation, differentiation and migration. Furthermore S1P is involved in various pathologic conditions and has been implicated as an important mediator of angiogenesis, inflammation and osteoclastogenesis. We previously reported S1P/S1P receptor 1 ($S1P_1$) signaling played an important role of synoviocyte proliferation and cyclooxygenase-2-induced prostaglandin E_2 production by RA synoviocytes (A&R 2006;54:742-53). In the pathogenesis of RA, receptor activator of nuclear factor-κB ligand (RANKL) plays an essential role in the osteoclastogenesis. Recently, it is reported that S1P regulates the osteoclast differentiation and osteoclast-osteoblast coupling. In the present study we have investigated the role of S1P/S1P1 signaling in RANKL expression of RA synoviocytes and human $CD4^+$ T cells.

Method: To investigate the expression of $S1P_1$ and RANKL mRNA and protein in human RA synoviocyte cell line (MH7A cells) and human $CD4^+$ T cells, we performed the reverse transcriptase-polymerase chain reaction (RT-PCR) and western blot analysis for $S1P_1$ and RANKL mRNA and protein expression, respectively. Next, we determined the effects of S1P for RANKL mRNA expression in MH7A cells and $CD4^+$ T cells. These cells were incubated with various concentrations (0-0.1μM) of S1P. After 6 to 24 hours incubation, RANKL mRNA in these cells was examined by RT-PCR. Moreover, MH7A cells were incubated with S1P alone or in combination with 100ng/ml of TNFα. After 24 hours incubation, RANKL mRNA in MH7A cells was similarly examined by RT-PCR. Finally, we examined whether these effects of S1P were sensitive or insensitive for pertussis toxin (PTX), the specific G_i/G_o inhibitor.

Results: $S1P_1$ mRNA and protein were detected in MH7A cells and $CD4^+$ T cells as well as RANKL mRNA and protein. S1P induced RANKL expression of MH7A cells and human CD4+ T cells in a dose dependent manner, and enhanced TNFα-induced RANKL expression in MH7A cells. In addition, these effects of S1P were inhibited by pretreatment of PTX.

Conclusion: These results indicate that $S1P/S1P_1$ signaling may play an important role of osteoclastogenesis via the RANKL expression of synoviocytes and $CD4^+$ T cells. $S1P/S1P_1$ signaling of RA synoviocytes is closely connected with synovial hyperplasia, inflammation, angiogenesis and osteoclastogenesis. Thus, the regulation of $S1P/S1P_1$ signaling may become a novel therapeutic target in RA.

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The Selective Adhesion of α5β1^{high} Memory T Cells by βig-h3 in Rheumatoid Arthritis. Young Mo Kang, Jin Hee Kang, Kheum Hee Sa, Hyun Jung Cho, Eun Joo Song, Eon Jeong Nam and In San Kim, Kyungpook National University School of Medicine, Daegu, South Korea

Purpose: During the early stage of transendothelial migration, T cells come in contact with extracellular matrix proteins, including βig-h3 which is over-expressed within the rheumatoid synovium. βig-h3 has been shown to mediate the adhesion of α5β1^{high} T cells that are expressing activation markers. The aim of this study was to investigate whether βig-h3 is involved in the selective recruitment of subsets of T cells into the rheumatoid synovium.

Method: T cells were isolated using negative selection kit with MACS, following separation of mononuclear cells with Ficoll gradient centrifugation from peripheral blood (PB) and synovial fluid (SF) of rheumatoid arthritis (RA) and controls. Cell surface markers were evaluated using flow cytometry. T cell subsets were isolated with antibodies against CD4, CD45RO, and α5 integrin using FACS Aria^{TM}. Adhesion of T cell subsets was investigated on microtitre plate coated with wild-type βig-h3 and inhibition assay was performed by the preincubation of T cells with function blocking antibodies against integrins.

Results: T cells isolated from SF of RA were expressing higher level while most of those from PB of controls were expressing lower level of α5β1 integrin. Enhanced adhesion of SF T cells on the coated βig-h3 compared with normal or RA PB T cells was efficiently inhibited by the function blocking antibody against α5β1 integrin. RGD peptide, which binds to αvβ5 integrin, did not block βig-h3-mediated adhesion of T cells, while dhfas-1, a fragment of the 4th fas-1 domain of βig-h3, blocked the adhesion in a dose-dependent manner. The proportion of CD45RO^{+} cells among T cells was increased in the PB of RA compared to PB of controls, and was highest in the SF of RA. Most of the CD45RO^{+} T cells were α5β1^{high} population, while almost all the CD45RO^{-} T cells were α5β1^{low} population. βig-h3-mediated adhesion were higher in the CD4^{+}CD45RO^{+}α5^{high} T cells compared with CD4^{+}CD45RO^{+}α5^{low} and CD4^{+}CD45RO^{-}α5^{low} T cells (0.40 ± 0.03 vs 0.19 ± 0.03 and 0.22 ± 0.02, $p<0.01$). Among CD8^{+} T cells, CD45RO^{-}α5^{high} subpopulation, which was not observed in the CD4^{+} T cells of normal PB, consisted of CD28^{Null} cells.

Conclusion: The present data indicate that βig-h3 may play a critical role in the regulation of inflammation by the selective recruitment of memory T cells into the synovial tissues of RA through the interaction with α5β1 integrin.

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Serum Amyloid A Protein Stimulates Th17-Related Cytokines Production in Rheumatoid Synoviocytes. Tomohiro Koga[1], Kiyoshi Migita[2], Satoshi Yamasaki[1], Mami Tamai[1], Shin-ya Kawashiri[1], Naoki Iwamoto[1], Hideki Nakamura[1], Tomoki Origuchi[1], Hiroaki Ida[1], Atsushi Kawakami[1] and Katsumi Eguchi[1], [1]Nagasaki University, Nagasaki, Japan, [2]NHO National Nagasaki Medical Center, Nagasaki, Japan

Purpose: Rheumatoid arthritis (RA) is characterized by a systemic inflammatory response that exhibits elevated levels of pro-inflammatory cytokines and acute-phase reactants, such as serum amyloid A protein (SAA). High levels of SAA and its receptor formyl peptide receptor-like 1 (FPRL1) have been demonstrated in the rheumatoid synovium and a relationship between SAA and rheumatoid inflammation has been suggested. Th17 cells are a defined subset of proinflammatory T cells that contribute to the rheumatoid synovitis. Although the in vitro requirements for human Th17 development are well established, it is less clear their requirements in rheumatoid synovium. To study the contribution of acute phase reactants to the induction of Th17 cells in rheumatoid synovium, we investigated the effects of SAA on Th17-related cytokine production.

Method: Synoviocytes isolated from rheumatoid arthritis (RA) patients were stimulated with recombinant SAA. The cellular supernatants were analysed by a RayBio Human Cytokine Antibody Array V (Ray Biotech, Inc. Norcross, GA) and IL-6, CCL20-specific ELISA. IL-1b, IL-6, IL-23p19, IL-12p40, CCL-20 mRNA expression was analysed by real-time polymerase chain reaction (PCR). Assays for chemotaxis of peripheral blood mononuclear cells were performed using 5 μm pore polycarbonate filters in a transwell chamber (Costar, Cambridge, MA) with SAA-stimulated or control RA synoviocyte-conditioned media.

Results: SAA is a most potent inducer of IL-6, CCL20, IL-23p19 production in RA synoviocytes compared to other inflammatory cytokines (IL-1, TNF-a, IL-17A). SAA stimulation induced IL-1b, IL-6, IL-23p19, IL-12p40, CCL-20 mRNA expression in RA synoviocytes, which was not affected by polymyxin B pretreatment. SAA-induced CCL20 production was down-regulated by NF- kB inhibition and partially by JNK inhibition. SAA-induced IL-6, CCL20 production was also suppressed by dexamethasone or FK506.

Conclusion: These findings suggest that SAA may promote the generation and recruitment of CCR6-expressing Th17 cells, in RA synovium by up-regulating Th17-related cytokine production by synoviocytes.

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Fas-Associated Death Domain Protein Expression Regulation by Secretion in Rheumatoid Arthritis. Lea Tourneur[1], Sylvie Mistou[2] and Gilles Chiocchia[3], [1]Inserm U567, Paris, France, [2]INSERM; CNRS; Paris Descartes University, Paris, France, [3]Institut Cochin, INSERM U567, Paris, France

Fas-Associated Death Domain Protein Expression Regulation by Secretion in Rheumatoid Arthritis

Background: Although Fas-associated death domain (FADD) is the key adaptor transmitting the apoptotic signal mediated by death receptors, it is also implicated in numerous non apoptotic functions. In particular, FADD can regulate inflammatory processes. In rheumatoid arthritis (RA), FADD can act as an anti-inflammatory molecule by inhibiting the NF-kB inflammatory signal mediated by IL-1β and TLR4 ligands, which are expressed in the joint of patients. Thus, an absence of FADD expression in synoviocytes could contribute to TLR4- and IL-1R1-mediated chronic inflammation. FADD protein can localize both in the cytoplasm and nucleus of most cells. Recently, we demonstrated the existence of a new localization of FADD in microvesicles and a new regulatory mechanism of the protein by secretion. Moreover, we identified adenosine receptors (AR) as regulators of this FADD secretion process.

Purpose: Since we have demonstrated the existence of an AR-dependent FADD protein expression regulation by secretion, and since adenosine is present at high concentration in the synovial fluid (SF) from RA patients, we tested whether FADD protein could be released in the SF from RA patients, as compared to osteoarthritis (OA, non inflammatory disease) suffering patients.

Methods: FADD protein expression in SF (50 µl) from two independent cohort of patients was assessed by sandwich-ELISA. Results are expressed in arbitrary units. Statistical analyses were performed by using the Student's t test. P-values of <0.05 were considered to indicate statistical significance.

Results: We found that FADD protein was detected at high level in the SF from 65% of RA patients (17/26), whereas it was detected significantly in the SF from only 17% of OA patients (6/36). In two independent cohorts of patients, mean secreted FADD in SF from RA and OA patients was 0.098 +/- 0.025 vs 0.014 +/- 0.005 (P=0.002) and 0.252 +/- 0.052 vs 0.022 +/- 0.012 (P=0.001), respectively.

Moreover, we are presently looking for secreted FADD in more than 800 sera of untreated recently diagnosed arthritis suffering patients including 545 RA affected patients (ESPOIR consortium cohort), using FADD-specific quantitative ELISA.

Conclusion: This is the first demonstration that human FADD protein could be secreted specifically during the course of an inflammatory disease, and it suggests that secreted FADD could be a new inflammatory marker. Moreover, these results confirmed that absence of FADD in joints through a release of the protein in SF could contribute to the development of RA.

Disclosure: L. Tourneur, None; **S. Mistou**, None; **G. Chiocchia**, None.

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Expression of Human TIM-3 and Its Correlation with Disease Activity in Rheumatoid Arthritis. Jaejoon Lee[1], Ji-Min Oh[1], Joong Kyong Ahn[1], Eun-Kyung Bae[1], Ji Young Chai[2], Chan-Hong Jeon[3], Jinseok Kim Kim[4], Eun-Mi Koh[1] and Hoon-Suk Cha[1], [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Jesang Hospital, Seongnam, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea, [4]Cheju National University College of Medicine, Cheju, South Korea

Purpose: T cell immunoglobulin-and mucin-domain-containing molecules (TIMs) are a novel family of transmembrane proteins that are involved in the regulation of Th1- and Th-2 cell-mediated immunity. TIM-3 is preferentially expressed on terminally differentiated Th1 cells and negatively regulates Th1 responses. Recently, Galectin-9, a ligand to TIM-3, has been shown to induce apoptosis of TIM-3 expressing cells in vitro and in vivo. The role of TIM-3 and its interaction with Galectin-9 in Rheumatoid Arthritis (RA), an autoimmune disease traditionally thought of as Th-1 mediated process, has not been fully understood. Thus, this study was undertaken to investigate the expression of TIM-3 in synovial tissue and peripheral blood mononuclear cells (PBMCs) in RA patients using quantitative real-time PCR and its correlation with RA disease activity measured by DAS28. We also investigated Galectin-9 mRNA expression in PBMCs and its correlation with FoxP3 mRNA level.

Method: Synovial tissues were available from 5 RA and 5 OA patients for immunohistochemistry and real time PCR. Blood samples were collected from 39 RA patients and 31 healthy controls. DAS28 was obtained at the time of venipuncture.

Results: TIM-3 mRNA expression was significantly higher in the synovial tissue in RA patients compared to those in OA patients (p=0.03). Immunohistochemistry showed that TIM-3 was expressed in the synovial sublining area in RA patients. No significant difference in TIM-3 mRNA level was found between PBMCs from RA patients and those from healthy controls. However, we observed a negative correlation between TIM-3 mRNA expression in PBMCs with DAS28 (r_s= -0.379, P=0.039). Furthermore, Galectin-9 mRNA was overexpressed in PBMCs in RA patients compared to the healthy controls (p=0.01), and was significantly higher in RA patients with low disease activity (DAS28 <3.2) compared to those with moderate to high disease activity (DAS28 ≥3.2, p=0.034). We also found that Galectin-9 mRNA expression in PBMCs in RA patients was positively correlated with FoxP3 mRNA expression (r_s=0.544, P=0.0004). The plasma level of interferon-gamma was significantly correlated with DAS28 (r_s=0.472, P=0.015) in RA patients, whereas no such correlation was observed between plasma interleukin-17 level and DAS28.

Conclusion: Our data suggest that TIM-3 and its interaction with Galectin-9 are closely associated with RA disease activity and may represent a potential therapeutic target in RA. In addition to the negative regulatory effect of Galectin-9 on Th-1 cells mediated through TIM-3, Gal-9 may exert its suppressive effect on RA disease activity by upregulating FoxP3, thereby inducing regulatory T-cells.

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Inhibition of Bid Cleavage by High Akt Activity Protects Rheumatoid Synovial Fibroblasts From Fas-Induced Apoptosis. Carmen Conde, Samuel Garcia and Juan J. Gomez-Reino, Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain

Purpose: Synovial hyperplasia is a main feature of RA pathology that leads to cartilage and bone damage in the inflammed joints. There are several pieces of evidence suggesting that impaired apoptosis of resident synoviocytes is pivotal in this process. Apoptosis resistance involves defects in the extrinsic and intrinsic apoptotic pathways. Therefore, we aimed to investigate the connection between the two pathways and the role of PI3Kinase/Akt in the resistance to Fas-mediated apoptosis of FLS from rheumatoid athritis (RA) patients.

Method: FLS from RA patients were treated with two PI3 Kinase inhibitors, Wortmannine (Wort) and LY294002 (LY) before anti-Fas stimulation. Apoptosis was determined by two methods, quantification of nucleosomal release by ELISA and Hoechst staining. Bid expression was suppressed in RA FLS by small interfering RNA (siRNA) transfection. It was overexpressed by transfection with the pDsRed2-Bid vector. Western blot was used to determine phosphorilated Akt, caspase-9 and Bid expression.

Results: Apoptosis of RA FLS induced by anti-Fas stimulation was highly increased after treatment with PI3 Kinase inhibitors (p=0.008). Surprisingly, this change was accompanied by an increase in Bid cleavage. To check if the two findings are related, we suppressed Bid expression with siRNA. Absence of Bid made RA FLS completely resistant to Fas-induced apoptosis even in presence of Akt inhibition. On the contrary, Bid overexpression leads to significantly higher apoptosis (p=0.008). To further confirm that the mitochondrial pathway is involved in Fas-induced apoptosis in RA FLS, we pretreated with the caspase-9 inhibitor, LEHD before Fas stimulation. This treatment almost completely blocked apoptosis induced even in cells overexpressing Bid and treated with Wort.

Conclusion: These results show that the high typical phosphorilation of Akt protects RA FLS against apoptosis induced by Fas through inhibition of Bid cleavage, which is the bridge between the extrinsic and intrinsic apoptotic pathways. Therefore, PI3Kinase is a potential RA therapeutic target.

Disclosure: C. Conde, None; **S. Garcia**, None; **J. J. Gomez-Reino**, None.

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Altered Expression of MiR-155 and MiR-181a in Periphery Blood Mononuclear Cells of Rheumatoid Arthritis. Li Long[1], Jinxia Shi[1], Ru Li[1] and Zhanguo Li[2], [1]Bejing Univ People's Hosp, Beijing, China, [2]Peking University People's Hospital, Beijing, China

Purpose: 1. To Screen for the miRNAs differently expressed in Periphery Blood Mononuclear Cells (PBMCs) of RA by microarray experiments. 2. To further evaluate the expression of miR-155 and miR-181a in PBMCs of RA. 3. To determine the relevance between the expression of miR-155/miR181a and clinical as well as laboratory features. 4. To test whether inflammatory mediators can induce miR-155 and miR-181a in PBMCs of RA.

Method: 1. Total RNA was isolated from peripheral blood mononuclear cells obtained from 5 patients of RA and 5 normal controls. Expression profiling of miRNAs was performed in a microarray analysis. 2. MiR-155 and miR-181a were identified for further study by stem-loop real-time RT-PCR based on SYBR-Green. PBMC from 26 patients of RA and 23 normal controls were collected. 3. Associations between miR-155/miR-181a and the clinical and laboratory features of RA were evaluated. 4. Induction of miR-155 following stimulation with TNF-α , IFN-γand LPS of cultures of RA PBMCs was examined by real-time RT-PCR.

Results: 1. Expression profiling of miRNAs revealed significant differential expression of 46 miRNAs. MiR-155 was up-regulated in PBMC of RA than in normal controls, and miR-181a was down-regulated in RA group. 2. The expression level of miR-155 had a positive correlation with serum CRP level. 3. Expression of miR-155 was markedly up-regulated in PBMCs of RA after stimulation with TNF-α, IFN-γ and LPS, especially with TNF-α. 4. Similar up-regulated expression of miR-155 upon stimuli was observed in healthy controls, however, RA PBMCs exhibit much higher expression of miR-155 in response to stimuli.

Conclusion: MiRNA-155 may be a positive regulator in RA pathogenesis, while miRNA-181a may be a negative one. The expression of miR-155 is induced by stimulation with TNF-α , IFN-γ and LPS. Further studies are required to elucidate the function of miR-155 and miR-181a.

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Human Six-Transmembrane Epithelial Antigen of Prostate 4 Is Induced by TNFα and Regulates IL-6 Secretion in Rheumatoid Synovium. Yoko Tanaka-Watanabe, Isao Matsumoto, Asuka Inoue, Reiko Minami, Taichi Hayashi, Daisuke Goto, Satoshi Ito and Takayuki Sumida, University of Tsukuba, Tsukuba, Japan

Purpose: Human six-transmembrane epitherial antigen of prostate 4 (STEAP4) is one of STEAP family as a homolog of mouse tumor necrosis factor-α-induced adipose-related protein (TIARP). The TIARP gene expression was remarkably increased in murine spleen and joints of glucose-6-phosphate isomerase (GPI)-induced arthritis in the effector phase, suggesting pivotal association to arthritis. TIARP mRNA and protein expression was known to be upregulated by TNFα in a dose-dependent manner by using adipocyte cell line, however a role of STEAP4 in rheumatoid arthritis (RA) is still unclear. We examined the expression of STEAP4 in PBMCs and joints from RA patients, and explored the relationship between STEAP4 and TNFα /IL-6.

Method: Complementary DNA was prepared from PBMC (20 RA, 16 healthy controls (HC)) and joint synovium (39 RA, 18 osteoarthritis (OA)).

1) The expression of STEAP4 gene was quantified by real time PCR.

2) The localization of STEAP4, EEA1 (known to be a lysosome marker) or CD68 was examined by fluorescence immunohistochemistry (IF).

3) Fibroblast like synoviocytes (FLS) obtained from RA synovium were treated with TNFα (2ng/ml), and the fluctuation of STEAP4 was evaluated by real time PCR, Western blot analysis or IF.

4) STEAP4 mRNA from primary synovial cell lines obtained from RA was knockdown by specific siRNA, and then cultured for 24 h. IL-6 mRNA was quantified by real time PCR.

5) STEAP4-GFP was transfected to FLS, then cultured for 24 h with TNFα. IL-6 secretion was detected by ELISA.

Results: 1) The expression of STEAP4 gene in RA synovium was not significantly different from OA (3.11±3.37 vs 4.16±3.61). The STEAP4 expression in PBMC from RA was not different from that in HC (0.57±0.54 vs 1.49±2.14). 2) STEAP4 was co-localized with CD68 in the FLS obtained from RA patients. STEAP4, EEA1 and CD68 were clearly co-localized in cytoplasm (lysosome) of the synovium. 3) In vitro analysis, the expressions of STEAP4 gene and protein in FLS were up regulated by TNFα-stimulation confirmed by real time PCR ($p<0.05$) and by Western blot analysis. 4) The expression of IL-6 mRNA was up regulated by STEAP4 siRNA ($p<0.05$). 5) The amount of IL-6 secretion was down regulated by over expression of STEAP4 ($p<0.05$).

Conclusion: STEAP4 expression was observed in human joints, clearly up regulated by TNFα stimulation, and controlled IL-6 secretion in FLS. Therefore, STEAP4 might play a potential role in the pathogenesis of TNFα- induced arthritis.

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Adiponectin Affects Gene Expression of Rheumatoid Arthritis Effector Cells Including Synovial Fibroblasts, Lymphocytes, Endothelial Cells and Chondrocytes. Klaus W. Frommer[1], Birgit Zimmermann[1], Dirk Schröder[1], Andreas Schäffler[2], Christa Büchler[2], Fabia Brentano[3], Steffen Gay[4], Ulf Müller-Ladner[5] and Elena Neumann[6], [1]Justus-Liebig-University of Giessen and Kerckhoff-Clinic, Bad Nauheim, Germany, [2]University Hospital Regensburg, Regensburg, Germany, [3]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [4]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [5]Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany, [6]Justus-Liebig-University of Giessen and Kerckhoff-Clinic, 61231 Bad Nauheim, Germany

Purpose: Rheumatoid arthritis (RA) is associated with increased production of adipokines. Elevated levels of these cytokine-like mediators are found both in synovial tissue and synovial fluid of RA patients. RA effector cells may be affected by these adipokines. We therefore investigated the effect of the adipokine adiponectin on human synovial fibroblasts (SF), lymphocytes, endothelial cells and chondrocytes. We focused on the expression of proinflammatory and matrix-degrading mediators induced by adiponectin. We also analyzed the signaling pathways of adiponectin in RASF.

Method: Human RASF, lymphocytes, endothelial cells and chondrocytes were stimulated in vitro with adiponectin. Affymetrix microarrays and protein arrays were used to screen for changes in gene expression. Real-time PCR and immunoassays were used to quantify mRNA and protein levels, respectively. Signaling analysis was performed using intracellular chemical inhibitors.

Results: Adiponectin stimulation of RASF induced the expression and secretion of chemokines (protein: e.g. ENA-78, 22.5-fold), proinflammatory cytokines (mRNA: e.g. IL-11, 24.3-fold), other inflammatory molecules (mRNA: e.g. PGE synthase, 3.4-fold), growth factors (mRNA: e.g. fibroblast growth factor 10, 5.0 fold), genes involved in bone metabolism (mRNA: e.g. stanniocalcin-1, 19.8-fold) and matrix remodeling proteins (mRNA: e.g. MMP3 62.5 fold; protein: e.g. pro-MMP1 15.4-fold). Increased chemokine and cytokine secretion (e.g. IL-8, IL-6) was a common response to adiponectin stimulation found in all cell types studied, while chondrocytes additionally secreted increased levels of MMPs. Adiponectin-induced secretion of IL-6, MCP-1 and MMP10 by RASF was decreased using inhibitors against p38 MAPK and PKC but not by inhibitors against PKA and NFkB.

Conclusion: Adiponectin promotes the progression of RA primarily by inducing the secretion of proinflammatory molecules, chemokines and matrix-degrading enzymes in cell types involved in RA pathophysiology. While proinflammatory molecules such as IL-6 and PGES promote inflammation directly, chemokines attract and activate inflammatory cells further increasing inflammation. Additionally, elevated levels of MMPs lead to degradation of extracellular matrix and cartilage. According to our results, adiponectin-induced signaling in RASF is not only mediated by p38 MAPK but also by PKC, whereas PKA and NFkB appear not to be involved. Our data further elucidate the complex molecular mechanisms of RA.

Disclosure: K. W. Frommer, None; **B. Zimmermann**, None; **D. Schröder**, None; **A. Schäffler**, None; **C. Büchler**, None; **F. Brentano**, None; **S. Gay**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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The Noxa/Mcl-1 Axis in Rheumatoid Arthritis Synovial Fibroblasts. Arthur M. Mandelin II and Richard M. Pope, Northwestern University Feinberg School of Medicine, Chicago, IL

Purpose: Apoptosis is critical for the resolution of inflammation, but despite an environment which should favor it, little apoptosis is seen in rheumatoid arthritis (RA) joint tissues. This implicates a failure of apoptosis in RA. The Noxa/Mcl-1 axis is a cell fate decision pathway involved in the mitochondrial control of apoptosis. We previously showed that anti-apoptotic Mcl-1 is more abundant in RA synovial fibroblasts (SF) and macrophages, and that forced reduction of Mcl-1 promotes their apoptosis. However, the contribution of Mcl-1's inhibitory partner Noxa has not been studied. Since SF are crucial in RA pathology, we sought to characterize the Noxa/Mcl-1 axis in SF in order to determine its suitability as a therapeutic target.

Method: Synovial tissue was taken from RA and osteoarthritis (OA) patients at joint replacement, or from undiseased autopsy specimens, and SF were isolated and cultured. Cell lysates were analyzed for Noxa and Mcl-1 by Western blotting. Since the investigational drug obatoclax is considered a Noxa mimetic, we sought to determine whether it alters cell viability in SF by exposing cultured SF to media containing obatoclax or diluent and then examining mitochondrial integrity by the colorimetric MTT metabolism assay.

Results: Western blot data reveal the ratio of Noxa to Mcl-1 in normal SF and OA SF is in approximate balance at 0.91±0.09 (SEM) and 0.86±0.20, respectively. In contrast, Noxa is relatively less abundant than Mcl-1 in RA SF at a ratio of 0.64±0.08 ($p=0.020$ vs. normal, $n=8$). MTT assay data (see table) show a dose-response effect of obatoclax on the viability of all types of SF, and further suggest that RA SF are more sensitive to the drug than normal SF ($p < 0.02$ at 1.25 μM drug). Attempts to amplify the effect in RA SF by co-administration of the kinase inhibitors roscovitine or stauroporine, which reduce Mcl-1 levels, did not result in a significant synergistic effect (data not shown). Obatoclax had no effect on human *in-vitro* differentiated macrophages (not shown), arguing against nonspecific toxicity.

Cell Viability (%)

	Obatoclax concentration (μM)						
SF type	0	0.25	0.5	1	1.25	2.5	5
Normal	100±3.0	81.4±7.9	73.2±8.6	70.8±10.3	69.4±4.8*	66.2±2.7*	60.1±3.6*
OA	100±2.0	74.0±6.5*	67.0±5.5*	66.3±4.8*	58.2±2.4*	59.4±5.3	53.0±4.6
RA	100±3.4	66.7±9.8	60.6±9.2	54.2±9.1*	52.6±4.0*	44.6±6.7*	44.2±6.7*
Macroph.	100±3.2	110.0±1.3	107.0±2.1	111.4±1.1	96.3±3.1	94.1±4.5	93.6±3.1

* for each cell type indicates $p \leq 0.03$ vs. no drug

Conclusion: Our data suggest that the Noxa:Mcl-1 ratio is decreased in RA compared to osteoarthritis (OA) and non-diseased SF. Based on these data, we conclude that a relative lack of Noxa permits the sustained action of Mcl-1 in RA SF, and is responsible for their pathologic resistance to apoptosis. We further conclude that obatoclax is an effective pro-apoptotic agent in SF, and that differential sensitivity to this agent between RA and normal SF indicates that it merits further study in the context of this disease.

Disclosure: A. M. Mandelin, None; **R. M. Pope**, None.

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Atorvastatin and Simvastatin Inhibit Osteoclastogenesis by Decreasing the Expression of Receptor Activator of Nuclear Factor κ B Ligand (RANKL) in Rheumatoid Arthritis Fibroblast-Like Synoviocyte. Jeong Yeon Kim, Eun Young Lee, Eun Bong Lee, Yun Jong Lee, Yoo Jin Hong, Ji Ah Park, Hyun Jung Yoo and Yeong Wook Song, Seoul National University College of Medicine, Seoul, South Korea

Purpose: To determine the effects and their mechanism of simvastatin and atorvastatin on the expression of osteoprotegerin (OPG) and receptor activator of nuclear factor κ B ligand (RANKL) in RA fibroblast-like synoviocyte (FLS) and whether they inhibit osteoclastogenesis.

Methods: FLS was isolated from 3 RA patients and cultured in the presence of 20 ng/ml of TNF-α with or without atorvastatin or simvastatin for 24 hours. RANKL expression was assayed by Western blotting and reverse transcription-polymerase chain reaction (RT-PCR). OPG expression was measured by enzyme-linked immunosorbent assay and RT-PCR. Mevalonate was added to reverse the effect of atorvastatin and simvastatin on RA FLS. Phosphorylation of mitogen-activated protein kinases (MAPKs) [p38, Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERKs)] and Akt was detected by Western blotting. Peripheral blood mononuclear cells (PBMC) and RA FLS were cocultured in the presence of macrophage colony stimulating factor, 1,25-dihydroxyvitamin D_3, and various concentrations of atorvastatin. Osteoclast formation was assayed by counting cells after staining for tartrate-resistant acid phosphatase.

Results: Both atorvastain and simvastatin inhibited the expression of RANKL in RA FLS in a dose dependent manner, and the suppression of RANKL was reversed by mevalonate. Atorvastatin and simvastatin did not affect the OPG expression in RA FLS. Atorvastatin suppressed TNF-α induced p38 phosphorylation in RA FLS and also significantly decreased TRAP-positive multinucleated osteoclast formation in the coculture of PBMC and RA FLS.

Conclusion: Both atorvastatin and simvastatin suppressed RANKL expression in RA FLS. Atorvastatin inhibited osteoclast formation in the coculture of PBMC and RA FLS. These results suggest that atorvastatin and simvastatin may inhibit osteoclastogenesis and bone destruction in RA patients.

Disclosure: J. Y. Kim, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. J. Lee**, None; **Y. J. Hong**, None; **J. A. Park**, None; **H. J. Yoo**, None; **Y. W. Song**, None.

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ENO1 Enhances TNF-α, IL-1α/β, IFN-γand PGE2 Production in PBMC and Synovial Fluid Cells From Rheumatoid Arthritis Patients. Jae Seung Kang[1], Seyeon Bae[1], Jinhyun Kim[2], Churl Hyun Im[2], Ji Ah Park[2], Eun Bong Lee[2], Eun Young Lee[2], Wang Jae Lee[1] and Yeong Wook Song[2], [1]Seoul National University College of Medicine, Seoul, South Korea, [2]Seoul National Universitiy College of Medicine, Seoul, South Korea

Purpose: a-Enolase1 (ENO1) is 60-70 kDa of protein expressed ubiquitously. Recently, we found that the production of prostaglandin E_2 (PGE_2) from Burkitt's lymphoma cell line and activated PBMC is increased upon ENO1 stimulation via the activation of nuclear factor kappa B (NF-kB). Therefore, we investigate the roles of ENO1 on the regulation of inflammation and chronic inflammatory disease, rheumatoid arthritis (RA).

Methods: Human peripheral blood mononuclear cells were purified from healthy donors, RA and osteoarthritis (OA) patients and synovial fluids mononuclear cells in knee joint were purified from of RA patients by Ficoll-density gradient. The expression of ENO1 on PBMC and synovial fluids mononuclear cells were analyzed by flow cytometry. The production of inflammatory cytokines and PGE_2 by ENO1 stimulation were measured by ELISA. ChIP assay and immunoblotting were performed to examine signaling mediators for inflammatory cytokines and PGE_2 by ENO1 stimulation.

Results: ENO1 is highly expressed on PBMC and synovial fluids mononuclear cells from RA patients, but not from OA patients. TNF-a, IL-1a/b, IFN-g and PGE_2 production were markedly increased from concanavalin A (Con A)-activated PBMCs by ligation of ENO1. In addition, We also observed that those of inflammatory mediators are increased from PBMCs and synovial fluid mononuclear cells of RA patients upon ENO1 stimulation. The increased production of TNF-a and IL-1b were completely suppressed by pre-treatment of inhibitors for p38 MAPK (SB203580) and NF-kB (Bay11-7082) before ENO1 stimulation. The phosphorylation of p38 MAPK were increased in Con A-activated PBMC and PBMC and synovial fluids mononuclear cells from RA patients in a time dependent manner after ENO1 stimulation. In addition, the binding of NF-kB after ENO1 stimulation on promoter of TNF-a and IL-1b was also confirmed by ChIP assay.

Conclusion: Our results strongly suggest that ENO1 plays a critical role on the disease progression of RA via the induction of disease-related pro-inflammatory cytokines and PGE_2 production. Therefore, ENO1 can be used for effective therapeutic target of RA.

Disclosure: J. S. Kang, None; **S. Bae**, None; **J. Kim**, None; **C. H. Im**, None; **J. A. Park**, None; **E. B. Lee**, None; **E. Y. Lee**, None; **W. J. Lee**, None; **Y. W. Song**, None.

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Notch Plays a Critical Role in Synovial Angiogenesis in Response to Hypoxia. Wei Gao, Aisling Kennedy, Chin Teck Ng, Catherine Sweeney, Douglas J. Veale and Ursula Fearon, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Purpose: Angiogenesis is a critical step in the progression of inflammatory arthritis, supporting cell recruitment and aberrant synovial proliferation. This process depends on endothelial cell (EC) survival mechanisms to preserve synovial blood vessels integrity. The Notch signaling pathway is critical for EC survival, however the upstream mechanisms involved in inducing these pathways in the inflamed joint remains to be elucidated.

Aim: To examine the expression and regulation of the Notch signaling pathways in the inflamed joint.

Method: Synovial whole tissue explants and primary synovial fibroblasts (RASFC) were established from synovial biopsies obtained at arthroscopy, along with microvascular endothelial cell cultures (HDEC). Hypoxia was measured *in vivo* in the synovial membrane using a LICOX probe. Notch 1IC, 3IC, 4IC an HIF-1a expression and distribution in synovial tissue, primary synovial fibroblasts and HDECs was assessed by immunohistology/immunofluorescence and/or western blot. The expression of Notch signaling components in response to growth factors VEGF and Angiopoietin-2 and potential upstream triggers of inflammation and hypoxia were assessed in RA synovial explants cultures and HDEC. siRNA or DAPT (a specific inhibitor of Notch) was utilized to directly block Notch expression.

Results: Notch 1IC, 3IC and 4IC and their downstream signaling components Hrt1, 2 and 3 and Hes were localized to perivascular and lining layer regions. We demonstrated strong expression of Notch 1IC, 3IC and 4IC by Western blot in RA and PsA synovial tissue lysates with minimal expression in OA. VEGF and Ang2 alone regulated Notch1-IC, 3IC and 4IC in RA synovial explants cultures and HDEC, however the combination of VEGF and Ang2 only had a synergistic effect on Notch 1IC expression compared to either alone. VEGF induced Notch 1IC was completely blocked in the presence of siRNA or DAPT, demonstrating a direct effect, which was reflected at a functional level by inhibition of MMP-2 and 9 expression and HDEC tube formation. We demonstrated profound hypoxia in synovial tissue (median [range] 3.2% [0.48-7%]). To mimic these conditions *in vitro* we exposed HDEC and RASFC to normoxic and hypoxic conditions of 3% (reflecting *in vivo* joint measurements) and demonstrated increased HIF-1a and Notch1-IC expression in response to 3% hypoxia.

Conclusion: These data demonstrate expression of Notch signaling pathways in the RA synovial joint. Notch 1IC is synergistically induced in response to VEGF +/- Ang2, which play a critical role in promoting angiogenesis and EC survival a process that maybe initiated upstream by hypoxia.

Disclosure: W. Gao, None; **A. Kennedy**, None; **C. T. Ng**, None; **C. Sweeney**, None; **D. J. Veale**, Wyeth Pharmaceuticals, 2, GlaxoSmithKline, 2, Schering-Plough, 5, Wyeth Pharmaceuticals, 8 ; **U. Fearon**, None.

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IL-17 Induces Production of Human Cartilage Glycoprotein-39 in Human Fibroblast Like Synoviocytes From Rheumatoid Arthritis Patients. Alison Gizinski, Judith Endres, Steven K. Lundy and David A. Fox, Univ of Michigan, Ann Arbor, MI

Purpose: We have previously shown that RA fibroblast-like synoviocytes (FLS) can function as antigen presenting cells (APC) and can present peptides derived from the human cartilage glycoprotein of 39 kD molecular mass (HC gp-39), a protein found within joint tissues, to activated T cells *in vitro*. Moreover, RA FLS can extract and present HC gp-39 from synovial fluid. It is also known that HC gp-39, a candidate autoantigen in RA, can be produced by FLS. These studies were undertaken to determine the influence of pro-inflammatory cytokines on the production of HC gp-39 in RA FLS, to further define the potential role of FLS in contributing to autoreactive immune responses in inflamed synovial tissues.

Methods: FLS were obtained by collagenase digestion of human

synovial tissue obtained at arthroplasty or synovectomy from RA and OA patients, and were used at passage >4 from primary cultures. Cells were maintained in CMRL medium supplemented with 20% fetal calf serum, 2 m*M* glutamine, 50 units/ml penicillin and 50 mg/ml

streptomycin. FLS were cultured in 6 well plates at 200,000/well and were allowed to adhere for 48 hrs prior to addition of cytokines. Supernatants were collected 120 hrs after exposure to cytokines for ELISA. mRNA was isolated 16 hrs after exposure to cytokines. ELISA for HC gp-39 protein was performed using a YKL-40 ELISA Kit (Quidel, San Diego, CA) according to manufacturer's protocol. Quantitative real time polymerase chain reaction (qRT-PCR) was used to provide quantitative measurements of gene transcription of HC gp-39 in human FLS that had been exposed to varying concentrations of IL-17, TNF-a and IFNg in cell culture.

Results: Exposure of FLS from RA patients to increasing concentrations of IL-17 resulted in significantly higher concentrations of HC gp-39 protein in cell supernatants as measured by ELISA compared to controls. Exposure to increasing concentrations of TNF-a and IFNg resulted in significantly decreased amounts of HC gp-39 protein that could be detected in the supernatants of FLS from RA patients compared to controls. Exposure to varying concentrations of IL-15, IL-1b and IL-6 had no discernable effect on HC gp-39 protein concentration in cell supernatants. After exposure to IL-17 at varying concentrations for 16 hrs, no change in mRNA for HC gp-39 was measured by qRT- PCR compared to controls. Likewise, after exposure to TNF-a for 16 hours, no change in mRNA for HC gp-39 was measured by qRT-PCR compared to controls. However, when human FLS from RA patients were exposed to increasing concentrations of IL-17 and TNF-a simultaneously for 16 hrs, there was a significant four fold increase in mRNA for HC gp-39 compared to GAPDH and appropriate controls.

Conclusion: RA and OA FLS can not only function as APCs for the human autoantigen HC gp-39, but also express high levels of this protein. The effects of pro-inflammatory cytokines on expression of HC gp39 mRNA and secretion of HC gp39 protein are distinct, and our results indicate a primary role for IL-17 in upregulation of this arthritogenic autoantigen. These findings suggest the possibility of a positive feedback loop within the RA joint, involving T cell activation by an autoantigen that is in turn upregulated by the T cell cytokine IL-17.

Disclosure: A. Gizinski, None; **J. Endres**, None; **S. K. Lundy**, None; **D. A. Fox**, Genentech and Biogen IDEC Inc., 2 .

ACR/ARHP Poster Session C

Rheumatoid Arthritis Clinical Aspects: Treatment Response - Biologics

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Safety Profiles of Disease-Modifying Anti-Rheumatic Drugs and Biologics in Patients with Rheumatoid Arthritis: Observations From the RADIUS Registry. Allan Gibofsky[1], W. Palmer[2], Edward C. Keystone[3], Michael H. Schiff[4], JingYuen Feng[5], Scott Baumgartner[5] and Joseph A. Markenson[6], [1]Hospital for Special Surgery, New York, NY, [2]Westroads Medical group, Omaha, NE, [3]Professor of Medicine/University of Toronto, Toronto, ON, [4]University of Colorado, Greenwood Village, CO, [5]Amgen Inc., Thousand Oaks, CA, [6]Hosp for Special Surgery, New York, NY

Purpose: To assess the safety profiles of traditional DMARDs and biologic agents in patients (pts) with RA being treated at rheumatology clinics in North America.

Methods: Rheumatoid Arthritis DMARD Intervention and Utilization Study (RADIUS) comprises 2 prospective, 5-year, multicenter observational registries of over 10000 pts with RA. RADIUS registries were designed to gain a better understanding of the safety of different treatment patterns prescribed by rheumatologists. Pts with RA who required a new DMARD or biologic (either addition or switch) were eligible for enrollment. In RADIUS 1 (R1), pts initiated any new DMARD at entry; in RADIUS 2 (R2), pts initiated etanercept (ETN) at entry. Pts in both registries could switch to any other approved RA therapy at the discretion of their rheumatologist. Safety events analyzed include serious adverse events (SAEs); serious infectious episodes (SIEs) and other infections; and events of medical interest. Exposure-adjusted event rates represent the number of events per 100 pt-yrs of exposure. Safety events were coded using MedDRA terminology.

Results: Safety data from R1 (4968 pts enrolled) and R2 (5103 pts enrolled) reported in these analyses were collected through December 2008. Of pts who had received ETN at entry, 71% of pts in R1 and 63% in R2 were still receiving ETN at month 12. Exposure-adjusted incidence rates of SAEs and events of interest are shown (Table). All 95% confidence intervals for relative risk (RR) compared to methotrexate crossed 1 (P = not significant). The most common SAE recorded in both registries was pneumonia. Of all enrolled pts, 181 pts

in R1 and 131 pts in R2 have died, for adjusted rates of 1.23 and 0.84 events/100 pt-yrs and standardized mortality ratios (observed vs expected deaths) of 0.89 and 0.83, respectively.

Conclusion: In this large group of pts with extended follow-up, no unexpected safety signals and no trends of concern have been noted. Across multiple therapies, the rates for SAEs, SIEs, and events of interest in this pt population are comparable to the rates observed with methotrexate treatment. Results from this registry and others are important in validating data reported in pharmaceutical long-term extension safety studies and thereby provide information for use in rheumatology practice.

Exposure-Adjusted Event Rates for Adverse Events (Full Analysis Set)

	All Treatments[a]		ETN		ETN + MTX		ETN + Other	
	R1	R2	R1	R2	R1	R2	R1	R2
No. Pts	4343	4819	248	2819	581	2782	294	1189
Exposure[b]	12763	13667	347	3273	1691	6248	469	1667
SAE								
No. events	2057	2151	41	441	128	751	59	231
Rate[c]	16.2	15.8	11.8	13.5	11.7	14.3	12.9	13.9
RR	-	-	0.98	0.78	0.93	0.82	0.95	0.77
SIE								
No. events	528	615	8	126	38	219	19	65
Rate[c]	4.1	4.5	2.3	3.9	3.5	4.2	4.1	3.9
RR	-	-	0.95	0.98	1.54	0.97	1.65	0.92
Malignancy								
No. events	106	147	4	37	4	42	3	18
Rate[c]	0.8	1.1	1.2	1.1	0.4	0.8	0.7	1.1
RR	-	-	1.02	0.78	0.32	0.49	0.58	0.67
CV Event								
No. events	157	117	5	25	7	38	6	14
Rate[c]	1.2	0.9	1.4	0.8	0.6	0.7	1.3	0.9
RR	-	-	1.41	0.57	0.59	0.55	1.28	0.64

[a]All therapies, including biologics; [b]Exposure = Pt-yrs; [c]Rate = (no. events/exposure)x100; CV, cardiovascular; ETN, etanercept; RR, Relative risk of event compared to MTX alone

Disclosure: A. Gibofsky, Abbott Laboratories, 1, Abbott Laboratories, 8, Pfizer Inc, 1, Pfizer Inc, 8, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 8, Amgen/Wyeth, 8, Amgen, 1, Roche Pharmaceuticals, 5, Abbott Laboratories, 5 ; **W. Palmer**, Amgen Inc., 2, Amgen Inc., 5, Amgen Inc., 8, Wyeth Pharmaceuticals, 5, Wyeth Pharmaceuticals, 8, Abbott Laboratories, 2, Abbott Laboratories, 8, Genentech/Roche, 2, Genentech/Roche, 5, Genentech/Roche, 8, Rigel Pharma, 2, Pfizer Inc, 2, Pfizer Inc, 8, Takeda , 8, UCB, 8 ; **E. C. Keystone**, Amgen, 8, Amgen, 5, Amgen, 2 ; **M. H. Schiff**, None; **J. Feng**, Amgen Inc., 3, Amgen Inc., 1 ; **S. Baumgartner**, Amgen, 3 ; **J. A. Markenson**, Abbott Laboratories, 8, Bristol-Myers Squibb, 8, Amgen Inc., 8, Wyeth Pharmaceuticals, 8, NiCox, S.A., 5, Wyeth Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5, Amgen, 2, Abbott Laboratories, 2 .

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Do Men and Women with Rheumatoid Arthritis Respond Differently to Treatment? Damini Jawaheer[1], JingYuan Feng[2], James Louie[1] and Harold Paulus[1], [1]UCLA, Los Angeles, CA, [2]Amgen Inc., Thousand Oaks, CA

Purpose: To examine gender differences in treatment responses in rheumatoid arthritis (RA) patients.

Method: We examined gender differences in RA in two unique, real-world prospective observational cohorts, each with patients from approximately 350 rheumatology practices across the US, as part of the RA DMARD Intervention and Utilization Study (RADIUS). Patients requiring a new disease-modifying anti-rheumatic drug (DMARD) were enrolled in RADIUS 1 (n=4359), and patients initiating etanercept (ETN) were enrolled in RADIUS 2 (n=4623). We investigated gender differences a) in disease manifestations, and b) in proportions of patients who achieved a modified ACR20 (mACR20) [1] response 6 months after start of treatment, using Chi-square tests for categorical variables, and the Wilcoxon-Mann-Whitney test and t-test for continuous variables.

Results: Overall, a higher proportion of women had been treated with DMARDs than men prior to study entry (RADIUS 1: 74.8% vs. 68.7%, p=0.0001; RADIUS 2: 92.4% vs. 90.6%, p=0.059). At study entry, all patients had active disease, as assessed by the Clinical Disease Activity Index (CDAI) (mean±SD:35.6±16.7 RADIUS 1; 36.2±15.9 RADIUS 2). Men had significantly later mean age at onset than women and shorter disease duration, whereas women had worse function (HAQ), increased arthritis-related pain (pain visual analog scale, VAS), and higher physician global scores (table 1). Interestingly, no consistent gender differences were observed in seropositivity for rheumatoid factor, tender and swollen joint counts and disease activity (CDAI). Among patients with moderate/severe RA (CDAI>10), there was a non-significant trend for higher proportions of men achieving a mACR20 response at 6 months follow-up, for all treatment regimens (table 1). Similar results were observed when we restricted our analyses to patients with early RA (< 1 year duration).

Conclusion: These results demonstrate that, in RA, significant differences in disease manifestations relating to function and pain are observed between men and women. It is uncertain whether the observed trend toward differences in treatment response between men and women, at 6 months, is influenced by gender, disease state, or both.

[1] Goldman et al. (2006). Ann Rheum Dis 65: 1649-52

Table 1

Disease features at baseline			
RADIUS 1	**Male (n=1032)**	**Female (n=3327)**	**p-value**
Mean age at onset (yrs)	51.2	47.6	<0.0001
RA duration (yrs)	6.5	7.5	0.0001
Health Assessment Questionnaire (HAQ) score	1.08	1.36	<0.0001
Pain VAS	5.52	5.98	<0.0001
Physician global score	5.74	5.88	0.0434
RADIUS 2	**Male (n=1066)**	**Female (n=3557)**	**p-value**
Mean age at onset (yrs)	46.6	43.1	<0.0001
RA duration (yrs)	7.4	9.1	<0.0001
HAQ score	1.11	1.42	<0.0001
Pain VAS	5.81	6.21	<0.0001

Physician global score	5.88	6.04	0.0122
Treatment regimens	**Patients with moderate/severe RA who reached a modified ACR20 response at 6 months**		
	Male	**Female**	**p-value**
RADIUS 1			
MTX	76/171 (44.4%)	190/488 (38.9%)	0.2063
MTX + Infliximab (IFN)	55/135 (40.7%)	163/454 (35.9%)	0.3068
MTX + other non-biologic DMARD	57/155 (36.8%)	195/554 (35.2%)	0.7171
RADIUS 2			
Etanercept (ETN)	89/187 (47.6%)	232/538 (43.1%)	0.2890
ETN + MTX	167/364 (45.9%)	567/1284 (44.2%)	0.5600
ETN + other non-biologic DMARD	58/123 (47.2%)	185/425 (43.5%)	0.4760

Disclosure: D. Jawaheer, None; **J. Feng**, Amgen Inc., 1, Amgen Inc., 3 ; **J. Louie**, Abbott, Amgen, Genentech, Gilead, UCB, 5, Amgen, 8, Genentech , 1 ; **H. Paulus**, Amgen, 5 .

1595

Rheumatoid Arthritis: Insights, Strategies and Expectations—Global Results of the RAISE Patient Needs Survey. Iain B. McInnes[1], B. Combe[2] and Gerd R. Burmester[3], [1]University of Glasgow, Glasgow, United Kingdom, [2]Immuno-Rheumatology, Montpellier, France, [3]Charite University Hospital, Berlin, Germany

Purpose: Understanding the perceptions of patients who live with rheumatoid arthritis (RA) and their views on its treatment can provide a valuable perspective to the rheumatologist and may help to shape our management strategies. The RAISE survey was designed to reveal the perceptions of RA patients on their disease and therapy.

Method: A questionnaire was developed with input from 53 rheumatologists from 8 European countries and Canada. Questions included, but were not limited to, the following topics: diagnosis, disease information sources, daily living with RA, quality of life (QoL) and views on current therapy and treatment options. Surveyed patients were either on biologic therapy or biologic naïve but eligible for biologic treatment based on broad criteria of a DAS28 >3.2 or an acute phase response, plus erosive disease and moderate-to-severe active RA.

Results: A total of 586 patients, approximately 30 biologic naïve and 35 on anti-TNF therapy from each of 9 countries, were interviewed. Mean age at onset of RA symptoms was 41 years. Patients reported that most physician-patient communication centered on symptoms and treatment; less frequently discussed was the impact of RA on QoL. While all patients reported improvement on their current versus previous treatment, biologic users had significantly more ‘good’ days per month than biologic-naïve patients (71% vs 61%, respectively). The survey revealed a large percentage of patients (22%) reporting high levels of pain. For most patients, biologic therapy improved their symptoms and overall QoL compared with their previous non-biologic therapy. Biologic-experienced patients were significantly more satisfied with their treatment than biologic-naïve patients. Patients (41%) use the internet as a resource for information about RA. Approximately 20% of biologic users require help (emotional and/or physical) in preparing and/or administering subcutaneous injections and have concerns around injection site pain or irritation. Despite being eligible for biologic therapy by a broad definition of criteria, 62% of biologic-naïve patients were not aware of biologic therapies and the majority (88%) were never recommended a biologic treatment. Factors influencing

willingness to try a new medication included symptom control, stopping disease progression and improving the overall experience of living with RA. Patients were most interested in a product that worked consistently (76%), was simple to use (69%) and had a less frequent dosing schedule (75%).

Conclusion: This large patient survey provides key insights into how RA patients live with their disease and how therapy has impacted them. The data reveal that biologic therapy has had significant impact on improving patients' lives. However, all patients reported some level of continuing symptoms and current pain indicating unmet clinical need.

Disclosure: I. B. McInnes, Schering-Plough, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 2, Abbott Laboratories, 5, Abbott Laboratories, 2 ; **B. Combe**, Schering-Plough, 5, Wyeth Pharmaceuticals, 5, Wyeth Pharmaceuticals, 8 ; **G. R. Burmester**, Abbott Laboratories, 2, Abbott Laboratories, 5, Schering-Plough, 2, Schering-Plough, 5, Essex Pharma, 2, Essex Pharma, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Wyeth Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5 .

1596

The Comparative Effectiveness of Biologic Therapies Versus Traditional DMARDs for Fatigue in Rheumatoid Arthritis - A Systematic Review of Clinical Trials. Richard CJ Campbell, Gabrielle H. Kingsley and D. L. Scott, King's College London, London, United Kingdom

Purpose: The OMERACT initiative have considered the appropriateness of fatigue as an outcome measure in RA and recently concluded was that, where relevant, fatigue should be measured in RA clinical trials. Recent studies, largely investigating effectiveness of newer biologic therapies, have been including fatigue as an outcome. Here, the comparative effectiveness of biological therapies versus traditional DMARDs is compared across clinical trials.

Method: Original clinical trials limited to English language were retrieved using MEDLINE, EMBASE and The Cochrane Library through the OVID gateway and analysis of retrieved bibliographies. The 'population' was RA patients. The 'intervention' was anti-rheumatic drugs exploded to include therapies used in routine clinical practise. These were combined with terms fatigue, tiredness and lassitude. Other search terms included were FACIT-F and SF-36.

A quality checklist was employed to check studies against 6 specific quality criteria. Studies were ranked according to this checklist and size of study.

All identified studies were analysed for therapeutic approaches, type of fatigue data collected, length of intervention and mean change in fatigue. Data were presented narratively and also graphically, where possible, for each fatigue scale. Mean differences for FACIT-F, SF36 and Fatigue VAS weighted for number of study participants were calculated for the RCTs only (extension studies were excluded from this analysis).

Results: 16 clinical trials were identified (9 RCTs, 3 extension studies and 3 observational studies). All RCTs were considered to be of high quality. Of 6 quality criteria, 7 studies fulfilled all and 2 fulfilled all but one criterion. 6 different types of outcomes for fatigue were used altogether. FACIT-F was the most common. Intervention periods ranged from 8 weeks to 52 weeks (3 years for the longest extension study).

All 9 RCTs compared fatigue between biologic therapies and standard DMARD therapies. All of the 12 primary trials except one found that mean fatigue reduced most in the biological treatment arm. Mean differences in mean change in fatigue (weighted for number of study participants) between biological and control arms for FACIT F was 3.41, SF36 was 4.14 and fatigue VAS 15.8mm (all in favour of biological treatment arms).

Conclusion: This study suggests that biological therapies reduce RA fatigue more than traditional DMARDs in clinical trials. The one study that does not is cross sectional in design, where treatment followed clinical practise rather than pre- determined protocol. Many of the studies are for relatively short intervention periods (although the few extension studies suggest maintenance of this superiority). Some studies compared newly introduced biologic treatments against established DMARD regimes which, when presenting results regarding change, may be misleading since they do not account for rate of change between these newly introduced and established regimes.

Disclosure: R. C. Campbell, None; **G. H. Kingsley**, None; **D. L. Scott**, None.

1597

Physician Preference Motivates Use of Anti-TNF Therapy Independent of Clinical Disease Activity. Jeffrey R. Curtis[1], Lang Chen[1], Leslie R. Harrold[2], Pongthorn Narongroeknawin[1], George Reed[3] and Daniel H. Solomon[4], [1]UAB, Birmingham, AL, [2]UMass Medical Schl, Worcester, MA, [3]University of Massachusetts Medical School, Worcester, MA, [4]Brigham & Womens Hospital, Boston, MA

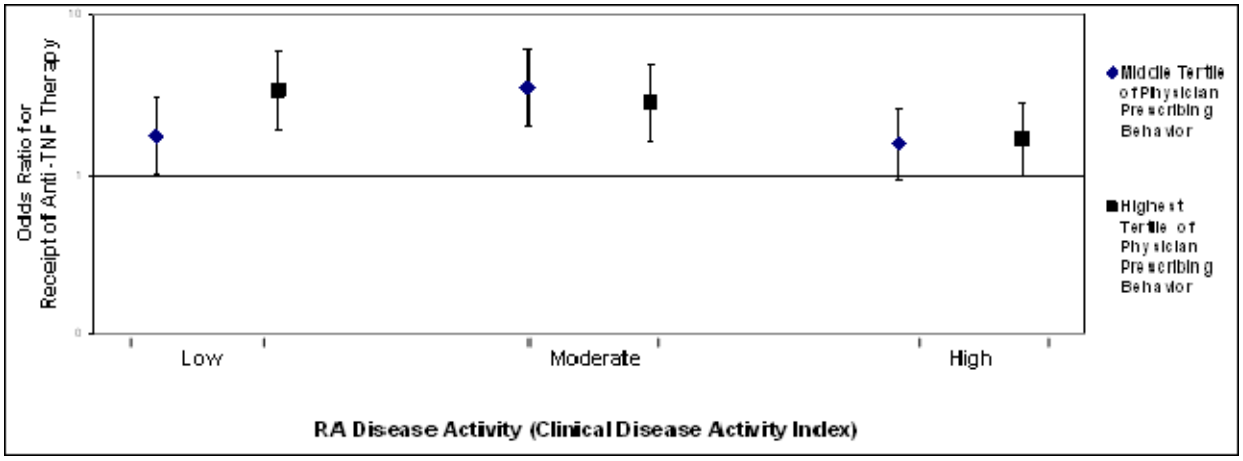
Purpose: Physician preference has been previously shown to be an important determinant of prescription patterns, independent of patient-specific factors. We evaluated whether physician preference was important in the decision to select anti-TNF therapy rather than non-biologic disease modifying anti-rheumatic drugs (DMARDS) among rheumatoid arthritis (RA) patients initiating a new RA medication.

Method: Using data from the Consortium of Rheumatology Researchers of North America (CORRONA), we identified biologic-naïve RA patients initiating either anti-TNF therapy or a DMARD in 2001-2008. Physician preference for use of anti-TNF agents was calculated using data from the preceding calendar year for each physician's other RA patients. Multivariable logistic regression with generalized estimated equations accounted for clustering of patients within physician practice and evaluated the relationship between physician preference and receipt of anti-TNF therapy, controlling for patient-related factors and disease activity using the Clinical Disease Activity Index (CDAI).

Results: We identified 1,532 RA patients initiating anti-TNF therapy or a DMARD. In models adjusting for tender and swollen joint counts and global disease activity, physician preference for use of anti-TNF therapy was an independent predictor of receipt of these agents. Patients of physicians in the highest and middle tertiles of physician preference had a 2.76 (95% CI 2.02 – 3.77) and 1.79 (1.33 – 2.40) greater likelihood to receive anti-TNF medications, respectively. As shown in the Figure, physician preference for use of anti-TNF therapy had a somewhat greater influence on prescribing decisions for RA patients with low or moderate disease activity (CDAI) than for patients with high disease activity.

Conclusion: Physician preference is an important determinant of patients' receipt of anti-TNF therapy and may be useful to examine in future studies of RA treatment patterns, costs, and medication safety.

Figure: Adjusted Relationship Between Physician Preference For Use of Anti-TNF Therapy (calculated using data from his/her other RA patients) and the Initiation of Anti-TNF Therapy (vs. non-biologic DMARDs) for the next RA patient, by Disease Activity*



Note: the lowest tertile of physician preference for Anti-TNF therapy is referent and corresponds to an Odds Ratio of 1.0

* RA disease activity quantified using the Clinical Disease Activity Index (CDAI) and categorized as low (CDAI <= 10), moderate (CDAI > 10 to <= 22), or high (> 22)

Disclosure: J. R. Curtis, Novartis, 2, Amgen, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8 ; **L. Chen**, None; **L. R. Harrold**, None; **P. Narongroeknawin**, None; **G. Reed**, None; **D. H. Solomon**, None.

1598

Physician's Perception of (in)Acceptable Disease Activity in Rheumatoid Arthritis: Some Clues From a 7 Year Follow-up Study of Patients Treated with Infliximab. Bert Vander Cruyssen[1], Patrick Durez[2], Rene Westhovens[3] and Filip De Keyser[4], [1]University Hospital Ghent, Ghent, Belgium, [2]Univ Catholique de Louvain, Brussels, Belgium, [3]University Hosp KU Leuven, Leuven, [4]Ghent University Hospital, Ghent, Belgium

Purpose: The definition of (in)acceptable disease activity state in rheumatoid arthritis (RA) is important not only for standardization of care in daily practice; in some countries social security instances are seeking to implement such definitions as reimbursement criteria for expensive biological treatments. This study is based on the results from a Belgian expanded access program in which 511 patients with active refractory and erosive RA were treated with intravenous infusions of infliximab (IFX) in combination with methotrexate (MTX). Patients were followed over 7 years.

Method: Between 2000 and 2001, 511 patients were enrolled in this nationwide program. Patients had a median disease duration of 10 years and had failed an average of 3.9 disease modifying anti-rheumatic drugs (DMARDs), including MTX. Patients were treated with IFX at week 0, 2, 6 and every 8 weeks thereafter with a standard dose of 3 mg/kg. From week 30 on, patients could receive a dose increase, which was decided at week 22. This decision to give or not to give a dose increase is the first proxy of “physician’s perception of acceptable/inacceptable disease activity state”. A second proxy of this perception is given by the DAS28 measured at the moment to stop IFX treatment due to inefficacy

Results: ROC analysis at week 22 (decision to give a dose increase; data collected between 2000 and 2002) provides a clue to define cut-offs of "acceptable/inacceptable disease activity”. A DAS28 score of 3.2 corresponded with 90% sensitivity; DAS28 score of 5.2 corresponded with 90% specificity. As such, a cut-off can be proposed in function of the desired sensitivity and specificity (table 1). Mean DAS28 at the moment of stopping the treatment due to inefficacy evolved over years from 5.6 in 2001 to 4.8 in 2008. Regression analysis confirmed this trend of a decline of cut-off for acceptable/inacceptable disease activity with 0.17 units of DAS28 per year.

Conclusion: This analysis provides some clues to define DAS28 cut-offs for (in)acceptable disease activity in RA. Over years, in parallel with the increase in the number of treatment options becoming available, less remaining disease activity seemed to be acceptable.

Table 1: ROC-analysis for the association of DAS28 and the decision to give a dose increase (data collected between 2000 and 2002)

DAS-cut-off	Sensitiviy	Specificity
2.0	0.99	0.13
2.5	0.99	0.22
3.0	0.98	0.38
3.2	0.96	0.46
3.5	0.94	0.54
3.7	0.90	0.58
4.0	0.79	0.66
4.5	0.76	0.77
5.0	0.58	0.87
5.2	0.51	0.90

5.5	0.43	0.95
6.0	0.34	0.97
6.5	0.19	0.98

Disclosure: B. Vander Cruyssen, None; **P. Durez**, None; **R. Westhovens**, None; **F. De Keyser**, Roche Pharmaceuticals, 5, gsk , 5, Schering-plough , 5, Abbott Laboratories, 5 .

1599

Risk Factors Associated with Depletion of Endothelial Progenitor Cells in Rheumatoid Arthritis Patients and Effect of Anti-TNF Therapy On EPCs Restoration. Yun-Jung Park[1], Ki-Jo Kim[2], Ji-Young Kim[3], Jin-Jung Choi[4], Wan-Uk Kim[5] and Chul-Soo Cho[6], [1]Catholic University of Korea, South Korea, [2]Catholic University of Korea, St. Mary's Hospital, Seoul, South Korea, [3]Catholic univeristy of Korea, Seoul, South Korea, [4]Bundang CHA General Hospital, CHA University, Bundang, South Korea, [5]St. Vincent Hospital, Suwon, South Korea, [6]St. Mary's Hospital, Seoul, South Korea

Purpose: It has been shown that circulating endothelial progenitor cells (EPC) decreased in rheumatoid arthritis (RA) patients, but the precise factors linked to reduction of EPC remain elusive. In this study, we determined the circulating EPC number in RA patients and variables associated with its depletion, and compared the effects of anti-TNF therapy and disease modifying anti-rheumatic drugs (DMARD) on the restoration of EPC.

Method: 164 RA patients and 67 age-gender matched control subjects were included. Circulating EPC was quantified by flow cytometry based on expression of CD34 and KDR. 85 RA patients were randomly assigned in 24-week comparator-controlled study to receive anti-TNF therapy (n=59) and DMARD alone (n=26). Endothelial function assessed by flow-mediated dilatation (FMD) was measured before and after the completion of study.

Results: The median EPC number was significantly reduced in RA patients than control subjects (44 vs 71 cells/ml, $P<0.01$). EPC number was significantly lower in RA patients with rheumatoid factor, anti-CCP antibody and bony erosion ($p=0.04$, $p=0.01$, and 0.03, respectively). The EPC number was inversely correlated with disease duration and cumulative C-reactive protein levels ($p<0.01$ for both). In multiple regression analysis, longer disease duration, cumulative CRP levels, and ESR were associated with EPC depletion. Compared to DMARD treatment, anti-TNF therapy led to further increase the EPC number and FMD change ($p<0.05$ for both). In parallel, patients in the highest tertile of EPC showed significantly higher FMD than the others at 24 weeks ($p<0.05$).

Conclusion: Circulating EPC was reduced in RA patients. Longer disease duration, inflammatory burden were associated with reduction of EPC. Anti-TNF therapy has beneficial effect on restoration of EPC depletion but also improving endothelial dysfunction.

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1600

Quantification of Dyslipidemia Among Patients with Rheumatoid Arthritis and Changes Associated with Initiation of Anti-TNF Therapy: A Retrospective Database Analysis. J. R. Curtis[1], A. John[2] and O. Baser[3], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Roche, Nutley, NJ, [3]University of Michigan Health Systems, Ann Arbor, MI

Purpose: Previous research suggests that onset of rheumatoid arthritis (RA) results in decreased lipid levels. Several small studies have shown that tumor necrosis factor-α inhibitor (TNFi) treatment in RA patients (pts) generally leads to increases in total cholesterol (TC), high-density lipoprotein (HDL), and triglyceride (TG) levels (Choy, 2009). This analysis compared lipid levels in pts with RA and osteoarthritis (OA) [objective 1] and determined lipid level changes in RA patients after initiation of TNFi treatment [objective 2].

Method: We used medical and pharmacy claims and laboratory results from a national commercial administrative claims database. Adults had diagnoses of either RA or OA between April 2005 and March 2008; test results for TC, low-density lipoprotein (LDL), HDL, or TG; and

no other inflammatory diseases. For objective 1, baseline was defined as 6 months before lipid test results. For objective 2, pts had at least1 lipid test before and 1 at least 6 weeks after TNFi initiation; baseline was defined as 6 months before TNFi initiation. Results were stratified by whether patients were already taking lipid-lowering medication (LLM) at the time of TNFi initiation. Propensity score matching [objective 1] and multivariate regression [objectives 1, 2] were used to control for baseline differences between RA and OA pts.

Results: We identified 12,319 RA pts and 29,621 OA pts who met eligibility criteria. The proportion of pts with diagnosed hyperlipidemia was significantly lower for RA than OA (49% vs 57%, $p<0.0001$). RA (vs OA) pts were younger (54 vs 59 mean years) and had higher mean Charlson Comorbidity Index (1.2 vs 0.5) and Chronic Disease Score (4.5 vs 3.1). Use of baseline LLM was lower in RA pts (27% vs 30%; $p<0.0001$). After controlling for baseline differences, pts with RA (vs OA) had significantly lower TC and LDL levels (Table); RA (vs OA) pts had lower adjusted mean TC (196 mg/dL vs 201 mg/dL, $p<0.0001$) and LDL (113 mg/dL vs 117 mg/dL, $p<0.0001$) values. Among the subgroup of RA pts not taking LLM, we observed small but significant increases after initiation of TNFi in TC (5 mg/dL; $p<0.0001$), LDL (4 mg/dL; $p=0.004$), and HDL (1 mg/dL; $p=0.02$). These changes associated with TNFi initiation were not observed in the subgroup of RA pts already taking LLM.

Conclusion: Results of this real-world analysis indicate that RA pts have lower average lipid levels compared with OA pts. In RA pts, initiation of TNFi therapy reversed this effect and modestly increased lipid levels except in pts already taking LLM. Aggressive management of dyslipidemia and decreasing systemic inflammation with biologic agents may reduce excess cardiovascular disease associated with RA.

Table. Proportion of RA and OA pts in each ATP-III lipid category after propensity score matching

Lipid level, mg/dL	RA n=11,053 % of pts	OA n=11,053 % of pts	*p*
Total cholesterol			
Desirable, <200	58.1	52.4	<0.0001
Borderline high, 200-239	30.5	33.0	0.0001
High, ≥240	11.4	14.6	<0.0001
Low-density lipoprotein			
Optimal, <100	36.6	31.6	<0.0001
Near optimal/above optimal, 100-129	36.6	35.8	0.22
Borderline high,130-159	18.7	22.0	<0.0001
High,160-189	6.1	8.1	<0.0001
Very high, ≥190	2.0	2.5	0.01
High-density lipoprotein			
Low, <40	10.8	10.3	0.28
Normal, 40-59	53.9	56.1	0.0009
High, ≥60	35.3	33.6	0.005

Disclosure: J. R. Curtis, Proctor & Gamble Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, 8, Centocor, Inc., 5, Amgen, 5, Proctor & Gamble Pharmaceuticals, 5, UCB, 5, Roche Pharmaceuticals, 5, Centocor, Inc., 2, Roche Pharmaceuticals, 2, Eli Lilly and Company, 2, Proctor & Gamble Pharmaceuticals, 2, Amgen, 2, Novartis Pharmaceutical Corporation, 2, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8, Corrona, 2 ; **A. John**, Roche Pharmaceuticals, 3 ; **O. Baser**, Roche Pharmaceuticals, 5, STATinMED Research, 9 .

1601

Women with Rheumatoid Arthritis Have Better Responses to Anti-TNF Therapy in the First Year, but Men Respond Significantly Better in the Long-Term – Results From the Danish DANBIO Registry. Damini Jawaheer[1], Jorn Olsen[1] and Merete L. Hetland[2], [1]UCLA, Los Angeles, CA, [2]DANBIO, Copenhagen Univ. Hospital, Copenhagen, Denmark

Purpose: To investigate gender differences in anti-TNF treatment outcomes over time in rheumatoid arthritis (RA) patients.

Method: We investigated treatment outcomes over 54 months in men and women with RA who initiated anti-TNF therapy between January 2003 and June 2008 in Denmark. Demographic and clinical data collected every 6 months by trained rheumatologists from hospitals* nationwide were documented in the DANBIO Registry. Gender differences in disease features at baseline were examined using Chi-square tests for categorical variables, and the Mann-Whitney and t-tests for continuous variables. Using a generalized estimating equations (GEE)

model for repeated measures, we also examined changes in disease outcomes in men and women over time, including ACR20 and EULAR responses, adjusting for baseline values of the disease activity score (DAS28CRP4), disease duration and anti-TNF treatment.

Results: At initiation of anti-TNF therapy (baseline), men (n=656) and women (n=1,852) had equally active disease (mean±SD DAS28CRP4: 5.1±1.3). Men had significantly later age at diagnosis, shorter disease duration, and higher C-reactive protein (CRP) (table 1). Women had worse disability (HAQ-DI), pain visual analogue scale (VAS), patient global scores, and fatigue VAS, and more tender joints. There were no differences in physician global scores, swollen joint counts and in proportions of men and women with erosions (73%). The GEE models revealed that, although women showed better responses during the first 12 months of treatment, in the longitudinal setting, men were more likely to achieve an ACR20 treatment response as well as a EULAR "good" response; these differences were statistically significant, and of clinical relevance, from 3 years onwards (ACR20: p=0.037, EULAR: p=0.035) (fig 1). Loss to follow up was similar in both genders and hence did not account for differences in response. No significant gender differences were observed in DAS28CRP4 scores, HAQ-DI, pain VAS, patient global scores and fatigue VAS over time, although women consistently had higher mean scores.

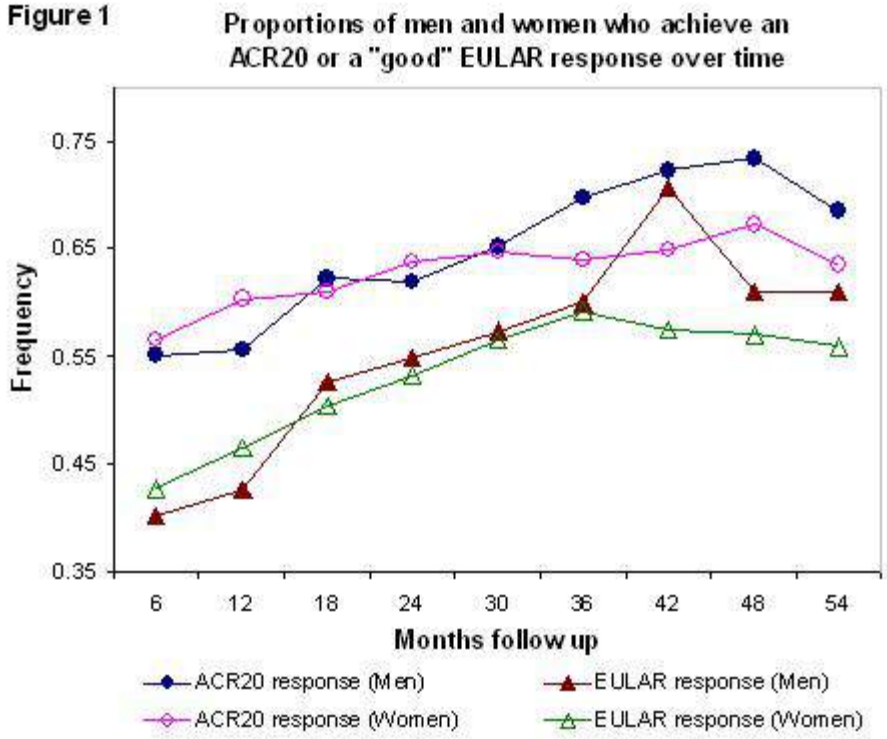
Conclusion: In this RA cohort, women had a better response to anti-TNF therapy for the first year of treatment. However, in the long-term, men responded better, with a significantly better response after 3 years of treatment.

* Ålborg, Århus, Bispebjerg, Esbjerg, Frederiksberg, Gentofte, Glostrup, Gråsten, Hjørring, Holbæk, Holstebro, Horsens, Hvidovre, Hørsholm, Kolding, Næstved/Nykøbing Falster,Odense, Randers, Rigshospitalet, Roskilde/Køge, Silkeborg, Slagelse, Svendborg/Fåborg, Vejle and Viborg

Table 1

Baseline characteristics	**All patients (n=2,508)**	**Men (n=656)**	**Women (n=1,852)**	**p value**
	mean ± SD, or median			
Age at diagnosis	45.3 ± 14.7	46.5 ± 13.3	45.0 ± 15.2	0.01
Disease duration	10.6 ± 9.9	9.6 ± 9.1	11.0 ± 10.2	0.003
DAS28CRP4	5.1 ± 1.3	5.1 ± 1.3	5.1 ± 1.3	0.25
Swollen joint count	7	7	7	0.73
Tender joint count	8	8	9	0.0008
CRP	14	16	14	0.008
HAQ-DI	1.3	1.0	1.4	<0.00005
Pain VAS	59	56	60	0.05
Patient global score	64	62	65	0.03
Fatigue VAS	57	47	60	0.06

Figure 1



Disclosure: D. Jawaheer, None; **J. Olsen**, None; **M. L. Hetland**, None.

1602

Validation of An Algorithm Using Genome-Wide SNP Analysis for Prediction of Responders and Non-Responders, and Adverse Events of Infliximab- or Etanercept-Treated RA Patients by Using Two Population Samples From Multiple Medical Cohorts.

Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], Sayumi Toriyama[3], Kunihiko Nakahara[3], Takafumi Hagiwara[1], Takako Miura[1], Kosuke Okuda[1], Akira Sagawa[4], Takeo Sakurai[5], Hiroaki Matsuno[6], Tomomaro Izumihara[7] and Eisuke Shono[8], [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]HuBit genomix, Inc., Tokyo, Japan, [4]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [5]Inoue Hospital, Takasaki, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [8]Shono Rheumatology Clinic, Fukuoka, Japan

Purpose: Infliximab (IFX) and etanercept (ETN) are efficient biologic agents for inflammatory diseases such as RA. However, there is no method for prediction of responders or non-responders, and which patients are prone to adverse events. We established and validated an SNP algorithm for prediction of responders or non-responders, and adverse events among IFX- or ETN-treated RA patients by using multiple medical cohorts.

Methods and Patients**:** The first population samples included 187 RA patients and the second population samples included 206 patients, total 393 patients from 6 hospitals in different regions of Japan. Efficacy was determined by DAS28(CRP) within 24-30 weeks after the initial treatment with the biologics according to EULAR criteria (good and moderate response group- 'responders', poor response group- 'nonresponders'), and adverse events such as fever, skin manifestations, and GI tract symptoms were documented. Genome-wide SNP genotyping was performed by HumanHap300K chip. Case-control analyses between 285,548 SNPs and efficacy or adverse events were examined by chi-square tests. We selected 10 SNPs associated with IFX- or ETN- responsiveness, or adverse events which are common in both analyses of the first and second populations ($p < 0.02$).

Results: For IFX responsiveness, accuracy ((true positive+true negative)/total) of the algorithm of the first, second and total populations were 85.1%, 80.4% and 82.8%. For IFX adverse events, accuracy of the algorithm of the first, second and total populations were 86.3%,

88.0% and 87.3%. In responsiveness of ETN, accuracy of the algorithm of the first, second and total populations were 95.5%, 96.3% and 95.9%. The accuracy of the algorithm of ETN adverse events in the first, second and total populations were 78.3%, 88.8% and 83.4%. An endocrine hormone-acting gene was revealed in the associated genes, linking association of TNF with the endocrine hormone.

Conclusion: The highly accurate algorithm using SNP analysis may prove useful in the prediction of responsiveness or determining those patients prone to adverse events before treatment of IFX or ETN, and may facilitate future tailor-made treatment of anti-TNF biologic agents.

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1603

Anti Tumour Necrosis Factor Alpha Therapy Improves Insulin Resistance in Normal-Weight but Not in Obese Patients with Rheumatoid Arthritis. Antonios Stavropoulos-Kalinoglou[1], Giorgos S. Metsios[1], Vasileios F. Panoulas[2], Yiannis Koutedakis[1] and George D. Kitas[2], [1]University of Wolverhampton, Walsall, United Kingdom, [2]Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom

Purpose: Insulin resistance (IR) associates with obesity and is a predisposing factor for cardiovascular disease (CVD) and type-II diabetes. In Rheumatoid Arthritis (RA), IR is common and is a potential contributor to the increased CVD risk of these patients. Anti tumour necrosis factor alpha (anti-TNFa) therapies are suggested to reduce CVD risk in RA; they have also been suggested to improve insulin kinetics. However, obesity – a potent contributor to IR – might influence the way anti-TNFa therapy affects insulin kinetics in RA. The aim of this longitudinal study was to compare the effects of anti-TNFa therapy on insulin kinetics between normal weight and obese individuals with and without IR.

Method: Patients embarking on anti-TNFa treatment, who were of normal-weight but had IR (N+IR), or were obese and had IR (O+IR), were invited to participate. Assessments included body mass index (BMI), CVD risk factors and RA disease characteristics before and following six months of anti-TNFa treatment. The results of the N+IR and O+IR patients were compared to age-, gender-, BMI-, disease duration- and smoking status-matched normal-weight patients without IR (N-IR) and obese patients without IR (N-IR) respectively. IR was defined as a HOMA (Homeostasis Model of Assessment) ≥ 2.5, or a QUICKI (quantitative insulin-sensitivity check index) ≤ 0.333. Patients with diabetes mellitus, or using anti-diabetic medication were excluded from the study. A total of 20 patients (16 women, age range 45-69), 5 in each of the groups, were assessed for this study.

Results: One-way Analysis of Variance (ANOVA) found no differences in BMI in any of the groups following six months of treatment ($p>0.05$). Inflammation and disease activity were significantly reduced in all groups ($p<0.05$) but to a similar extend (p for differences between groups >0.05 in all cases). Repeated measures ANOVA showed that the treatment resulted in greater (beneficial) changes in HOMA ($p=0.031$), QUICKI ($p=0.025$), systolic BP ($p=0.048$) and triglycerides ($p=0.034$) in N+IR patients compared to N-IR. In the obese groups, there was only a non-significant trend of improvement in IR [O+IR ($p=0.075$); O-IR ($p=0.082$)]. There were no differences in the magnitude of improvements between these two groups in HOMA, QUICKI, or any other CVD risk factors.

Conclusion: Anti-TNFa therapy improves insulin kinetics in normal weight but not in obese RA patients with IR. This suggests that in normal weight RA patients, IR associates mostly with active inflammation and is largely reversible, while in obese RA patients IR associates mostly with obesity and does not reverse with potent anti-inflammatory therapy, such as the anti-TNFs. This has obvious implications for CVD prevention strategies in RA.

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1604

Is the Response to Infliximab Influenced by Body Mass Index in Rheumatoid Arthritis Patients? Ruth Klaasen, Carla A. Wijbrandts, Danielle M. Gerlag and Paul P. Tak, Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: The influence of body mass index (BMI) on rheumatoid arthritis (RA) is unclear. Obesity is characterised by low-grade inflammation and could potentially aggravate disease activity and severity. On the other hand, an association has been suggested between high BMI and less erosive disease (1). Therefore, we investigated prospectively the influence of the BMI on the response to infliximab therapy in RA patients. Infliximab was chosen, as it is dosed per body weight.

Methods: In 91 patients with active RA (DAS28≥3.2) in spite of stable methotrexate treatment, we calculated the BMI before initiation of infliximab treatment (3 mg/kg according to the standard dosing regimen). At week 16 the clinical response was defined by a decrease in DAS28 ≥ 1.2 (twice the measurement error of the DAS28 over time, representing a clinically significant improvement).

Results: Mean BMI was 26.11 (SD ± 4.88) and BMI varied between 17.40 and 42.19. BMI was <20 in 8.8%, between 20 and 30 in 73.6% and >30 in 17.6% of the RA patients. At baseline there was a positive correlation between BMI and DAS28 (r = 0.340; P = 0.001). Anti-citrullinated peptide antibody (ACPA, measured by the anti-CCP test) positive patients had a higher BMI than ACPA negative patients (28.9 SD ± 6.1 versus 25.3 SD ± 4.2, respectively, P = 0.003). Of 91 patients 61 (67%) responded to treatment. An inverse correlation was found between the decrease in DAS28 after 16 weeks of therapy and BMI (r = -0.214; P = 0.055). Because DAS28 at baseline was positively correlated to BMI, and BMI was higher in ACPA negative patients, we performed a stepwise backward linear multi-regression analysis. When DAS28, BMI and ACPA were put into this model as dependent variables, BMI at baseline (P = 0.001) and DAS28 at baseline (P < 0.001) predicted the decrease in DAS28 after 16 weeks (R^2 = 0.205). BMI tended to be higher in non-responders compared to responders (26.8 SD ± 4.4 versus 25.5 SD ± 4.7). When we performed stepwise backward binary logistic regression and included BMI, DAS28 and ACPA into the model, DAS28 (P = 0.010) and BMI (P = 0.038) predicted clinical response to infliximab treatment (Nagelkerke R^2 = 0.139).

Conclusion: Although infliximab dosage is based on body weight, RA patients with a high BMI responded less well to infliximab, also when controlled for ACPA status. These results support the notion that fat tissue may be involved in the disease process.

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1605

Perioperative Complications in Patients with RA Receiving Tumor Necrosis Factor Inhibitor. Kosei Kawakami, Katsunori Ikari, Takuji Iwamoto, So Tsukahara and Shigeki Momohara, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Tumor necrosis factor inhibitors are established as therapeutic agents for active rheumatoid arthritis (RA) resistant to conventional drug treatment. However, these agents have been associated with risks for surgical site infections (SSI) and other complications due to systemic blockade of tumor necrosis factor. Furthermore, while deep vein thrombosis (DVT) is considered to be one of the most significant complications after major orthopedic surgery of the lower limbs, risk for DVT in RA patients receiving tumor necrosis factor inhibitor remain unclear. Our objective is to analyze the risk of infectious complications, and to clarify the risk for developing postoperative deep vein thrombosis in RA patients receiving tumor necrosis factor inhibitor treatment after major orthopedic surgery of the lower limbs.

Method: We evaluated 45 operations (33 total knee arthroplasties, 8 total hip arthroplasties, 1 total ankle arthroplasty, 1 femoral head replacement, 1 ankle arthrodesis and 1 fracture) in 34 RA patients receiving tumor necrosis factor inhibitor treatment (infliximab [n=23] and etanercept [n=22]) performed at our hospital between May 2004 and March 2009. There were 34 women and 11 men with a mean age of 56.8 years (range, 30-73 years). Forty-five operations in 44 RA patients without receiving tumor necrosis factor inhibitor who were matched for sex and the type of operation were enrolled as controls. SSI was diagnosed according to the criteria of the Centers for Disease Control. The diagnosis of DVT was based on ultrasonography. Multivariate logistic regression analysis was performed to test the association of SSI or DVT with the putative risk factors (sex, age, body mass index, disease duration, preoperative CRP, the use of biological agent, methotrexate, sulfasalazine [for analyzing SSI], NSAID, prednisone dosage, antiplatelet [for analyzing DVT], past DVT [for analyzing DVT]).

Results: We identified biological agents use as a risk for SSI (P=0.03, OR=2.31) and developing DVT (P=0.03, OR=2.83) after major orthopedic surgery. Eighteen percent of the patients receiving biological agents had SSI (8/45), while 2 percent of the patients without

receiving biological agents had SSI (1/45). Fifty-one percent of the patients receiving biological agents were DVT positive (23/45), while only 26 percent of the patients without receiving biological agents were DVT positive (12/45).

Conclusion: Biological agents use is a risk for SSI and developing DVT in RA patients after major orthopedic surgery.

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1606

Improvement of Thyroid Function During Six Months Adalimumab. Hennie G. Raterman[1], Anna Jamnitski[2], W.F. Lems[1], Alexandre E. Voskuyl[1], Ben A.C. Dijkmans[3], W.H. Bos[2], Suat Simsek[4], Paul Lips[1], Rob v.d. Stadt[2], Margret de Koning[2] and Michael T. Nurmohamed[2], [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Institute, Amsterdam, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands, [4]Medical Center Alkmaar, Alkmaar, Netherlands

Purpose: Rheumatoid arthritis (RA) is an inflammatory disease characterized by high levels of cytokines as tumor necrosis factor (TNF). TNF appears to have an etiologic role in thyroid dysfunction and, interestingly, thyroid dysfunction is a common comorbidity in RA. Therefore, thyroid dysfunction in RA patients might be beneficially influenced by TNF blocking agents.

Method: At baseline and after 6 months thyroid function (thyroid stimulating hormone [TSH], free thyroxine [fT4] and antibodies against thyroid peroxidase [TPOabs]) were assessed in an observational cohort of consecutive adalimumab treated RA patients (n = 180). Patients were categorized in 3 groups:euthyroid, hypothyroid (TSH > 4.0 or a known verified diagnosis) and hyperthyroid (TSH < 0.3 or fT4 > 24 or a known verified diagnosis). In these groups changes in thyroid status were determined.

Results: At baseline (see table), 21 (12%) and 9 (5%) RA patients were hypothyroid and hyperthyroid, respectively. At baseline 23 (13%) RA patients were positive for TPOabs (levels > 34 IU/ml) and after six months median TPOab levels decreased from 267 IU/ml to 201 IU/ml (p = 0.026) in TPOab positive patients. After 6 months treatment fT4 decreased from 24 (20 – 25) to 21 (18 – 24) pmol/l (p = 0.086) in hyperthyroid patients and TSH decreased from 4.0 (1.8 – 5.1) to 3.5 (1.6 – 6.0) mU/l (p = 0.085) in hypothyroid patients. In hyperthyroid patients without thyroid hormone substitution TSH levels increased from 0.5 (0.3 – 0.8) to 0.7 (0.4 – 1.5) (p = 0.075) and fT4 decreased significantly from 24 (19 – 25) to 20 (18 – 24) pmol/l. In hypothyroid patients without thyroid hormone substitution a trend (p = 0.071) for declining levels of TSH was found. Interestingly, in TPOab positive hypothyroid patients without thyroid hormone replacement TSH levels improved significantly from 12.5 (6.7 – 18.4) to 7.1 (4.9 – 13.8) mU/l (p = 0.043).

Conclusion: Anti-TNF treatment improves thyroid function in patients with thyroid dysfunction, providing further evidence that cytokines as TNF play an important role in thyroid disturbances.

	hypothyroid (n = 21)	euthyroid (n = 150)	hyperthyroid (n = 9)
TSH, mU/l	4.0 (1.8 - 5.1)	1.4 (1.0 - 2.1)	0.5 (0.23 - 0.86)
fT4, pmol/l	17 (13 - 21)	17 (16 - 19)	24 (20 - 25)
TPOab positive, n (%)	11 (52)	10 (7)	2 (22)
TPOab levels, IU/ml	98 (9 - 339)	8 (7 - 11)	12 (8 - 50)
Use of L-thyroxine, n (%)	9 (43)	0 (0)	1 (11)

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1607

How Early Can We Predict Remission at 1 Year in Early Rheumatoid Arthritis? - A Subanalysis of PREMIER. Maxime Dougados[1], Edward C. Keystone[2], Benoît Guerette[3], Kaushik Patra[4] and Frédéric Lavie[3], [1]University of Paris V, Cochin Hospital, Paris, France, [2]Professor of Medicine/University of Toronto, Toronto, ON, [3]Abbott Laboratories, Rungis, France, [4]Abbott Laboratories, Abbott Park, IL

Purpose: Previous analyses of PREMIER, a 2-year trial in patients (pts) with early rheumatoid arthritis (RA), demonstrated that adalimumab (ADA)+methotrexate (MTX) was superior to MTX monotherapy in preventing nearly all radiographic progression, regardless of clinical response to therapy.[1] Current recommendations from international societies define remission as the treatment goal in early RA. In pts with persistent active disease, therapy adjustment is recommended at least every 3 months. However, data suggest that the efficacy of currently available therapies increases overtime, at least during the first year. Using the PREMIER database, we aimed to answer the following questions: (1) After initiating a therapy because of active disease, how long should we wait before considering this treatment ineffective and deciding to change it?; (2) Is the time to reach this decision the same regardless of the treatment used?

Methods: Data from intent-to-treat pts in PREMIER were analyzed. Clinical outcomes were Disease Activity Score 28 (DAS28) at Weeks 4, 8, 12, and 26 and change (Δ) from baseline in DAS28. Predicted probability plots of remission at 1 year were obtained, depending on DAS28 or ΔDAS28 at Weeks 4, 8, 12, 26. At each time point, probability of remission was also evaluated for 4 categories of DAS28 (<2.6, 2.6–<3.2, 3.2–<5.1, and ≥5.1) and 2 categories of ΔDAS28 (improvement of ≤0.6 or >0.6) for both treatment groups (MTX and ADA+MTX).

Results: Probability of remission at 1 year was greater for pts treated with ADA+MTX vs. MTX alone for each level of DAS28 or ΔDAS28 at all time points ($p<0.05$). The table shows the predicted probabilities to reach remission at 1 year for each level of DAS or ΔDAS28. A probability of <15% to reach remission at 1 year was found as early as Week 8 for MTX-treated pts with an improvement of <0.6 in their DAS28. In ADA+MTX-treated pts with the same level of response, a <15% probability of remission was not observed before Week 26.

Predicted Probabilities for Each Level of DAS28 or DDAS28 at Each Time Point

Variable		**MTX***				**ADA+MTX***			
		Week 4 N=183	Week 8 N=183	Week 12 N=184	Week 26 N=186	Week 4 N=207	Week 8 N=210	Week 12 N=213	Week 26 N=209
Absolute DAS28	<2.6	59	55	73	71	76	74	86	83
	2.6–<3.2	50	57	46	41	69	76	66	59
	3.2–<5.1	40	28	25	11	59	46	42	21
	≥5.1	19	17	11	3	34	32	21	7
Improvement in DAS28	≤0.6	21	11	11	5	41	25	26	13
	>0.6	32	32	31	30	56	56	55	30
*Each number=% of pts achieving DAS28 remission at 1 year.									

Conclusion: These data suggest that the time to the decision to change treatment in pts with early RA may vary, depending on the treatment and the pt's response category. Some pts treated with MTX and presenting nonsignificant improvement of their DAS28 at Week 8, or a DAS28 ≥5.1 at Week 12, or a DAS28 ≥3.2 at Week 26 could be considered good candidates for treatment adjustment. In patients treated with ADA+MTX, clinicians should consider waiting ≥6 months before adjusting therapy.

References: [1]Breedveld FC, et al. *Arthritis Rheum*. 2006;54:26–37.

Disclosure: M. Dougados, Abbott Laboratories, 5 ; **E. C. Keystone**, Abbott Laboratories, 2, Centocor, Inc., 2, Amgen, 2, Abbott Laboratories, 5, Centocor, Inc., 5, Amgen, 5 ; **B. Guerette**, Abbott Laboratories, 3 ; **K. Patra**, Abbott Laboratories, 3 ; **F. Lavie**, Abbott Laboratories, 3 .

1608

Impact of Disease Duration On the Outcome of RA Patients Treated with Infliximab (The RemiTRAC Study). Denis Choquette[1], William G. Bensen[2], Hayssam Khalil[3] and John S. Sampalis[4], [1]University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]McMaster University, Hamilton, ON, [3]Schering Plough Canada, Kirkland, QC, [4]JSS Medical Research, Westmount, QC

Purpose: In recent years, the efficacy of anti-tumor necrosis factor (TNF-alpha) agents in the treatment of rheumatoid arthritis (RA) has been demonstrated in controlled clinical trials. The time to initiation of treatment may impact effectiveness of treatment.

Method: RemiTRAC is a Canadian registry providing real – life data on patients treated with infliximab that was initiated in 2002 at more than 70 rheumatology offices. Patients enter the cohort at the time of initiation of treatment and are followed prospectively indefinitely. The current analysis assesses the impact of disease duration on the real–life effectiveness of infliximab in the treatment of RA.

Results: A total of 679 RA patients were enrolled by December 31, 2008 of which 112 completed 36 months of treatment and are included in this report. Disease duration was ≤ 3 years (as per ERA population, ASPIRE trial) for 26 patients and > 3 years for 86 patients. Mean age of the two groups was 56 and 57 years respectively. The table describes laboratory and clinical parameters of the cohort during the first 36 months of treatment. The results show that although both groups experienced significant improvement in all clinical parameters patients with ≤ 3 years of disease duration at treatment onset had significantly more improvement in the Health Assessment Questionnaire (HAQ), swollen joint count (SJC) and higher proportion with ACR70 endpoint.

Parameter	**≤ 3 years (N = 26)**			**> 3 years (N = 86)**			**P – Value**
Mean (SD)	**Baseline**	**Change at 36 months**	**P – Value**	**Baseline**	**Change at 36 months**	**P – value**	
AM Stiffness (min)	70.5 (39.8)	-44.0 (41.3)	< 0.001	75.8 (42.2)	-51.5 (48.8)	< 0.001	0.480
CRP (mg/L)	19.5 (18.9)	-15.2 (19.0)	0.001	23.2 (27.5)	-14.8 (25.6)	< 0.001	0.950
ESR (mm/h)	33.1 (22.5)	-10.7 (22.4)	0.025	39.3 (27.2)	-13.5 (27.7)	< 0.001	0.648
HAQ (0-3)	2.0 (0.6)	-1.1 (0.8)	< 0.001	1.8 (0.7)	-0.7 (0.7)	< 0.001	0.012
Pain (VAS)	68.5 (26.0)	-49.0 (43.6)	< 0.001	64.8 (21.9)	-37.8 (28.4)	< 0.001	0.129
SGA	71.9 (24.5)	-50.2 (42.3)	< 0.001	68.5 (19.5)	-42.3 (30.0)	< 0.001	0.289
PGA	74.0 (16.2)	-54.4 (21.8)	< 0.001	68.7 (18.2)	-51.1 (19.7)	< 0.001	0.469
SJC	15.5 (6.8)	-13.3 (8.4)	< 0.001	11.8 (6.3)	-9.7 (6.2)	< 0.001	0.021
TJC	17.7 (7.0)	-12.2 (10.0)	< 0.001	14.9 (7.1)	-10.5 (7.3)	< 0.001	0.337
ACR20: N (%)	19 (73.1)			57 (66.3)			0.515
ACR50: N (%)	19 (73.1)			50 (58.1)			0.170
ACR70: N (%)	18 (69.2)			37 (43.0)			0.019

HAQ = Health Assessment Questionnaire. PGA = Physician Global Assessment of Disease Activity. SGA= Patient Global Assessment of Disease Activity. TJC=Tender Joint Count. SJC=Swollen Joint Count.

Conclusion: The results of this observational study have shown that infliximab is effective in managing RA, however, earlier initiation of treatment may increase the beneficial effect.

Disclosure: D. Choquette, Schering Canada, 5 ; **W. G. Bensen**, Schering Canada, 5 ; **H. Khalil**, Schering Canada, 3 ; **J. S. Sampalis**, Schering Canada, 5 .

1609

Anti-Tnfα Therapy: Cardiac Safety in Rheumatoid Arthritis and Ankylosing Spondylitis with Subclinical Diastolic Dysfunction.
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Purpose: Recent studies have suggested that N-terminal pro-brain natriuretic peptide (NT-proBNP), a sensitive marker used for diagnosis of heart failure (HF), is elevated in rheumatoid arthritis (RA) without an association with clinical cardiac dysfunction. We therefore have prospectively evaluated this biochemical parameter concomitantly with a new highly sensitive non-invasive tissue Doppler imaging (TDI) in RA and Ankylosing Spondylitis (AS) patients pre- and post- anti-TNFα therapy in order to accurately define the presence of subclinical myocardial injury.

Methods: Twenty-five patients, 11 RA (ACR criteria) and 14 AS (NY criteria) were prospectively enrolled. Exclusion criteria were history of HF, coronary disease, renal insufficiency and severe hypertension. Patients were evaluated at baseline (BL) and 6 months (6M) after anti-TNFα therapy for demographic, clinical and laboratory data. Myocardial function was determined by NT-proBNP (electrochemiluminescence immunoassay) and echocardiogram [M- mode, TDI and conventional Doppler techniques] using GE Vingmed Vivid-3 Expert.

Results: BL evaluation revealed for RA and AS, respectively: mean age 49.4±11.9 and 35.5±10.6 yrs old; female gender 100 and 28.6%; white race 63.6 and 78.6%; current smoker 27.3 and 16.7%; hypertension 27.3 and 7.1%; body mass index 24±2.9 and 24.3±3,3kg/m^2 and prednisone current dose 8±4.6 and 2.7±4.4mg/d. Initial measurements demonstrated diastolic ventricular dysfunction (DVD) in 9/11 (81.8%) RA and 4/14 (28.6%) AS, p=0.015. None of these 9 RA worsened and 3 recovered after 6M with a tendency of improvement in right ventricle lateral wall velocities (LWV) [S wave (p=0.05), A wave (p=0.07)] in the TDI, whereas no change was observed in left ventricle LWV and interventricular septum (p>0.05). All other parameters (fraction of ejection, E mitral wave, A mitral wave, desaceleration time and isovolumetric relaxed time (p>0.05) remained stable. With regard to echocardiographic finding in AS, 2(50%) improved and the other 2 had no change. NT-proBNP, in RA, was initially elevated in 5 (45.6%), all with DVD, contrasting with normal levels in AS. Mean NT-proBNP RA levels reduced significantly at 6M (145±146 vs. 79.±73pg/mL, p=0.046). Disease activity parameters comparing BL and 6M were for RA [DAS 28 (5.7± 0.9 vs. 3.9±1.4, p= 0.0019), CRP (11.1±13.1 vs. 5.5±7.1mg/L, p=0.06) and ESR (29±19.8 vs. 16.6±12.5mm, p=0.06)], and for AS [BASDAI 4.3±2.2 vs. 1.9±2.6 p=0.019), CRP (28.5±28 vs. 5.5±9.2mg/L, p=0.0013) and ESR (24.1±22.3 vs. 5.1±5.6mm, p=0.026].

Conclusion: Our data supports the cardiac safety of anti-TNFα therapy for RA and AS patients in spite of the remarkable high frequency of subclinical diastolic dysfunction in severe RA patients determined by TDI. This finding is further emphasized by the longitudinal reduction of NT-pro-BNP

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1610

Characteristics of Rheumatoid Arthritis (RA) Patients Starting Abatacept and Rituximab.
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Purpose: Studies have shown that both abatacept and rituximab are effective in RA patients. Currently, it remains unclear which biological agents should be used among those patients who have already failed tumor necrosis factor inhibitors (TNF-I). Understanding current treatment prescribing pattern can provide insight and guidance for future use of biological agents. We sought to determine the rates of use and factors affecting the prescription pattern of abatacept and rituximab among RA patients.

Method: 20,455 RA patients with 114,659 visits enrolled in the CORRONA database were evaluated. The primary outcome was the rate of abatacept and rituximab use as a factor of several demographic and disease specific characteristics. Odds ratio (OR) for using abatacept or rituximab was evaluated using multivariate logistic regression analysis.

Results: Since 3/06, 849 RA patients initiated abatacept (71%) or rituximab (29%). Majority were Caucasians (85%), seropositive for rheumatoid factor (RF, 73%) with mean disease duration of 14 years. Rituximab users were younger (56.3 vs 59.6, p=0.001) with a higher prevalence of cancer (16.5% vs 7.6%), especially lymphoma (8.6% vs 0.2%). Approximately 75% were on at least 1 concomitant DMARD. Both groups had comparable level of disease activity (rituximab vs abatacept: mHAQ 0.63 vs 0.61, DAS28 4.5 vs 4.7) at initiation of these drugs. Abatacept initiators had higher estimated patient global assessment of arthritis (VAS 46.3 vs 42.9, p=0.094) than rituximab initiators. While the majority had previously failed TNF-I, 12.4% of abatacept and 14.6% of rituximab users were TNF-I naive. TNF-I naive abatacept users were older (66.0 vs 58.6, p<0.001) with shorter disease duration (10.3 vs 14.6, p=0.001) and less disease activity (mHAQ 0.44 vs 0.66, MD and patient VAS global 22.0 vs 30.9 and 33.3 vs 48.1 respectively; p< 0.001) than TNF-I exposed users. TNF-I naive rituximab users had lower patient derived measures of disease activity and swollen joint count (4 vs 6, p=0.048) than TNF-I exposed. Patients who are younger (OR 0.97) with history of lymphoma (OR 62.1) were more likely to receive rituximab than abatacept (p<0.001). The type of practice (academic, private) was not significantly associated with receiving abatacept vs rituximab.

Conclusion: The overall prevalence of abatacept and rituximab use was 6% overall and 14% of prevalent biologic users. 13% were TNF-I naive. While age, disease activity, and history of cancer affected prescription pattern of abatacept and rituximab, RF and clinic type did not influence the rate of overall use.

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1611

The Effect of Tocilizumab On the Risk Factors for Atherosclerosis Development. Kentaro Susaki[1], Hiroaki Dobashi[1], Tomohiro Kameda[1], Katsuharu Kittaka[1], Ikuko Ohnishi[2], Masayuki Inoo[2], Michiaki Tokuda[3] and Toshihiko Ishida[1], [1]Faculity of Medicine, Kagawa University, Kagawa, Japan, [2]Utazu-hama clinic, Utazu-cho, Japan, [3]Sanuki Municipal Hospital, Kagawa

Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease induced by several inflammatory cytokines including TNF-alpha and interleukin-6 (IL-6). TNF-alpha and IL-6 are considered as the most important cytokine in the pathogenesis of RA. On the other hand, TNF-alpha is one of the adipocytokines known as the substances of physiological activity secreted by adipose cells. TNF-alpha interferes the phosphorylation of intra-cellular domain in the insulin receptor on target organs, such as skeletal muscle and liver, which results in enhancement of insulin resistance. Recently, it is reported that the insulin resistance of skeletal muscle in model rat can be decreased by treatment with soluble TNF-alpha receptor to neutralize serum TNF-alpha. The insulin resistance in RA is induced by administration of corticosteroid treatment or TNF-alpha released from arthritic joint. In this study, we examined the effect of two anti-TNF therapy agents, infliximab (IFX) or etanercept (ETA) and anti-IL-6 receptor antibody (Tocilizumab; Toc) on insulin resistance, adipocytokine expression, serum lipids and visceral fat of RA patients.

Methods: Ninety-four subjects diagnosed with RA according to the criteria of the American College of Rheumatology were included in this study. They (IFX; 46, ETA; 33, Toc; 13 cases) were given IFX at weeks 0, 2, 6, following every 8 weeks or given twice a month injections of ETA and treated with Toc for every 4 weeks. Blood samples were collected at 0, 54 weeks. Weinvestigated the insulin resistance of each RA patient using the Homeostasis Model Assessment Insulin Resistance (HOMA-IR). Insulin secretion ability was analyzed with Homeostasis Model Assessment Insulin Secretion (HOMA-beta). Serum lipids and adipocytokines (adiponectin, resistin and leptin) were measured by commercial available Enzyme-Linked Immunosorbent Assay.

Results: The disease activity of RA was decreased in all patients. HOMA-IR decreased more dominantly in patients treated with ETA than IFX and Toc. All biologics enhanced the expression of adiponectin at 54 weeks. There was no significant difference of the modulatory effect on adipocyokine expression between IFX and ETA. LDL-cholesterol and atherosclerosis index were tended to decrease in patients treated with ETA. All cases treated with biologics were decreased HbA1c level.

Conclusion: Anti-TNF and anti-IL-6 R antibody therapy could improve insulin resistance and disorders of lipid metabolism in RA patients. It suggested that ETA had an advantage effect on glucose metabolism and atherosclerosis development compared with IFX.

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1612

The Measure of Disease Activity, but Not Reduction of the Acute Phase Response (APR), Determines Attainment of Disease Activity States by Tocilizumab. Josef S. Smolen, Farideh Alasti and Daniel Aletaha, Medical University of Vienna, Vienna, Austria

Purpose: The APR is a major component of disease activity measures. In the DAS28, it is ESR which is strongly weighted (Bakker et al, ARD 2007). In the Simplified Disease Activity (DA) Index (SDAI), it is CRP with a low weight. The Clinical DAI (CDAI) is the SDAI without CRP, thus purely clinical. The APR is activated by IL-6 in the liver, and tocilizumab (TCZ), which inhibits IL-6 receptor signalling, could contribute to improvement of APR beyond clinical effects. We determined the effects of TCZ on DA, including attainment of remission (REM), using measures of DA that do and do not comprise APR, to learn on the contribution of effects on APR in the response in clinical trials.

Method: We were provided an 80% sample of patient level data from 3 TCZ trials of patients with active disease despite MTX/DMARDs (LITHE, OPTION, TOWARD) and pooled the 8mg/kg arms (n=899). DAS28, SDAI and CDAI were calculated and disease activity states defined according to the criteria for these indices.

Results: In the TCZ group, with similar baseline values (not shown), changes in DAS28, SDAI and CDAI were significantly higher when compared with placebo (3.2±1.5 vs 1.3±1.3; 26.0±15.8 vs 15.6±15.0; 23.7±15.1 vs 15.1±14.5, resp., all p<0-0001). However, TCZ-REM rates were much higher with DAS28 than SDAI or CDAI (30%, 7.9%, 6.6%, resp). Among patients with DAS28-REM, 26% had SDAI-REM and 20.7% CDAI-REM. The others were in low or moderate disease activity states by SDAI or CDAI. Individual variables in patients with DAS28-REM/CDAI-non-REM were significantly higher for all core set variables except APR (Table).

Table. Relative change from baseline to 6 months (mean %±SD) of individual core set variables in patients with DAS28-REM at 6 months who did, or did not achieve CDAI or SDAI REM upon TCZ+MTX/DMARD therapy (SJC, TJC: swollen/tender joint count; EGA/PGA: evaluator/patient global assessment)

Change in variable	DAS28-REM/CDAI-REM	DAS28-REM/CDAI-nonREM	DAS28-REM/SDAI-REM	DAS28-REM/SDAI-nonREM
SJC	98.1±6.4	49.5±58.3*	97.1±7.5	48.9±58.5*
TJC	96.9±13.4	56.7±55.5*	95.6±13.8	56.3±55.7*
EGA	91.0±9.8	53.9±38.5*	89.8±10.6	53.5±38.6*
PGA	86.2±20.7	35.7±74.7*	85.7±19.3	35.0±75.0*
HAQ	66.6±33.0	30.5±51.1*	66.4±31.8	82.8±42.8*
ESR	76.2±32.3	72.1±66.1**	79.8±29.3	71.7±66.6**
CRP	89.4±22.5	83.1±42.4**	91.8±15.7	82.8±42.8**

*p<0.0001; **p=ns

Conclusion: Disease activity is reduced by TCZ irrespective of the type of composite measure. Patients in DAS28-REM but not CDAI- or SDAI-REM had significantly larger changes of joint counts, HAQ and global assessments, but not APR than those in CDAI- or SDAI-REM. Thus, a major determinant of remission rates is not improvement in APR, but rather the selection of composite measure.

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Disclosure: J. S. Smolen, Roche Pharmaceuticals, 5 ; **F. Alasti**, None; **D. Aletaha**, Roche Pharmaceuticals, 5 .

1613

Gastrointestinal Safety in Patients with Rheumatoid Arthritis Treated with Tocilizumab: Data From Roche Clinical Trials. Ronald F. van Vollenhoven[1], Edward C. Keystone[2], R. Furie[3], A. Blesch[4], C. Wang[4] and J. R. Curtis[5], [1]Karolinska Univ Hosp, Stockholm, Sweden, [2]Professor of Medicine/University of Toronto, Toronto, ON, [3]NS-LIJHS, Lake Success, NY, [4]Roche, Nutley, NJ, [5]University of Alabama at Birmingham, Birmingham, AL

Purpose: To characterize upper and lower gastrointestinal (GI) perforation events in the tocilizumab (TCZ) worldwide rheumatoid arthritis (RA) Roche clinical trials database and to compare with GI perforation event rates among RA patients enrolled in a managed care database.

Method: Cases of GI perforations have been systematically identified on a quarterly basis since 1Q2006 using the TCZ worldwide RA clinical trials database. Cumulative safety data through February 6, 2009, for adverse events were integrated for patients with RA from the Roche clinical trials database. Rates of GI perforations that occurred in patients with RA in clinical practice were analyzed using administrative claims data from the United Health Care database.

Results: In worldwide Roche clinical trials, 4009 patients with RA have received at least one dose of TCZ (4 mg/kg or 8 mg/kg), with a total cumulative exposure of 9414.3 patient-years (PY). There were 26 cases of GI perforations reported for patients with RA from Roche TCZ clinical trials and long-term extension studies. The rate for lower GI perforation was 1.9 per 1000 PY (Table). The mean age of the 26 individuals experiencing a perforation was 63 years at the initiation of the trials. The majority of patients who perforated were taking chronic corticosteroids (up to 10 mg/day prednisone), one or more NSAIDs, and methotrexate. Three deaths were secondary to GI perforations or associated complications, one of which was an iatrogenic esophageal perforation. Sixteen of the 18 (89%) patients with colonic perforations had diverticulitis. The majority were recognized only after the perforation had occurred. The GI perforation rate in patients with RA who were exposed to corticosteroids in the United Health Care database was 3.9 per 1000 PY (95% CI, 3.1-4.8), and in those exposed to anti-TNFs, it was 1.3 per 1000 PY (95% CI, 0.8-1.9).

Conclusion: Most patients receiving TCZ who experienced GI perforation were also receiving corticosteroids, NSAIDS, and methotrexate. The rate of GI perforations in patients treated with TCZ in the Roche clinical trials was within the range of the rates observed in populations of RA patients treated with corticosteroid and/or anti-TNF therapy in the United Health Care database.

Anatomic Distribution of GI Perforation Cases in RA Patients Exposed to TCZ in Clinical Trials or Open Label Extensions

Anatomic Location	Number	Rate per 1000 Patient-Years[a]
Upper GI		
Esophagus	1	
Stomach and duodenum	1	
Jejunum and ileum	3	
Appendix	2	
Abdominal abscess	1	
Lower GI		
Colon	18	1.9
Diverticular (including abscess, fistula)	**16**[b]	**1.7**
Total	**26**	**2.8**

[a] Total exposure = 9414.3 patient-years.

[b] One patient had a diverticular perforation in the jejunum and was not included as a colon diverticular perforation case.

Disclosure: R. F. van Vollenhoven, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 ; **E. C. Keystone**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 9 ; **R. Furie**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 ; **A. Blesch**, Roche Pharmaceuticals, 3 ; **C. Wang**, Roche Pharmaceuticals, 3 ; **J. R. Curtis**, Proctor & Gamble Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, 8, Centocor, Inc., 5, Amgen, 5,

Proctor & Gamble Pharmaceuticals, 5, UCB, 5, Roche Pharmaceuticals, 5, Centocor, Inc., 2, Roche Pharmaceuticals, 2, Eli Lilly and Company, 2, Proctor & Gamble Pharmaceuticals, 2, Amgen, 2, Novartis, 2, Roche Pharmaceuticals, 8, Eli Lilly and Company, 8, CORRONA, 2 .

1614

A Clinical Study to Assess the Effect of Tocilizumab at a Therapeutic Dose & a Supra-Therapeutic Dose of Tocilizumab On QT/QTc Interval After a Single Dose in Healthy Subjects. Susan Grange[1], Christophe Schmitt[1], Angela Georgy[2], Banken Ludger[1], Barbara Kuhn[1] and Xiaoping Zhang[2], [1]Roche, Basel, Switzerland, [2]Roche, Nutley, NJ

Purpose: Tocilizumab (TCZ) is a humanized IL-6 receptor inhibitor that has demonstrated significant improvements in the signs and symptoms of moderate-to-severe rheumatoid arthritis (RA). This study was designed to evaluate the threshold pharmacological effect on cardiac repolarization, as detected by changes in the QT/QTc interval on 12-lead ECGs in healthy volunteers.

Method: This was a multi-center, double-blind, placebo- and active-controlled, parallel group study. A total of 121 healthy male & female subjects received either an intravenous infusion of TCZ 10 mg/kg (N=30) or 20 mg/kg (N=31), oral moxifloxacin 400 mg (MOX, N=31), or placebo (N=29). Triplicate ECGs were obtained at predose and 2 hr post dose on Day 1 and Days 8, 15 and 29 to cover entire TCZ serum concentration-time profile. Time-matched ECGs were taken on Day -1 for baseline corrections. All ECGs were centrally read by a blinded cardiologist. Study-specific corrected QT (QTcS) was derived from linear regression of individual mean QT on individual mean RR interval data obtained at baseline (Day -1). The change from time-matched baseline in QTcS was determined at each time point. An analysis of variance with the fixed factors treatment and day and their interaction and the random factor subject was applied to time-matched change from baseline in QTcS to estimate the placebo-corrected mean change from baseline together with one-sided upper 95% confidence intervals (CI). Blood samples for pharmacokinetic analyses were collected at predose and up to 28 days post dose.

Results: Of 121 subjects dosed, 67 were female and 54 male. Mean age varied from 29 to 37 years with an age range of 18 to 64 across groups. The majority of subjects were white. For TCZ at both 10 and 20 mg/kg doses, the estimated placebo-corrected mean change from time-matched baseline was negative at all time points and ranged from -5.4 msec to -1.0 msec. The associated upper one-sided 95% confidence limit was below 10 msec. Similar results were obtained for QTcF (Fridericia correction). The estimated placebo-corrected mean change from time-matched baseline for MOX was around 6.8 msec (95% CI: 0.8 to 12.7 msec). The upper bound of the 2-sided 95% CI is comparable to the literature reported value for MOX, establishing study assay sensitivity. There were no clinically significant abnormalities for other ECG parameters (QRS, PR, heart rate, RR, T-wave and U-wave morphology). There were no ECG abnormalities that constituted an adverse event. Following 10 and 20 mg/kg TCZ dosing, the time to reach maximum serum concentration was 2 hours post dose and the mean half-life was 9.3 days for 10 mg/kg and 12 days for 20 mg/kg. Both doses of TCZ were well tolerated and no unexpected safety findings were observed.

Conclusion: Analysis of the 12-lead ECG data obtained from this study indicates that there is no QT prolonging effect of clinical concern by TCZ at both the low (10mg/kg) & high (20mg/kg) dose.

Disclosure: S. Grange, Roche Pharmaceuticals, 3 ; **C. Schmitt**, Roche Pharmaceuticals, 3 ; **A. Georgy**, Roche Pharmaceuticals, 3 ; **B. Ludger**, F-Hoffmann-La Roche AG, Basel, Switzerland , 3 ; **B. Kuhn**, Roche Pharmaceuticals, 3 ; **X. Zhang**, Roche Pharmaceuticals, 3 .

1615

Serious Infections in Patients with Rheumatoid Arthritis (RA) Treated with Anakinra (ANA): Experience From the BSR Biologics Register (BSRBR). J. B. Galloway[1], W. G. Dixon[2], L. K. Mercer[3], K. D. Watson[3], M. Lunt[4], K. L. Hyrich[3], D. P. Symmons[1] and On behalf of the BSRBR[3], [1]University of Manchester, Manchester, United Kingdom, [2]The University of Manchester, Manchester, [3]The University of Manchester, Manchester, United Kingdom, [4]arc Epidemiology Unit, University of Manchester, Manchester, United Kingdom

Purpose: A recent Cochrane review of trials of ANA (an interleukin-1 receptor antagonist) in RA identified no significant difference in serious infection (SI) rates compared to placebo. Our aim was to explore the influence of ANA on SI rate using data from the BSRBR, a prospective cohort study set up in 2001 to monitor the safety of biologic therapies in the UK.

Method: Consecutive RA patients treated with ANA were recruited between October 2001 and May 2008 by the BSRBR and were followed 6 monthly via consultant and patient questionnaires until December 2008, end of follow up or death. A comparison cohort with active RA on disease modifying anti-rheumatic drugs (DMARD) was recruited and followed up in the same way. SI was defined as an infection requiring

hospitalisation or intravenous antibiotics or resulting in death. Incident cases of SI were identified from follow-up questionnaires and verified via medical records. SI was attributed to ANA if it was diagnosed while on drug or within 30 days of the last dose. Event rates in the ANA and DMARD cohorts were compared using Cox proportional hazard ratio estimates adjusted for age, gender, disease severity, prior joint replacement, co-morbidity, year of entry into the study and steroid use.

Results: 111 patients received ANA as their initial biologic. Patients prescribed ANA were younger, had more severe disease, longer disease duration, and higher exposure to steroids than the comparison cohort (Table). Drug survival on ANA was short (median survival on drug 5 months (IQR 3 – 12)) and 84% of patients switched biologic agent during follow up. In total 15 SI occurred in 10 patients on ANA, with the most common sites being respiratory and skin / soft tissue. 3 ANA treated patients died from SI. The crude rate of first SI was 92/1000 pyrs (95% CI 44, 170) in the ANA cohort compared to 34/1000 pyrs (30, 38) in the DMARD cohort. The unadjusted hazard ratio (HR) for first SI was 2.8 (1.5, 5.3) in the ANA cohort. After adjusting for confounding factors the HR was 2.5 (1.0, 6.4)

Conclusion: The rate of SI in the ANA cohort appears higher than in the DMARD cohort; however the number of events in the ANA cohort were small and there may be residual confounding.

Table:

No of patients ever received the drug	**Control cohort** **n=3515**	**Anakinra cohort** **n=111**
Number	3515	111
Person years follow up (pyrs)	9062	108
Age (mean / SD)	60 (12)	56 (10)*
Gender (% female)	75	72*
Disease duration years median (IQR)	6	13*
DAS mean (sd)	5.1 (1.3)	6.4 (1.0)*
HAQ mean (sd)	1.5 (0.8)	2.0 (0.6)*
Steroid use %	23	50*
Total serious infections (n)	290	10
HR (unadjusted) 95% CI	Ref	2.8 1.5, 5.3
Age & gender adjusted 95% CI	Ref	3.7 1.9, 7.0
Fully adjusted 95% CI	Ref	2.5 1.0, 6.4

*p values <0.001

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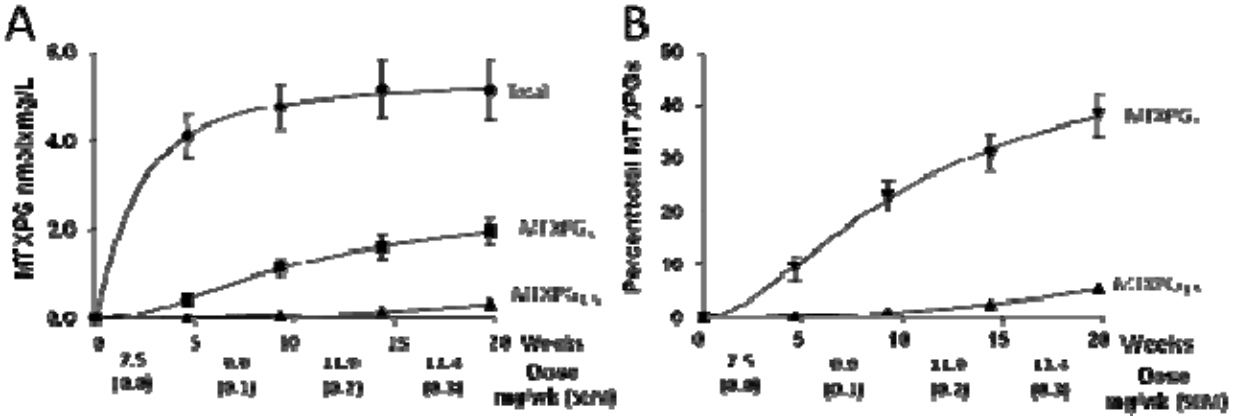
1616

Intracellular Methotrexate Pharmacokinetics in Rheumatoid Arthritis: Selective Emergence of Methotrexate Polyglutamates as a Function of Time and Dose Intensity. Thierry Dervieux[1], Rong Zablocki[1] and Joel M. Kremer[2], [1]Cypress Bioscience, San Diego, CA, [2]Albany Medical College, Albany, NY

Purpose: Methotrexate (MTX) is a prodrug producing antiarthritic effects through a Folylpolyglutamate Synthase (FPGS) mediated activation to active MTX polyglutamates (MTXPGs). We sought to evaluate the intracellular pharmacokinetics of MTXPGs during a dosage escalation of oral MTX in rheumatoid arthritis (RA).

Method: A total of 47 adult patients with RA were enrolled in a longitudinal study. Oral MTX was initiated at 7.5mg weekly and increased by 2.5mg every 4-6 weeks to reduce disease activity. Intracellular MTXPG concentrations ($MTXPG_{1-5}$) were measured in erythrocytes using liquid chromatography. Pharmacokinetics analyses consisted of non linear mixed models. Because dosing was increased with time, the change in MTXPG concentrations was analyzed after normalization with dose (i.e. MTXPG/dose expressed in nmolxmg/L). Covariates included in the pharmacokinetic models consisted of glomerular filtration rate (GFR), age and dose as appropriate.

Results: The figure (A) highlights the buildup of dose normalized $MTXPG_s$ in the erythrocytic compartment from initiation of therapy to the fourth study visit corresponding to 19.8±0.5 weeks MTX therapy at a final dosage of 13.4±0.3 mg/week. The accumulation of $MTXPG_{1-5}$ (total) followed a Michaelis-Menten kinetics (V_{max}=5.7±0.3; K_m=1.7±0.5, average±SEM) with V_{max} as the maximum level and K_m as the time needed to achieve half-maximum. After 7 weeks of therapy, 80% of the V_{max} (steady state) was reached. Older age and decreased GFR were both associated with increased V_{max} and decreased K_m ($p<0.001$). A total of 93% of the intra-patient variability was explained by this model. The change in dose normalized long-chains $MTXPG_3$ and very long-chains $MTXPG_{4-5}$ were best modeled using allosteric sigmoidal kinetics with a total of 91% and 83% of the intrapatient variance explained, respectively. After 4 weeks MTX therapy the vast majority of MTXPGs in the erythrocytic compartment consisted of short-chains $MTXPG_{1-2}$ (90%±1.2; average±SEM), while additional exposure and further MTX dosage escalation produced a selective redistribution toward longer chain MTXPGs (Figure B). Higher percentage $MTXPG_3$ in RBCs was associated with higher MTX dosage administered (estimate= 1.3±0.5%; p=0.019) thereby indicating that the selective emergence of these active metabolites was a function of dose intensity.



Conclusion: The data indicate that steady state $MTXPG_{1-5}$ concentrations are achieved after 7 weeks therapy in patients treated with weekly oral MTX. However, increasing time of exposure and dose escalation contribute to a selective redistribution of $MTXPG_{1-5}$ toward longer chain derivatives that are known to produce enhanced de novo purine biosynthesis inhibition compared to shorter chains MTXPGs. This data are consistent with an activation of FPGS during MTX therapy as previously described (Blood. 1994 84:564-9) and support the notion that the effects of this prodrug increase over time.

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1617

Adverse Events and Factors Associated with Toxicity in Patients with Early Rheumatoid Arthritis Treated with Methotrexate (the CAMERA study). S.M.M. Verstappen[1], M.F. Bakker[2], A.H.M. Heurkens[2], M.J. van der Veen[2], A.A. Kruize[2], M. Geurts[2], J.W.G. Jacobs[2], J.W.J. Bijlsma[2] and Utrecht Arthritis Cohort study group, [1]arc Epidemiology Unit, the University of Manchester, Manchester, United Kingdom, [2]Utrecht Arthritis Cohort study group, Utrecht, Netherlands

Purpose: In the CAMERA study (Computer Assisted Management in Early Rheumatoid Arthritis) we found that more patients with rheumatoid arthritis (RA) in the intensive methotrexate (MTX) strategy group compared to the conventional MTX strategy group achieved at least one period of remission. However, to compare the value of the two strategies, both beneficial effects and adverse events (AE) are important to weigh. Therefore, the objective of this study was to evaluate toxicity profiles in patients with early RA treated either according to an intensive or a conventional treatment strategy approach with MTX and to study factors associated with MTX related toxicity.

Method: Data were used from the CAMERA study in which AEs were recorded at each visit using a predefined form. Data on AEs were compared between the intensive strategy group (n=149) and conventional strategy group (n=140). Logistic regression analyses were used to identify possible associations between factors assessed at baseline, including demographic variables, clinical factors and laboratory values, and withdrawal due to MTX related AEs (adjusted for treatment group and NSAID use at baseline) in the total study population and for liver toxicity at follow-up (adjusted for NSAID use at baseline) for the two strategy groups separately. We present Odds ratios (OR) with 95% confidence intervals (95%CI).

Results: Although significantly more patients in the intensive strategy group (95%) experienced MTX related AEs compared to the conventional strategy group (90%), all recorded AEs were relatively mild and often reversible. The percentages of patients with an event were respectively: GI symptoms (66% vs 54%, p=0.030); mucocutaneous (54% vs 40%, p=0.025); CNS (59% vs 39%, p=0.001); hepatic (55% vs 35%, p=0.001); renal (39% vs 44%, p=0.403); haematological (26% vs 11%, p=0.001); and general AE (27% vs 15%, p=0.015). None of the baseline variables was associated with withdrawal due to MTX related AEs in the univariate regression analyses, but a higher BMI was significantly associated with withdrawal due to MTX related adverse events in the multiple regression analyses (OR 1.21, 95%CI 1.02 to 1.44). There was a trend towards an association between diminished creatinine clearance and MTX withdrawal (OR 0.97, 95%CI 0.94 to 1.00). For liver toxicity, increased serum transaminase and creatinine levels at baseline were associated with liver toxicity during follow-up.

Conclusion: Although the occurrence of AEs was higher in the intensive strategy group than in the conventional strategy group, the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles. When starting MTX, attention should be given to patients with a high BMI and those with increased transaminase levels and decreased renal function.

Verstappen et al. Ann Rheum Dis 2007;66:1443-9

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1618

Tight Control Aiming at a DAS28 Remission Is More Effective in Reaching High Remission Rates Than Usual Care in Rheumatoid Arthritis. Lydia G. Schipper[1], Marloes Vermeer[2], Ina H. Kuper[2], Monique Hoekstra[3], Cees J. Haagsma[4], Alfons A. Den Broeder[5], Piet L.C.M. van Riel[1], Jaap Fransen[1] and Martin A.F.J. van de Laar[2], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands, [3]Isala Klinieken, Zwolle, Netherlands, [4]Ziekenhuisgroep Twente, Almelo, Netherlands, [5]Sint Maartenskliniek, Nijmegen, Netherlands

Purpose: The ultimate treatment goal in Rheumatoid Arthritis (RA) is to achieve and sustain clinical remission as early as possible. In clinical trials, tight control was shown to be very effective in achieving this goal. However, the question is in how far these promising results can be transferred into daily clinical practice. Therefore, the aim of this study was to investigate whether a tight control treatment strategy is more effective than treatment according to usual care in reaching remission after 1 year of follow-up in patients with early RA.

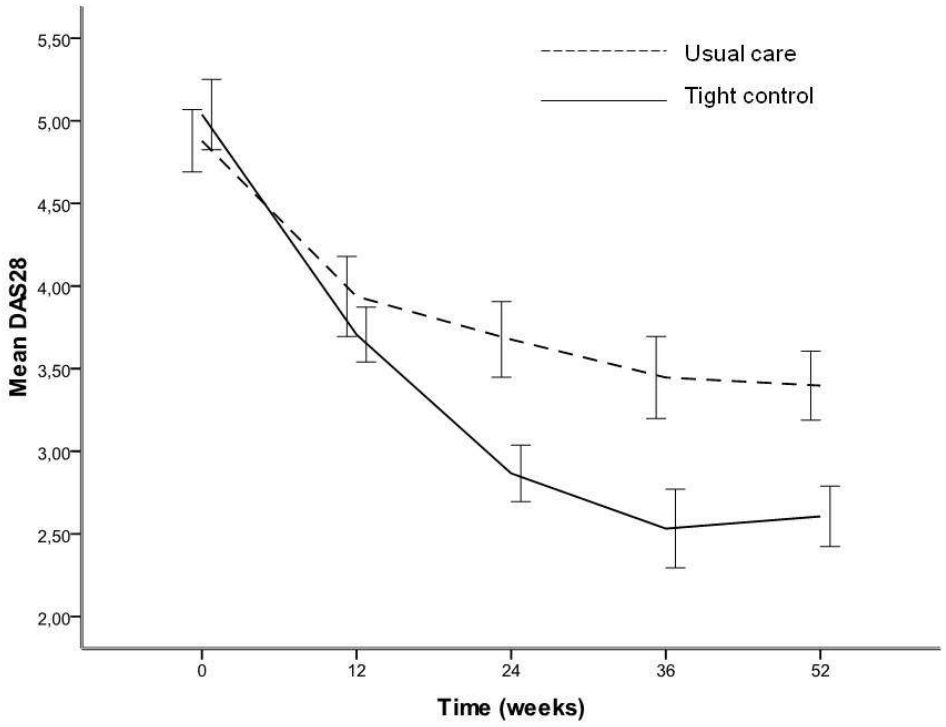
Methods: Two early RA inception cohorts from two different regions including patients who fulfilled the ACR criteria for RA and disease duration <1 year were studied. In both cohorts, DAS28 was evaluated every 3 months. Patients in the tight control cohort (n=126) were treated between 2006-2008 according to a DAS28-driven step-up treatment strategy starting with MTX, addition of SSZ, exchange of SSZ

by anti-TNF. Patients in the usual care cohort (n=126) were treated between 2004-2008 and were mainly treated with MTX or SSZ monotherapy at discretion of the rheumatologist, thus without DAS28 guided treatment decisions. Primary outcome was the percentage of patients in remission (DAS28<2.6) after 1 year. Secondary outcome measure was the mean change in the DAS28 from baseline to 1 year.

Results: At baseline, the tight control and usual care cohorts were comparable: age 56 vs 59 years, 63% vs 74% rheumatoid factor positive, baseline DAS28 was 5.0 vs 4.8 and baseline HAQ 1.2 vs 0.9, except for female gender (62% vs 48%). After 12 months, 55% of patients in the tight control cohort had a DAS28<2.6, versus 30% of usual care patients (P<0.0001, OR 3.1 (95% CI 1.8-5.2), adjusted for baseline DAS28). The median time to first remission was 19 weeks for tight control and 26 weeks for usual care (P<0.0001). The DAS28 was decreased with -2.5 in the tight control cohort and -1.5 in the usual care cohort, the between-group difference adjusted for baseline DAS28 was 0.85 (95% CI 0.58 - 1.12, P<0.0001) (Fig. 1).

Conclusion: In daily clinical practice, a tight controlled treatment strategy aiming for remission leads to more rapid and higher percentages of DAS28 remission after 1 year than treatment according to usual care.

Figure 1: Mean decrease of DAS28 in tight control and usual care groups.



Disclosure: L. G. Schipper, None; **M. Vermeer**, None; **I. H. Kuper**, None; **M. Hoekstra**, None; **C. J. Haagsma**, None; **A. A. Den Broeder**, None; **P. L. C. M. van Riel**, None; **J. Fransen**, None; **M. A. F. J. van de Laar**, None.

1619

Preliminary Estimates and Significance of Red Blood Cell Methotrexate Polyglutamate Measurements IN the Rheumatology Practice Setting. Thierry Dervieux, Mariko Matsutani, Debbie Stimson, Mary Barry and Curtis McGuyer, Cypress Bioscience, San Diego, CA

Purpose: Large interpatient variability in Methotrexate (MTX) absorption, excretion and activation to MTX Polyglutamates (MTXPGs) contributes to a wide spectrum of therapeutic responses in patients with rheumatoid arthritis (RA). We previously reported that red blood cell (RBC) MTXPG concentrations were associated with MTX efficacy in RA (Arthritis Rheum. 2004 50:2766-74). As the blood test was recently made available, our clinical and scientific impetus was to compare RBC MTXPG levels observed in our clinical study cohort to those observed in routine clinical practice setting.

Method: In 256 patients enrolled in a previous clinical study, lack of good response and poor response were associated with low RBC MTXPG levels, high weekly MTX dosage and low RBC MTXPGs per mg MTX administered (polyglutamation rate). Among RBC MTXPG levels recently requested in the course of clinical care by practicing rheumatologists a total of 1045 measurements were available along with MTX dosing information. RBC MTXPGs levels were measured in our accredited clinical laboratory using liquid chromatography. Concentrations were reported as nmol/L RBCs. To maintain patient privacy, all specimens were de-identified prior to the analysis. Differences between groups were assessed using non parametric tests or $\chi 2$ as appropriate. Data are presented as average±SD.

Results: The Table indicates that RBC MTXPG levels from our laboratory specimens were lower than those observed in good responders ($p<0.001$) but similar to those lacking good response ($p=0.90$). The proportion of laboratory test results was over-represented in the low level category (<20 nmol/L) but underrepresented in the high level category (>60 nmol/L) when compared to good responders ($p<0.01$). A 33% lower polyglutamation rate was observed between the clinical laboratory test results and good responders to MTX ($p<0.001$). On a population basis, estimates indicated that an average dose of 20 mg/week MTX may increase RBC MTXPG levels from 35 nmol/L to 44 nmol/L, the average observed in good responders (44 nmol/L/2.2 nmolxmg/L =20 mg).

	Clinical study: Good response	Clinical study: Lack of good response	Clinical Laboratory: test results
Weekly MTX dose (mg)	13.7±4.1	14.4±4.8	16.9±5.2
RBC MTXPGs (nmol/L)	44±25	35±20	35±22
RBC MTXPG per mg MTX (nmolxmg/L)	3.3±1.9	2.6±1.5	2.2±1.6
Low MTXPG: <20 nmol/L (%)	16.2%	28.0%	28.0%
High MTXPG: >60 nmol/L (%)	28.7%	8.5%	14.0%

Among patients who received a weekly MTX dose ≥15mg, RBC MTXPG concentrations were below the quantification limit (<5 nmol/L) in 6.3% of clinical laboratory specimens compared to 2.8% who presented with a poor response and 0% in patients without a poor response ($p=0.02$). Poor compliance and/or rapid excretion of un-metabolized MTX may explain these results.

Conclusion: These observations are consistent with our recommendation to assess MTX exposure in the context of poor MTX efficacy. These measurements may help rheumatologists to optimize MTX dosing and exposure in RA.

Disclosure: T. Dervieux, Cypress Bioscience, 3 ; **M. Matsutani**, Cypress Bioscience, 3 ; **D. Stimson**, Cypress Bioscience, 3 ; **M. Barry**, Cypress Bioscience, 3 ; **C. McGuyer**, Cypress Bioscience, 5 .

1620

Disease Activity, Joint Damage and Functional Disability and the Effect of Methotrexate Treatment in Patients with Undifferentiated Arthritis with or without Anti-Citrullinated Protein Antibodies. Karen Visser[1], J. van Aken[1], H. van Dongen[1], L.R. Lard[1], H.K. Ronday[2], I. Speyer[3], A.J. Peeters[4], R.E.M. Toes[5], Désirée M.F.M. van der Heijde[5], C. Allaart[1] and T.W.J. Huizinga[1], [1]LUMC, Leiden, Netherlands, [2]HAGA hospital, The Hague, Netherlands, [3]Bronovo hospital, The Hague, Netherlands, [4]GDGG, Delft, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands

Background: In rheumatoid arthritis (RA) treatment is aimed at minimal disease activity as this is associated with less radiographic progression and better functional ability. For undifferentiated arthritis (UA) these relationships are yet unclear.

Purpose: To investigate the relationships between disease activity, radiographic progression and functional disability, and the effect of treatment with methotrexate (MTX), in UA patients with or without anti-citrullinated protein antibodies (ACPA).

Methods: In the PROMPT study, 110 UA patients (ACR 1958 probable RA criteria, symptoms <2 years) were randomized to one year MTX or placebo therapy. Every three months, the disease activity scores (DAS), health assessment questionnaires (HAQ) and patient-reported symptoms on a VAS were measured. Radiographic progression, scored on 6-monthly radiographs of hands and feet using the Sharp-van der Heijde score (SHS) was defined as an increase of >=3. The longitudinal relationships between DAS-HAQ, SHS-HAQ and DAS-SHS, and the effect of MTX treatment on all outcomes were analyzed via longitudinal regression analysis with generalized estimating equations (GEE) or logistic regression analysis. Differential associations for ACPA positive and ACPA negative patients were explored via interaction terms. All analyses were corrected for age, gender, ACPA, treatment group, and baseline values of the studied variables.

Results: The DAS (beta=0.14, p=0.001), the baseline erosion score (beta=0.04, p=0.045), but not the momentary SHS, were longitudinally associated with the HAQ across time. A higher DAS in the initial 6 months was associated with radiographic progression after 12 months in logistic regression (OR=4.1, 96%CI 1.0-16.5, p=0.050). The above relationships were not different for ACPA positive or negative patients (interaction terms not significant). MTX treatment was associated with a lower DAS across time (beta=-1.0, p<0.001), including ESR, swollen (SJC) and painful (RAI) joints, lower patient's VAS for pain (beta=-10.8, p=0.039) and for disease activity (beta=-12.4, p=0.015) and less damage progression after 12 months (OR=0.2, 95%CI 0.04-0.8, p=0.027) in ACPA-positive, but not in ACPA-negative patients. The HAQ decreased significantly in the ACPA positive patients (beta=-0.027, p=0.002), but not in the ACPA negative patients (beta=-0.003, p=0.515).

Conclusion: Similar to RA, in UA, disease activity is related to functional disability and future radiographic progression, irrespective of ACPA status, providing prove of concept and a rationale for early intensive treatment of UA. MTX, however, is only beneficial for ACPA positive UA, thus effective therapy for ACPA negative UA needs yet to be found.

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Meta-Analysis of Tight Control Strategies in Rheumatoid Arthritis: Protocolized Treatment Has Additional Value with Respect to the Clinical Outcome. Lydia G. Schipper, Laura T.C. van Hulst, Marlies E.J.L. Hulscher, Piet L.C.M. van Riel and Jaap Fransen, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose: Randomized controlled trials show that tight control in Rheumatoid Arthritis (RA) is effective. Several ways for tight control have been studied, varying from ‘monitoring with using a treatment protocol' to ‘monitoring without applying a treatment protocol'. Whether these approaches differ in terms of clinical efficacy is not clear yet. Therefore, the efficacy of monitoring with protocolized treatment adjustments was compared to the efficacy of monitoring without protocolized treatment adjustments.

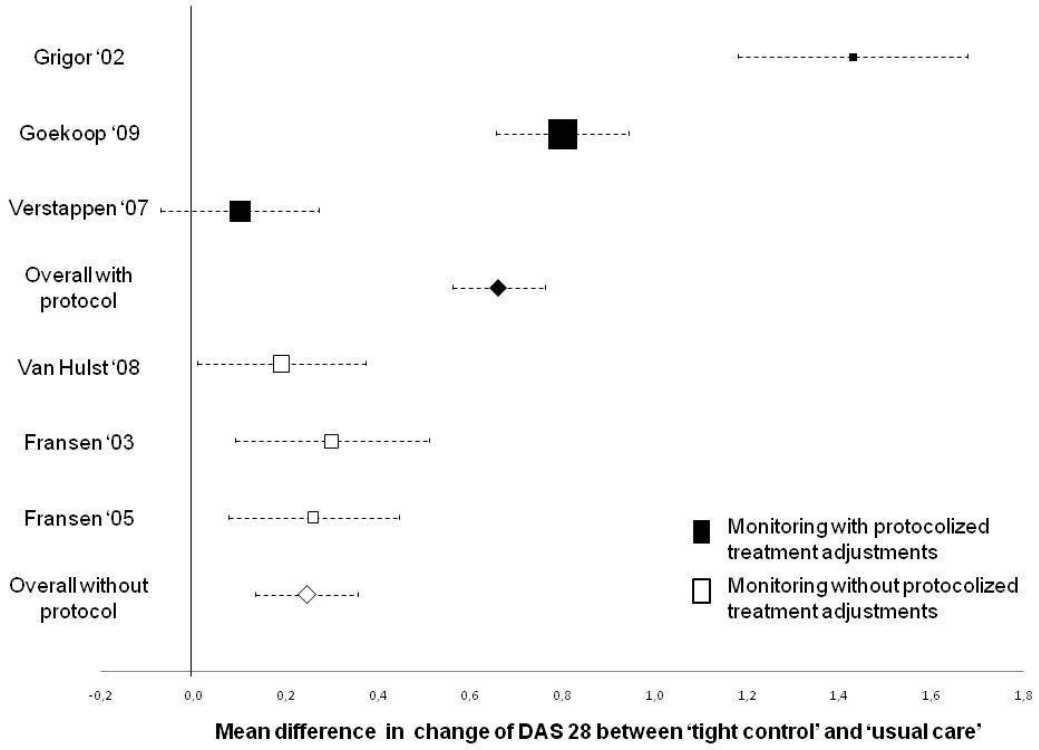
Methods: A systematic literature search was performed to identify clinical trials evaluating the effect of tight control compared to usual care. PubMed was used to find clinical trials from 1995 up to August 2008. The efficacy of both types of tight control interventions was determined by calculating the difference between usual care and the intervention in Disease Activity Score (DAS28) decrease from baseline to end of trial. If DAS values were calculated instead of the DAS28 the translation formula was used to calculate a DAS28. These differences were used in a meta-analysis to compare the effect of monitoring in combination with protocolized treatment adjustments versus monitoring without protocolized treatment adjustments. Outcomes were reported as weighted mean differences (WMD), obtained by pooling the mean changes. Differences were tested using the Z-statistic.

Results: Six tight-control studies were included in the meta-analysis: three studies used tight control with a treatment protocol and three applied tight control without a treatment protocol. All studies showed that tight control leads to a higher decrease in disease activity after one year of treatment compared to usual care (WMD=0.47, 95% 0.33-0.62). Treatment protocol-driven tight control was far more effective than usual care (WMD=0.66, 95% CI 0.46-0.86), if no treatment protocol was used tight control was only slightly more effective than usual care

(WMD=0.25, 95% 0.03-0.46) (Figure 1). This resulted into a significant difference in change of disease activity after one year (0.41, P<0.0001) between protocol-driven and no protocol-driven tight control.

Conclusion: In the treatment of RA, a tight control approach is more effective if monitoring is combined with protocolized treatment adjustments compared to tight control consisting of monitoring alone. Therefore, in tight control of RA, monitoring should be followed by protocolized treatment adjustments to accomplish the largest difference.

Figure 1: Mean difference in change of DAS28 between usual care and tight control.



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1622

Knowledge of Methotrexate in a Multiethnic Cohort of Adults with Rheumatoid Arthritis. J. Barton[1], John Imboden[1], Jonathan Graf[1], Vladimir Chernitskiy[2], Laura Trupin[3], E.H. Yelin[3] and Dean Schillinger[4], [1]UCSF, San Francisco, CA, [2]University of California, San Francisco, CA, [3]UCSF, SF, CA, [4]University of California, San Francisco, San Francisco, CA

Purpose: Methotrexate (MTX) is a recommended first line treatment for rheumatoid arthritis (RA) but adverse events are reported in over 70% of patients. Poor understanding of side effects and toxicity may limit use of MTX and cause unnecessary harm. We sought to determine RA patients' understanding of MTX among a diverse cohort of adults and assess whether knowledge varied by age, English language proficiency, or education.

Methods: Data were derived from a cohort of adults with confirmed RA seen at public hospital- and university hospital-based clinics. Subjects completed an annual structured telephone survey in English, Spanish, or Chinese, that included 11 questions on MTX (based on previously validated items). English language proficiency was assessed using the U.S. Census question “How well do you speak English?”

Those who reported “very well” were considered proficient [EP] and those who reported “well,” “not well” or “not at all” were considered to have limited English-proficiency [LEP]. Education level was dichotomized as less than high school [<HS] or high school graduate and beyond [HS/BA]. We compared frequencies of correct answers among patients with LEP and EP, <HS and HS/BA education, age < 55 and ≥ 55 using chi-square and t-tests. Multivariate linear regression was also performed.

Results: Ninety-four of 176 subjects reported taking MTX; 75% were female, 35% Hispanic, 31% non-Hispanic White, 25% Asian, 6% African American and 3% Other. Mean age was 55 ± 15 years; mean RA disease duration 8 years. Forty-four subjects had LEP, 57% were non-U.S. born, 30% had < HS education. Mean MTX knowledge score was 5.7 ± 2.7 (out of 11); scores did not differ by LEP/EP or education, but did by age (table). The table shows frequencies of correct responses by age <55 and age ≥ 55. Overall, 84% correctly identified weekly dosing and need for regular monitoring; 78% of women of childbearing age identified MTX as teratogenic. Knowledge of potential side effects was poor. In multivariate linear regression, age ≥ 55 was associated with decrease in score of 2.2 compared to subjects < 55 (adjusting for LEP, education and disease duration). LEP and education were not significant predictors in multivariate analyses.

Conclusion: Among ethnically diverse subjects with RA, knowledge of MTX weekly dosing, regular monitoring, and teratogenicity (among women of child-bearing age) was high. However, scores on a similar test of MTX knowledge in the Midwest were higher. Knowledge of potential side effects, and teratogenicity among males, was poor and may be due to lack of provider education. Interventions to increase knowledge of MTX and its side effects should be targeted to all patients, specifically to those ≥ 55, regardless of language proficiency or education.

Table. Methotrexate knowledge questionnaire results

Test (correct answers)	% correct N=94	Age < 55 N=46	Age ≥ 55 N=48	p-value
Drug safety				
MTX frequency (weekly)	84%	96%	83%	1.00
Alcohol intake (none)	64%	83%	48%	0.10
Frequency of blood tests (2-3 months)	84%	98%	77%	0.17
birth defects (yes)				
If female	89%	79%	29%	<0.001
If male	21%	60%	6%	0.07
Potential side effects				
Nausea (yes)	39%	49%	29%	0.02
low blood counts (yes)	24%	36%	16%	0.03
mouth sores (yes)	39%	49%	31%	0.16
pneumonitis (yes)	19%	22%	17%	0.81
liver problems (yes)	63%	96%	42%	0.02
Drug action				
MTX slows damage to joints	69%	78%	60%	0.04
Folic acid prevents side effects	69%	87%	60%	0.09
Mean score (out of 11)	5.7 ± 2.7	6.7 ± 2.5	4.7 ± 2.9	<0.001*

* two sample t-test

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Etoricoxib Improves Pain and Function in Rheumatoid Arthritis Patients On Background Biological Therapies. M. Greenwald[1], P. Peloso[2], A. Mehta[2], H. Wang[2], F. Hasler[3] and A. Gammaitoni[2], [1]Desert Medical Advances, Palm Desert, CA, [2]Merck & Co., Inc., Rahway, NJ, [3]Private Practice, Neue Bungertrechti, Switzerland

Purpose: Biologic therapy (i.e. TNF-α, IL-1 inhibitors) has altered the management of synovitis and long term outcomes in RA. Patients may still experience pain and impaired function; however, little is known about the efficacy of COX inhibitors in conjunction with biologics. We conducted this post-hoc analysis to explore the efficacy of etoricoxib, a COX-2 selective NSAID, in RA patients with or without biologic therapy.

Methods: RA patients were randomized to etoricoxib 10, 30, 60 or 90 mg or placebo in a double-blind 12-week study. Using the time-weighted change from baseline over 12 weeks, we evaluated: Patient global assessment of pain (Pain; 0- 100mm VAS); Swollen Joint Count (SJC; Out of 66 Joints); Tender Joint Count (TJC; Out of 68 Joints) and Health Assessment Questionnaire (HAQ; 0-3 Likert Scale). Three treatment groups were evaluated: placebo; pooled etoricoxib 10/30/60 mg; and etoricoxib 90mg. The following biologics were considered: etanercept; anakinra; adalimumab, natalizumab, infliximab, and abatacept. Least-square means were estimated from ANCOVA models with terms for baseline parameter, treatment, biologic usage and its interaction with study therapy.

Results: Of 761 patients randomized, 178 (23.4%) were on concomitant biologic therapy. Baseline values for those on/ not on biologicals, for each endpoint were similar, although patients on biologics demonstrated slightly lower pain, but higher TJC and SJC. For placebo, etoricoxib 10/30/60 mg, and etoricoxib 90 mg, baseline values for pain [no biologic (with biologic)] were 73.3 (70.8), 71.1 (70.0), and 71.1 (70.5); baseline values for SJC [no biologic (with biologic)] were 15.9 (16.8), 16.0 (19.8), and 15.5 (18.8); baseline values for TJC [no biologic (with biologic)] were 26.4 (29.4), 26.5 (31.2), and 25.8 (28.4); baseline values for HAQ [no biologic (with biologic)] were 1.3 (1.4), 1.3 (1.4), and 1.2 (1.5). LS mean changes vs. placebo for each group for patients on biologics and those not on biologics are in the table.

Conclusion: The biologics subgroup had significant pain and functional impairment at baseline. Etoricoxib 90 mg provided improvements in pain and function with and without concomitant biologic therapy, with greater improvements in TJC and SJC noted for those not on biologics. Etoricoxib is effective in RA patients who are taking concomitant biologicals and 90 mg is the most effective dose. Table

	Etoricoxib 10/30/60 mg	Etoricoxib 90 mg
	LS Mean Change (SE) vs. placebo; p-value	LS Mean Change (SE) vs. placebo; p-value
Pain		
No Biologics	-5.45 (2.42); <0.05	-15.53 (3.06); <0.001
With Biologics	-6.70 (4.66); NS	-12.92 (5.30); <0.05
TJC		
No Biologics	-2.45 (1.11); <0.05	-5.05 (1.41); <0.001
With Biologics	-1.53 (2.14); NS	-1.15 (2.43); NS
SJC		
No Biologics	-0.80 (0.65); NS	-2.92 (0.83); <0.001
With Biologics	-1.29 (1.26); NS	-0.68 (1.43); NS

HAQ		
No Biologics	-0.15 (0.05); p<0.01	-0.24 (0.06); <0.001
With Biologics	-0.18 (0.09); NS	-0.23 (0.10); <0.05
NS = not significant		

Disclosure: M. Greenwald, Merck Pharmaceuticals, 2 ; **P. Peloso**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1 ; **A. Mehta**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1 ; **H. Wang**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1 ; **F. Hasler**, None; **A. Gammaitoni**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3 .

1624

Prevalence of Alcohol Consumption Among Rheumatoid Arthritis (RA) Patients On Methotrexate (MTX) and Impact On Liver Function Tests. C. Iannaccone, M. Frits, J. Cui, M. E. Weinblatt and N. Shadick, Brigham & Women's Hospital, Boston, MA

Purpose: There is little data on the prevalence of alcohol consumption among RA patients, especially those taking MTX. The American College of Rheumatology (ACR) guidelines state that patients on MTX should limit alcohol intake to 2 drinks or less per month because it can significantly increase the risk of liver damage. This study looks at the prevalence and quantity of alcohol use in RA patients on MTX and evaluates whether alcohol consumption results in elevated liver function tests (LFTs), mainly aspartate transminase (AST) and alanine transminase (ALT).

Method: Eligible subjects are RA patients enrolled in a prospective observational cohort (BRASS). Data on patients' medication use was obtained from physicians and alcohol use was self-reported in an interview. A general linear model analysis was used to determine the differences between patients who reported drinking more than the ACR recommendations while on MTX (drinkers) versus those who followed the ACR guidelines (abstainers). A mixed model was used to compare the LFTs of patients on MTX who were drinkers versus abstainers evaluating multiple time points for the cohort adjusting for potential confounders.

Results: We examined 738 patients (563 on MTX). Six percent of the MTX users had a diagnosis of diabetes and 23% were obese (BMI>30). Alcohol use was reported by 56% of the patients on MTX (Mn=8 drinks/month) compared to 66% (Mn=17 drinks/month) of patients not on MTX (p=.0004). Of the MTX drinkers, 38% were drinking more than the recommended amount. After adjusting for gender and age, a general linear model showed MTX drinkers tended to have lower BMIs, a shorter disease duration, less pain and better physical function than those who abstained (see table).

Of the patients on MTX, we found no difference in the percentage of drinkers (34%) and abstainers (34%) having at least one abnormal LFT result. Also, the mixed model analysis adjusting for age and gender showed no difference in AST or ALT levels between MTX drinkers compared to abstainers (p=0.5, p=0.3) over time. Furthermore, in a subgroup analysis of those with diabetes and obesity, there was still no difference in AST or ALT levels among MTX drinkers compared to abstainers (p=0.5, p=0.9).

Conclusion: Despite warnings of the dangers of drinking alcohol while taking MTX, many patients continue to drink. However, we could find no further evidence that MTX drinkers had higher LFTs overall compared with abstainers. While MTX drinkers tended to report less pain and better physical function further study is necessary to determine the clinical impact of this level of alcohol use among MTX users.

MTX Drinkers vs. Abstainers	≥ 2 drinks/month (±SE)	< 2 drinks/month (±SE)	P-Value

BMI	26.4 ± 0.35	27.7 ± 0.35	0.0015
Disease Duration	11.4 ± 0.73	14.0 ± 0.73	0.0037
Physical Function *(MDHAQ)*	27.8 ± 1.63	36.1 ± 1.73	<0.0001
Pain Scale *(MDHAQ)*	30.1 ± 1.8	36.1 ± 1.92	0.0004
Physician Global Scale *(0-100)*	31.5 ± 1.39	34.3 ± 1.39	0.09

Disclosure: C. Iannaccone, None; **M. Frits**, None; **J. Cui**, Biogen Idec, 2, Crescendo Biosciences, 2 ; **M. E. Weinblatt**, Biogen/Idec, Crescendo, 2, Biogen/Idec, Crescendo, 5 ; **N. Shadick**, biogen idec, 2, crescendo biosciences, 2, Amgen, 2, Bristol-Myers Squibb Foundation, 2 .

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Tacrolimus-Induced Pulmonary Injury in Patients with Rheumatoid Arthritis. Ryuji Koike[1], Michi Tanaka[1], Yukiko Komano[1], Fumikazu Sakai[2], Haruhito Sugiyama[3], Toshihiro Nanki[1], Nobuyuki Miyasaka[1], Masayoshi Harigai[1] and Study Group for Tacrolimus-induced Pulmonary Injury[4], [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]International Medical Center, Saitama Medical University, Hidaka-shi, Japan, [3]International Medical Center of Japan, Tokyo, Japan, [4]Tokyo, Japan

Purpose: Tacrolimus has been approved for rheumatoid arthritis (RA) with inadequate response to other disease modifying anti-rheumatic drugs (DMARDs) in Japan since 2005. Post-marketing surveillance (PMS) of the drug and spontaneous reports to Astellas Pharma Inc. identified twenty-seven cases of exacerbation or new development of interstitial pneumonia (IP) among the 3,638 patients with RA by May 2007. The objective of this study was to identify patients with high likelihood for tacrolimus-induced pulmonary injury (TIPI) and describe clinical and radiological characteristics of TIPI.

Method: We sent a letter to the attending physicians who reported IP as an adverse event in the PMS or the spontaneous reports to the pharmaceutical company and collected eleven cases from eleven hospitals. Clinical, radiological and laboratory data of these cases were provided from the physicians. Each case was evaluated by the Study Group for Tacrolimus-induced Pulmonary Injury including a radiologist (F.S.) and a pulmonologist (H.S.). Cases were classified into four categories according to the clinical likelihood for TIPI: presumptive TIPI, probable TIPI, possible TIPI, non-TIPI. Presumptive TIPI indicates TIPI is clinically more likely than other pulmonary diseases including rheumatoid lung and pulmonary infections. Probable TIPI indicates both TIPI and other pulmonary diseases are likely to the same degree. Possible TIPI indicates other pulmonary diseases are more likely than TIPI. Non-TIPI indicates TIPI is unlikely.

Results: Ten out of the eleven cases were analyzed because of lack of radiological data other than chest X-ray in one case. Baseline data of the ten patients were as follows: mean age, 69.7 y/o; sex, female 70%; mean disease duration of RA, 9.4 years; mean CRP level, 3.67 mg/dl (n=9); pulmonary comorbidity, 90%. Six and four cases were classified as the presumptive and probable TIPI, respectively. Among the patients with the presumptive TIPI, TIPI developed 88.4 days after the initiation (n=5) or 5 days after reinstitution (n=1) of tacrolimus. Four and two cases were exacerbation of pre-existed IP and newly developed pulmonary injuries, respectively. Main radiological patterns of the patients in the presumptive TIPI were DAD- (n=2), NSIP- (n=1), COP- (n=1) and UIP-pattern (n=2). All patients with the presumptive TIPI received high dosage of corticosteroids and two received immunosuppressants. Four out of the six patients survived.

Conclusion: Rheumatologist should be aware of this rare, but possibly life-threatening adverse drug reaction of tacrolimus in patients with RA.

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1626

Early Effects of High Dose Glucocorticoids On Blood Pressure and Weight in Early Rheumatoid Arthritis. Debby den Uyl[1], Hennie G. Raterman[2], Michael T. Nurmohamed[3], Ben A.C. Dijkmans[4], Alexandre E. Voskuyl[2], Dirkjan van Schaardenburg[3], Pit J.S.M. Kerstens[3] and Willem F. Lems[1], [1]VU University medical center, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Jan van Breemen Institute, Amsterdam, Netherlands, [4]VU Medical Centre, Amsterdam, Netherlands

Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular morbidity and mortality, partly due to a higher prevalence of traditional cardiovascular risk factors as hypertension (HP) and a higher body mass index (BMI). Treatment with glucocorticoids (GC's) might result in a higher cardiovascular risk due to the induction of HP and weight gain. On the other hand, GC's might reduce cardiovascular risk in RA patients due to favourable effects on the disease activity.

Purpose: To evaluate the short term effects of high dose glucocorticoids on blood pressure and weight in patients with early rheumatoid arthritis.

Method: In this ongoing study, patients were randomised for treatment with COBRA (including 60mg prednisone, tapered in 6 weeks to 7,5mg/day) or COBRA-light (including 30mg prednisone, tapered in 9 weeks to 7,5 mg/day). At baseline, 2 weeks, 4 weeks and 8 weeks of treatment, blood pressure (BP), body weight and body mass index (BMI) were determined. HP was defined as a systolic BP≥140 and/or diastolic BP≥90. BP and weight at week 2, week 4 and week 8 were compared with baseline measurements by Wilcoxon tests **Results:** 40 patients had complete 8 weeks follow-up available for analyses. There were no differences in baseline characteristics between patients treated with COBRA and COBRA-light. Median systolic blood pressure (IQR) was 130 mmHg (120-140), median diastolic blood pressure (IQR) was 80 mmHg (75-86) and 36% had prevalent high blood pressure. Median weight (IQR) was 72 kg (64-81) and median BMI (IQR) was 25 (22,6-26,3). BP did not change significantly during treatment, while after 8 weeks weight increased significantly compared with baseline. (table)

Table Systolic blood pressure, diastolic blood pressure, weight and BMI during 2, 4 and 8 weeks treatment

	2 weeks	4 weeks	8 weeks
Delta Median Systolic BP, mmHg (IQR)	0,0 (-10 - 7)	-1,0 (-10 – 9,5)	0,0 (-10 – 6,8)
Delta Median Diastolic BP, mmHg (IQR)	-1,0 (-7 - 5)	0,0 (-5 – 2)	0,0 (-9,8 - 5)
Delta Median Weight, kg (IQR)	0,5 (-1,6 – 1,5)	0,4 (-1,0 – 2,0)	1,0 (-0,4 – 2,0)*
Delta Median BMI (IQR)	0,3 (-0,6 – 0,6)	0,0 (-0,4 – 0,7)	0,4 (-3 – 1,6)

*$p<0.05$ compared with baseline

Conclusion: In our preliminary analyses, short term treatment with high dose corticosteroids in patients with early RA does not significantly influence blood pressure and increases weight minimally.

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1627

Documenting Adequate Versus Incomplete Responses to Methotrexate (MTX) at Initiation of Biologic Agents in Routine Clinical Care, According to ESR, RAPID3, and Component Patient-Reported Scores for Physical Function, Pain and Global Estimate. Theodore Pincus[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: To analyze adequate responses to methotrexate (MTX) in patients who were not subsequently treated with biologic agents, compared to incomplete responses in patients who subsequently were treated with biologic agents in usual care of patients with rheumatoid arthritis (RA), according to five measures: erythrocyte sedimentation rate (ESR), multidimensional health assessment questionnaire (MDHAQ) scores for physical function (MDHAQ-FN), pain (PN), patient global estimate (PTGL), and RAPID3 (routine assessment of patient index data), an index of the 3 patient-reported RA Core Data Set measures.

Methods: Patients seen from 1990-2006 had scores for MDHAQ-FN, PN, and ESR available from each visit; PTGL and the capacity to score RAPID3 was introduced in 1996. Adequate responders were defined as having no treatment with a biologic agent, while incomplete

responders were defined as having treatment with a biologic agent months to years after initiation of MTX. The mean interval from MTX initiation to a biologic agent was 2.6 years, 5.4 years before 1999, and 1.6 years after 1999. Mean and median measures at MTX initiation were compared to values at initiation of a biologic agent in incomplete responders, and to values 2.6 years after initiation of MTX in adequate responders who never were treated with a biologic agent. The proportion of patients with normal or abnormal values was also computed, defined as: ESR □28 mm/h; MDHAQ-FN >2 (after conversion to 0-10 scale from 0-3); PN and PTGL >2 (0-10 scale), and RAPID3 >6 (0-30 scale). A "RAPID3-estimate" without PTGL (correlated with RAPID3 at r □0.9) was used to assess patients seen prior to 1996. RAPID3 severity categories are high >12, moderate 6.1-12, low 3.1-6, and remission □3.

Results: Median baseline values in 63 patients who had adequate responses to MTX and never took a biologic agent were: 25 mm/h for ESR, 2.3 for MDHAQ-FN, 4.1 for PN, 4.2 for PTGL, and 10.6 (moderate/high severity) for RAPID3 (0-30 scale). Overall, 46%, 53%, 73%, 75% and 76% had "abnormal" values for these 5 measures, respectively, at initiation of MTX. At follow-up of these patients, improvement was seen with values of 16 mm/h for ESR, 1.0 for MDHAQ-FN, 1.4 for PN, 0.9 for PTGL, and 3.6 for RAPID3 (indicating low severity/remission). Improvement in each measure was 33%, 56%, 66%, 79% and 66%, respectively, over the mean of 2.6 years since initiation of MTX. In 30 incomplete responders, mean baseline values were somewhat higher than in those who ultimately were adequate responders to MTX, including ESR of 28 mm/h, MDHAQ-FN 3.2, PN 5.2, PTGL 5.5 and RAPID3 score of 14.9 (high severity). However, at initiation of a biologic agent at a mean 2.6 years later, mean values were improved only for ESR, by 36%, with poorer status MDHAQ-FN of -3%, PN of -31%, PTGL unchanged, and RAPID3 of -9%, with a median of 14.9, indicating high severity.

63 patients MTX-only: Adequate responses – no biological agents					
	MTX start		Follow-up mean 2.6 years later		
	Median	% abnormal	Median	% abnormal	% improvement
ESR (mm/h)	24	46%	16	22%	33%
MDHAQ-FN (0-10)	2.3	53%	1.0	40%	56%
Pain (0-10)	4.1	73%	1.4	44%	66%
PTGL (0-10)	4.2	75%	0.9	35%	79%
RAPID3 (0-30)	10.6	76%	3.6	39%	66%
30 patients biologic agents: Incomplete response to MTX with addition of biologic					
	MTX start		Biologic start mean 2.6 years later		
	Median	% abnormal	Median	% abnormal	% improvement
ESR (mm/h)	28	50%	18	40%	36%
MDHAQ-FN (0-10)	3.2	63%	3.3	77%	-3%
Pain (0-10)	5.2	90%	6.8	83%	-31%
PTGL (0-10)	5.5	96%	5.5	87%	0
RAPID3 (0-30)	14.9	88%	16.2	87%	-9%

Conclusion: Adequate or incomplete responses to MTX can be documented effectively with quantitative RAPID3 collected in routine clinical care. MDHAQ-FN, pain, PTGL and RAPID3 are more likely to document adequate vs incomplete responses than ESR.

Disclosure: T. Pincus, None; **C. J. Swearingen**, None.

1628

Hydroxychloroquine Use: Significant Improvement of Lipid Profile in Rheumatoid Arthritis Patients. Stephanie Morris[1], Jennifer Sartorius[2], Lester Kirchner[2], Eric D. Newman[1], M. C. Wasko[3] and Androniki Bili[1], [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Medical Center, Danville, [3]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Purpose: Cardiovascular disease (CVD) is the leading cause of mortality in patients with rheumatoid arthritis (RA). Both traditional and nontraditional risk factors contribute to atherogenesis. Disease modifying-therapies that also improve metabolic risk factors for CVD, such as type 2 diabetes mellitus (T2DM) and dyslipidemia are desired. In a recent study, hydroxychloroquine (HCQ) use was associated with

reduction in T2DM risk. This study used an electronic health record (EHR) to determine if HCQ use was associated with an improvement in lipid levels in a large population-based cohort of RA patients.

Method: Patients diagnosed with RA from September 2000-February 2008 (ICD-9 code 714.0 at ≥2 office visits with a rheumatologist) were identified through the EHR (n= 2093). 1,078 patients did not have available lipid profiles after RA diagnosis and were excluded. Information on demographics, medical history, body mass index (BMI; kg/m^2), lab measures, and medications were collected at office visits. 1,015 patients had repeated post-RA lipid measurements, resulting in 4,408 lipid-level results. Each patient's post-RA diagnosis HCQ usage status was evaluated at each lipid measurement. Potential risk and protective factors for dyslipidemia were controlled for in the time-varying, random effects regression models for the following lipids: low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol, and triglycerides. The time in years from each patient's RA diagnosis date to each lipid result date was calculated and included in all models. Nonlinear time trends and interactions between HCQ and time were checked for all models.

Results: Patients were 70% female, 98% Caucasian, with median age of 65 y and body mass index (BMI) 29.5 kg/m^2. Rheumatoid factor (RF) (22% known) and anti-cyclic citrullinated peptide (anti-CCP) (17% known) antibodies were positive in 66% and 42%, respectively. Of the 1,015 patients that were included in the analysis, 236 (23%) were ever on HCQ. The median levels of individual lipids according to years post-RA diagnosis by HCQ use are shown in Table 1. In the regression models, after adjusting for demographic features, BMI, sedimentation rate, RF, anti-CCP, T2DM, hypertension, use of steroids, NSAIDs, anti-TNF agents, methotrexate, and lipid-lowering medications, HCQ use was associated with the following average changes in lipids over time: LDL – decrease of 8.40 mg/dl ($p<0.001$), total cholesterol – decrease of 8.49 mg/dl ($p<0.001$), triglycerides – decrease of 11.49 mg/dl ($p=0.023$), and HDL – increase of 1.97 mg/dl ($p=0.005$). These effects were found to be constant over time.

Conclusion: Use of HCQ in this RA cohort was independently associated with a significantly improved lipid profile over time with significant average decreases in total cholesterol, LDL, triglycerides, and increase in HDL. Considering these results, its safety profile, and low cost, HCQ remains a valuable initial or adjunct therapy in this high CVD risk patient population.

Table 1. Lipid Results over Time since RA Diagnosis by HCQ Medication Status (n=4,406)

Lipid	HCQ Status	Years since RA diagnosis to lipid result		
		0-3 (n=2389)	>3-6 (n=1779)	>6 (n=230)
LDL (mg/dl)	No (n=3501)	106 (83-132)	102 (80-126)	98 (72-123)
	Yes (n=661)	102 (79-126)	90 (72-111)	72 (57-93)
HDL (mg/dl)	No (n=3296)	52 (43-63)	50 (41-62)	46 (39-56)
	Yes (n=616)	59 (44-64)	57 (48-68)	60 (54-70)
Total Cholesterol (mg/dl)	No (n=3359)	192 (165-223)	187 (162-214)	183 (150-213)
	Yes (n=636)	188 (162-212)	176 (158-210)	158 (132-190)
Triglyceride (mg/dl)	No (n=3288)	146 (108-211)	145 (107-207)	148 (93-214)
	Yes (n=599)	140 (101-192)	113 (84-163)	84 (56-122)

n: number of individual lipid values from the 1,016 patients
Numbers are: Median (Interquartile Range)

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Decrease in the Ratio of Small Dense LDL to LDL in the RA Patients Treated with Anti-TNF-α Agents. Sachiko Onishi[1], Taku Yoshio[1], Takao Nagashima[1], Shoji Yamazaki[2], Masahiro Iwamoto[1] and Seiji Minota[1], [1]Jichi Medical University, Shimotsuke, Japan, [2]Jichi Medical University Hospital, Shimotsuke, Japan

Purpose: The mortality among patients with rheumatoid arthritis (RA) is higher than that among the healthy population. This increased mortality is largely associated with the complication of cardiovascular disease (CVD). Recently, small dense LDLs (sdLDLs) were reported to contribute to the risk for CVD, even when the total plasma LDL levels are not elevated. RA patients are also reported to have significantly increased sdLDL levels. Anti-TNF-α agents may improve the survival of RA patients; therefore, we examined the lipid profiles including sdLDL levels in RA patients who were treated with anti-TNF-α agents.

Method: 24 and 26 RA patients treated with infliximab and etanercept, respectively, were incluced in this study.Plasma samples were collected at the baseline (before drug initiation at week 0) and at 2 and 6 months and 1 year. The response to these agents was evaluated on the basis of the changes in the C-reactive protein (CRP) levels and the DAS28-CRP score. Serum lipid profiles were assessed using a high-sensitivity lipoprotein-profiling system with high-performance liquid chromatography.

Results: Both agents significantly decreased the DAS28 score, number of tender and swollen joints, global health scores, and CRP levels. The plasma levels of total cholesterol (TC), LDL-cholesterol, and HDL-cholesterol (HDL-C) significantly increased, but the atherogenic index, which was calculated as (TC – HDL-C)/HDL-C, did not change. Although the plasma sdLDL levels significantly increased, the ratio of sdLDL to LDL decreased from 35.3% to 27.6% (p=0.0006).

Conclusion: Anti-TNF-α agents may have beneficial effects by decreasing the sdLDL-to-LDL ratio, and may contribute to the improved mortality of RA patients.

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1630

Plasma Myeloperoxidase Activity Is Increased in Patients with RA Compared to Healthy Controls and Is Associated with Abnormal Anti-Inflammatory Function of High Density Lipoprotein. Christina Charles-Schoeman[1], Yuen Yin Lee[1], Sogol Amjadi[1], Maureen A. McMahon[2], Harold E. Paulus[1] and Srinivasa T. Reddy[1], [1]David Geffen School of Medicine at UCLA, Los Angeles, CA, [2]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: We have previously shown that abnormal anti-inflammatory function of high density lipoprotein (HDL) in RA patients is associated with high levels of systemic inflammation and an altered HDL-associated protein cargo. Myeloperoxidase (MPO) is a heme peroxidase abundant in activated neutrophils which has been shown to inhibit HDL function by oxidatively modifying apolipoprotein A-1 (apoA-1). Systemic MPO levels predict the presence and extent of coronary artery disease in the general population. The current work investigates whether plasma MPO activity is increased in RA patients compared to healthy controls, and whether higher MPO activity is associated with worse anti-inflammatory function of HDL in patients with RA.

Methods: 40 patients with RA were compared with 40 age and sex matched healthy controls. Plasma MPO activity was assessed by a commercially available colorimetric assay which uses a polyclonal antibody specific for human MPO. HDL's anti-inflammatory function was assessed by a previously published cell free assay which assesses the ability of patient HDL to inhibit oxidation of a stock LDL. Plasma levels of ApoA1 were assessed by standard ELISA and paraoxanase-1 (PON-1) activity was measured by a previously described arylesterase assay.

Results: Patient characteristics are described in the table below. Plasma MPO activity was higher in RA patients compared to healthy controls and was significantly correlated with HDL function in patients with RA (r = 0.41/p=0.009); higher plasma MPO activity was associated with worse HDL anti-inflammatory function as measured by the HDL inflammatory index (HII). Both MPO activity and HDL function were significantly correlated with RA disease activity measured by the DAS28 (r = 0.45 and 0.42 respectively, p values<0.008). Higher RA disease activity was associated with higher MPO activity and worse HDL function. The activity of PON-1, an anti-oxidant enzyme associated with HDL, was lower in RA patients compared to healthy controls (p=0.03). There were no significant differences in quantitative HDL, LDL, or ApoA-1 levels between the two groups.

Group	HII	Age (yrs)	F (%)	HSCRP (mg/L)	ESR (mm/h)	HDL (mg/dL)	LDL (mg/dL)	ApoA-1 (ug/ml)	MPO (ng/ml)	PON (mOD/min)
RA	0.84± 0.87*	56 ± 12	85	5.7 ± 8.7*	28 ± 26*	60 ± 20	103 ± 37	209 ± 109	31.7 ± 24.5*	3.9± 1.2*
Control	0.32± 0.19	52 ± 13	80	1.8 ± 2.5	14 ± 10	59 ± 18	114± 35	190 ±	20.5 ± 15.3	5.0± 2.1

								77		

F=Female; HII=HDL Inflammatory Index; *p value < 0.05 compared to controls.

Conclusion: Plasma MPO activity is increased in RA patients compared to healthy controls and is associated with abnormal HDL anti-inflammatory function and increased disease activity. Oxidative modification of HDL by MPO may provide another mechanism by which active RA increases cardiovascular morbidity and mortality.

Disclosure: C. Charles-Schoeman, Amgen, 2 ; **Y. Y. Lee**, None; **S. Amjadi**, None; **M. A. McMahon**, None; **H. E. Paulus**, Amgen, 5 ; **S. T. Reddy**, Bruin Pharma, 9 .

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Short Term Treatment of High Dose Glucocorticoids Improves the Lipid Profile in Early Rheumatoid Arthritis. Debby den Uyl[1], Hennie G. Raterman[2], Willem F. Lems[1], Ben A.C. Dijkmans[3], Alexandre E. Voskuyl[2], Dirkjan van Schaardenburg[4], Pit J.S.M. Kerstens[4] and Michael T. Nurmohamed[4], [1]VU University medical center, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands, [4]Jan van Breemen Institute, Amsterdam, Netherlands

Early rheumatoid arthritis (RA) is associated with an unfavourable lipid profile, i.e. a lower total cholesterol (TC) and an even more depressed high density lipoprotein (HDL)-cholesterol, resulting in a higher atherogenic index. Treatment with low-dose glucocorticoids might have favourable effects on the lipid profile.

Purpose: To compare the early changes of medium and high dose prednisone on lipid profile in patients with early rheumatoid arthritis.

Method: In this ongoing study, patients were randomised for treatment with COBRA (incl. 60mg prednisone, tapered in 6 weeks to 7,5 mg/day) or COBRA-light (incl. 30mg prednisone, tapered in 9 weeks to 7,5 mg/day). At baseline and after 2, 4 and 8 weeks of treatment, fasting blood samples were collected and C-reactive protein (CRP), TC, HDL-cholesterol, LDL-cholesterol and triglycerides were determined. The atherogenic index (AI) was assessed (TC/HDL). General estimation equations (GEEs) was used to analyse the time course of lipid levels and to investigate the influence of disease activity (i.e. CRP).

Results: 49 patients had complete 8 week follow-up data available for analysis. There were no differences in baseline characteristics between patients treated with COBRA and COBRA-light. During treatment CRP decreased rapidly. After 8 weeks an increase in lipids was seen; median TC by 15%, median HDL by 29%, median LDL by 10%, median triglycerides by 18%, while the median AI decreased by 12%. GEE analyses revealed that TC, HDL, LDL, triglycerides and the AI changed significantly over time, which remained significant after adjusting for age, gender and CRP. Table lipide profile during treatment

	Baseline	2 weeks	4 weeks	8 weeks
Median CRP, mg/l (IQR)	16 (6,5-44,5)	2,00 (1,0-4,25)*	2,75 (1,25-7,75)*	3,00 (2,0-11,5)*
Median total cholesterol, mmol/l (IQR)	4,7 (4-5,75)	5,2 (4,65-6,25)*	5,6 (5,0-6,4)*	5,5 (5,05-6,45)#
Median HDL-cholesterol, mmol/l (IQR)	1,29 (1,05-1,56)	1,79 (1,36-2,04)*	1,88 (1,46-2,36)*	1,69 (1,39-1,96)*
Median LDL-cholesterol, mmol/l (IQR)	2,89 (2,05-3,59)	2,92 (3,36-3,72)	3,01 (2,6-3,7)#	3,29 (2,63-4,04)*
Median Triglycerides, mmol/l (IQR)	1,14 (0,9-1,42)	1,27 (1,11-1,67)#	1,25 (1,0-1,71)#	1,39 (0,99-1,75)#
Median atherogenic index (IQR)	3,57 (2,82-4,82)	3,13 (2,54-3,88)*	2,90 (2,36-3,59)*	3,29 (2,65-4,14)*

*p<0.001 compared with baseline, # p<0,05 compared with baseline (Wilxocon test)

Conclusion: In our preliminary analyses, aggressive treatment with high dose corticosteroids in early RA rapidly increases total cholesterol and HDL-cholesterol and decreases the atherogenic index. Whether or not this results this favourable effect on the cardiovascular risk is ultimately offset by other side effects of corticosteroid use remains to be established.

Disclosure: D. den Uyl, None; **H. G. Raterman**, None; **W. F. Lems**, None; **B. A. C. Dijkmans**, None; **A. E. Voskuyl**, None; **D. van Schaardenburg**, None; **P. J. S. M. Kerstens**, None; **M. T. Nurmohamed**, None.

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The ApoB/ApoA1 Ratio Predicts Future Cardiovascular Events in Patients with Rheumatoid Arthritis. Solveig Wållberg-Jonsson, Maria Öhman and Solbritt Rantapää-Dahlqvist, Norrland University Hospital, Umeå, Sweden

Purpose: Patients with rheumatoid arthritis (RA) have increased mortality and morbidity due to cardiovascular disease (CVD). The reasons are not fully understood. A high apolipoproteinB (apoB)/apolipoproteinA1(apoA1) ratio has been shown to predict CV event in the general population. ApoA1 has, besides anti-atherogenic effects, been suggested to have anti-inflammatory properties (1). In a previous study we found a relationship between apoB and IL-1RA in RA (2). In the present study, we evaluated the importance of apoA1, apoB and the apoB/apoA1 ratio in addition to lipids, hemostatic variables and measures of disease activity, for the development of CVE during 18 years, in patients with RA.

Method: 74 patients (61 f/13 m, mean age 63.6 years, disease duration 22.1 years) with seropositive, inflammatory active RA (mean ESR 47.9±2.4mm/h) were investigated in a previous study (3) consecutively regarding apolipoproteins (apoA1, apoB), hemostatic factors (von Willebrand factor (vWF), tissue plasminogen activator (tPA) and its inhibitor (PAI-1), lipid levels (cholesterol, triglycerides (TG)), lipoprotein(a) and markers of inflammation (ESR, CRP, haptoglobin). A survey of all hospital records was made after 18 years with registrations of: First CVE during follow-up (myocardial infarction, stroke/TIA, deep vein thrombosis/pulmonary embolism, CABG), traditional CV risk factors (hypertension, smoking, diabetes mellitus, previous CVD) extraarticular disease and pharmacological treatment (DMARDs, corticosteroids).

Results: In all 33 patients had a new CVE during the follow-up. These patients had significantly higher apoB/apoA1 ratio (0.96 vs 0.81, $p<0.05$), significantly higher levels of TG (1.5 vs 1.2 mmol/l, $p<0.05$) and ESR (54.3 vs 42.6, $p<0.05$) and of vWF (212.6 vs 143.9%, $p<0.001$) than patients without development of CVE. No correlation was found between the apoB/apoA1 ratio and inflammatory variables. ApoA1 corrrelated weakly and inversely with haptoglobin ($p=0.056$). In multiple cox regression, the apoB/apoA1 ratio could predict a new CVE significantly besides vWF, ESR and previous CVD.

Conclusion: The apoB/apoA1 ratio was associated with the development of CVE during 18 years follow up in patients with active RA. There was no obvious association between apolipoproteins and inflammation. References: (1)Breshnihan B et al. Arthritis Res Ther 2004, (2) Ljung et al. Clin Exp Rheumatol 2007, (3) Wållberg-Jonsson et al. J Rheumatol 2000

Disclosure: S. Wållberg-Jonsson, None; **M. Öhman**, None; **S. Rantapää-Dahlqvist**, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis Treatment: Targeting TNF, B Cells and Co-Stimulatory Pathways

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Seven Year Follow-up of Infliximab (IFX) in Rheumatoid Arthritis (RA) Patients : Attrrition, Safety and Efficacy. Bert Vander Cruyssen[1], Patrick Durez[2], Rene Westhovens[3] and Filip De Keyser[4], [1]University Hospital Ghent, Ghent, Belgium, [2]Univ Catholique de Louvain, Brussels, Belgium, [3]University Hosp KU Leuven, Leuven, [4]Ghent University Hospital, Gent, Belgium

Purpose: This study is based on the results from a Belgian expanded access program in which patients with active refractory and erosive rheumatoid arthritis (RA) were treated with intravenous infusions of infliximab (IFX) in combination with methotrexate (MTX). The objective of this study was to evaluate the continuation rate of IFX and its clinical effect over a 7 year period.

Method: Between 2000 and 2001, 511 patients were enrolled in the program (ref). Patients had a median disease duration of 10 years and had failed an average of 3.9 disease modifying anti-rheumatic drugs (DMARDs), including MTX. Patients were treated with IFX at week 0, 2, 6 and every 8 weeks thereafter with a standard dose of 3 mg/kg, although dose increases with 1 extra vial (100 mg) were possible. After 7

years, apart from routine clinical follow-up, treating rheumatologists were asked to complete a questionnaire designed specifically for the present study to evaluate the current therapy with IFX, the level of disease activity (DAS28) and functional disability (HAQ) and to document the reasons for IFX discontinuation

Results: After 7 years, available data were obtained from 441 of 511 patients: 4 patients did not initiate treatment, 17 patients died and 49 patients were lost to follow-up. Of the remaining 441 patients, 160 were still on IFX-treatment at year 7. The major reasons for IFX discontinuation included lack of efficacy (104 patients), adverse events (107 patients) and elective change of therapy (70 patients).

50% of treatment discontinuation for safety reasons occurred during the first two years. There were no unexpected long-term safety issues. In contrast, discontinuation due to inefficacy, showed a more constant discontinuation rate over the 7 years. Mean DAS of patients still under treatment with IFX decreased from 5.7 (SE = 0.1) at baseline to 3.0 (SE= 0.12) at year 4 and remained that low till year 7. Mean HAQ was 1.07 (SE=0.06) at year 7. Low disease activity (defined as DAS28 < 3.2) was present in 60.9% of patients and 45.5% achieved remission (DAS28<2.6).

Conclusion: This study describes the 7 year follow-up of a cohort of 511 RA patients with longstanding, refractory disease who were treated with IFX in combination with MTX. After 7 years patients who continue to receive IFX experience sustained clinical benefit, as reflected by the maintenance of low DAS and HAQ scores. Long term treatment with IFX appears to be safe : safety issues occurred in a higher frequency during the first 2 years of IFX treatment.

Disclosure: B. Vander Cruyssen, None; **P. Durez**, None; **R. Westhovens**, None; **F. De Keyser**, None.

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Sustainability of Clinical Remission with Etanercept and Methotrexate, in Combination or as Monotherapy, in Early Active Rheumatoid Arthritis. Paul Emery[1], Patrick Durez[2], T.K. Kvien[3], Nicholas Manolios[4], Ronald Pedersen[5], Debbie H. Robertson[6], Joanne Foehl[5], Andrew S. Koenig[5] and Bruce Freundlich[5], [1]Leeds General Infirmary, Leeds, United Kingdom, [2]Univ Catholique de Louvain, Brussels, Belgium, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Westmead Hospital, Westmead, Australia, [5]Wyeth Research, Collegeville, PA, [6]Wyeth Pharmaceuticals, Collegeville, PA

Purpose: This subanalysis was done to identify those subjects with active early RA from the COMET trial who sustained remission from Week 24 to Week 104 while receiving etanercept (ETN) + methotrexate (MTX), ETN monotherapy, or MTX monotherapy.

Method: This double-blind, randomized study consists of two 12-month periods. In Year 1, subjects received either combination therapy or MTX monotherapy. In Year 2, a subset of the combination group dropped MTX and a subset of the MTX monotherapy group added ETN. Eligible subjects had disease duration ≤2 years, were MTX-naïve, and had active RA (DAS28 ≥3.2) with either elevated ESR (≥28 mm/hr) or CRP levels (≥20 mg/L). MTX was titrated from Wk 4 to a maximum of 20 mg/wk at Wk 8. An observed analysis of remission (DAS28 <2.6) was performed at Wk 24; from these responders; sustained remission was assessed by completers' analysis at Wks 52 and 104. Additionally, for subjects who completed Wk 24, evaluation of sustained remission at Wk 52 and again at Wk 104 was performed using nonresponder imputation (NRI).

Results: Of 542 subjects enrolled, 446 subjects were evaluated for remission at Wk 24; 348 of these completed 104 wks of study. 165/446 (37%) fulfilled the remission criteria at Wk 24; 112/165 (68%) of the Wk 24 responders sustained remission to Wk 52, and 90/165 (55%) sustained remission to Wk 104. The numbers of completers were less in groups MTX/ETN+MTX and MTX/MTX due to the larger dropout rate in the MTX monotherapy group *v* combination therapy group over 2 years. Remission by treatment arm is given in the Table. Results of the NRI analysis at Wks 52 and 104 were similar to those of the observed analysis.

Conclusion: In this population of early, active RA subjects, sustained remission from 24 to 52 to 104 wks was achieved in a greater percentage of subjects who were treated with combination therapy for at least 1 yr compared with those who received MTX monotherapy throughout the entire 2-yr study. Sustained remission in early RA subjects who achieve remission at 24 wks appears to be an attainable goal, based on both completers' and NRI analysis in this study. Further research on sustained radiographic nonprogression and normal function in this subset of Wk 24 responders is indicated.

N (%) of Subjects by Treatment Group, Completers' Analysis of Sustained Remission to Wk 104 Based on Wk 24 Responders

	ETN+MTX/ETN+MTX	ETN+MTX/ETN	MTX/ETN+MTX	MTX/MTX
Week 24	52/113 (46%)	54/122 (44%)	29/107 (27%)	30/104 (29%)
Week 52	37/48 (77%)	41/48 (85%)	20/26 (77%)	14/27 (52%)
Week 104	32/46 (70%)	32/41 (78%)	17/22 (77%)	9/23 (39%)

Disclosure: P. Emery, Wyeth Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5, Wyeth Pharmaceuticals, 8, Wyeth Pharmaceuticals, 9 ; **P. Durez**, Wyeth Pharmaceuticals, 9 ; **T. K. Kvien**, Wyeth Pharmaceuticals, 9 ; **N. Manolios**, Wyeth Pharmaceuticals, 9 ; **R. Pedersen**, Wyeth Pharmaceuticals, 1, Wyeth Pharmaceuticals, 3 ; **D. H. Robertson**, Wyeth Pharmaceuticals, 3, Wyeth Pharmaceuticals, 1 ; **J. Foehl**, Wyeth Pharmaceuticals, 1, Wyeth Pharmaceuticals, 3 ; **A. S. Koenig**, Wyeth Pharmaceuticals, 3, Wyeth Pharmaceuticals, 1 ; **B. Freundlich**, Wyeth Pharmaceuticals, 1, Wyeth Pharmaceuticals, 3 .

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Disease Remission, Radiographic Non-Progression and Normalization of Function Achieved at Year 1 Are Sustained Long-Term in a Majority of Patients: 5-Year Outcomes with Abatacept in Biologic-Naïve Patients. R. Westhovens[1], M. Dougados[2], S. Hall[3], D. Moniz Reed[4], J. C. Becker[4], J. Teng[4] and J. M. Kremer[5], [1]UZ Gasthuisberg, KU Leuven, Leuven, Belgium, [2]Hospital Cochin, Descartes Univ, Paris, France, [3]Cabrini Medical Center, Malvern, Victoria, Australia, [4]Bristol-Myers Squibb, Princeton, NJ, [5]Albany Medical College, Albany, NY

Purpose: EULAR/ACR recommendations stress the importance of reporting the sustainability of treatment outcomes[1]. In the AIM (Abatacept in Inadequate responders to MTX) trial at the group level, improvements in signs/symptoms were sustained or further improved in the majority of abatacept patients (pts) over 5 yrs[2]. Here, we present pt-level analyses examining sustained reduction of disease activity, inhibition of X-ray progression, and improvements in physical function and health-related quality of life (HRQoL) with abatacept from Yr 1 up to Yr 5.

Methods: These as-observed analyses were based on pts randomized to abatacept who entered the long-term extension (LTE). For Low Disease Activity State (LDAS; DAS28 □3.2), DAS28 (CRP)-defined remission (DAS28 <2.6), X-ray non-progression (change in Genant-modified Sharp total score □0), Health Assessment Questionnaire-Disability Index (HAQ-DI) normalization (≤0.5) and Short Form-36 mental and physical component scores (PCS and MCS, respectively [≥50]), the proportions of patients sustaining responses from Yr 1 to Yrs 2, 3, 4 and 5 were assessed.

Results: Overall, 378 pts randomized to abatacept entered the LTE and were eligible for analysis; 46, 21, 22 and 23 pts discontinued in Yrs 2, 3, 4 and 5, respectively (in the LTE, 22 [5.8%] due to lack of efficacy and 37 [9.8%] due to adverse events). Disease activity was >5.1 at baseline (mean DAS28: 6.4 and mean HAQ-DI: 1.7). Sustainability of LDAS, DAS28-defined remission, normalization of HAQ-DI, X-ray non-progression, and PCS and MCS □50 are presented (Table).

Conclusion: In approximately 2/3 of pts randomized to abatacept in AIM, clinical remission, radiographic non-progression, and normalization of physical function and HRQoL were maintained over 5 yrs of abatacept treatment. These data suggest that abatacept can provide sustained disease modification and restore normal physical function in patients with RA.

References:
1. Aletaha D, et al. *Ann Rheum Dis* 2008;**67**:1360–4
2. Kremer JM, et al. *Ann Rheum Dis* 2009:**68**;444. Abstract FRI0263

	Pts sustaining their response from Yr 1, %			
	Yr 1 to 2	**Yr 1 to 3**	**Yr 1 to 4**	**Yr 1 to 5**
LDAS (DAS28 □3.2)	79.9 (123/154)	74.5 (108/145)	75.5 (105/139)	71.2 (94/132)
DAS28-defined remission (DAS28 <2.6)	68.2 (60/88)	72.1 (62/86)	72.3 (60/83)	60.3 (47/78)
HAQ-DI normalization (□0.5)	76.6 (82/107)	73.5 (72/98)	77.2 (71/92)	74.2 (66/89)
X-ray non-progressors (total score change □0)	79.7 (137/172)	74.6 (129/173)	72.0 (121/168)	71.9 (100/139)
PCS □50	66.7 (38/57)	65.4 (34/52)	72.5 (37/51)	77.1 (37/48)
MCS □50	76.0 (133/175)	79.3 (130/164)	71.9 (110/153)	71.2 (104/146)

Disclosure: R. Westhovens, UCB, 2, Bristol-Myers Squibb, 5, Schering-Plough, 5, Centocor, Inc., 5, Roche, 5, Bristol-Myers Squibb, 8 ; **M. Dougados**, Bristol-Myers Squibb, Abbott, Roche, Wyeth, 8, Bristol-Myers Squibb, Abbott, Wyeth, Centocor, Roche, Schering Plough, 5, Bristol-Myers Squibb, Abbott, Wyeth, Centocor, Roche, Schering Plough, 2 ; **S. Hall**, None; **D. Moniz Reed**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **J. C. Becker**, Bristol-Myers Squibb, 9, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **J. Teng**, Bristol-Myers Squibb, 3 ; **J. M. Kremer**, Abbot, Amgen, Bristol-Myers Squibb, Centocor, Genentech, Merck, Pfizer, Roche, 2, Abbot, Amgen, Bristol-Myers Squibb, Centocor, Genentech, Merck, Pfizer, Roche, 5 .

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Safety of Infliximab in the Patients with Rheumatoid Arthritis and History of Hepatitis B Virus Infection. Xuewu Zhang, Xia Liu, Yuan An, Xu Liu and Zhanguo Li, Bejing Univ People's Hosp, Beijing, China

Purpose: The biological agents such as infliximab are becoming more and more important in treating autoimmune diseases (eg. RA). There was also evidence to prove the significant efficacy of these drugs in inhibiting disease progression and bone destruction. However, the risk of inducing or exacerbating infections by these agents has also been increasingly recognized. Furthermore, there were existing debates over whether to use these agents in patients with chronic HBV infection history. To evaluate the safety of treatment with tumor necrosis factor α (TNF-α) monoclonal antibody (Infliximab) in patients with rheumatoid arthritis(RA) who had the normal liver function and pre-existent HBV infection.

Method: In this multicenter study, all 41 cases met the ACR 1987 revised criteria for RA, including 7 men and 34 women, with average age of 46.2±2.72 years old and average disease course of 11.40±5.72 years. In patients were assessed for serological status(anti-HBC, anti-HbsAb, anti-HBeAb). Four of them were only anti-HBC (+); fifteen were anti-HBsAb (+), anti-HBeAb (+) and anti-HBc (+); six were anti-HBsAb (+) and anti-HBeAb (+); forteen were anti-HBsAb(+) and anti-HBc(+), two were anti-HBeAb (+) and anti-HBc (+); but normal for both alanine aminotransferase(ALT) and aspartate aminotransferase (AST), except one patient with positive anti-HBc showed elevated ALT before administration of infliximab (60U/L). All patients received intravenous Infliximab therapy with doses of 3 mg/kg at weeks 0, 2, 6, 14 and 22 respectively after testing liver function, Creatinine, T-bilirubin, leukocyte and platelet. All the above parameters were reexamined at week 26.

Results: 40 out of 41 patients, the ALT, AST, T-bilirubin, Creatinine, leukocyte and platelet were in the normal range, with no significant differences between HBV positive and HBV negative groups. As for the patients with elevated ALT and AST levels after the infusion, there was no statistically significant difference between the HBV patients and the non-HBV patients.

Conclusion: In RA patients with preexisting HBV infections, liver function abnormality were not observed during the Infliximab administration, as long as HBsAg was negative with normal liver function at baseline.

Disclosure: X. Zhang, Xian-Janssen Pharmaceutical LTD , 2 ; **X. Liu**, Xian-Janssen Pharmaceutical LTD , 2 ; **Y. An**, Xian-Janssen Pharmaceutical LTD , 2 ; **X. Liu**, Xian-Janssen Pharmaceutical LTD , 2 ; **Z. Li**, Xian-Janssen Pharmaceutical LTD , 2 .

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An Increasing Proportion of Patients Achieve a Low Disease Activity State or Remission When Switched From Infliximab to Abatacept Regardless of Initial Infliximab Treatment Response: Results From the ATTEST Trial. M. Schiff[1], M. W. Keiserman[2], D. Moniz Reed[3], M. Le Bars[4], J.-C. Becker[3], C. Zhao[3] and M. Dougados[5], [1]Univ of Colorado School of Medicine, Denver, CO, [2]Pontificial Catholic Univ, Porto Alegre, Brazil, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Bristol-Myers Squibb, Rueil-Malmaison, France, [5]Hospital Cochin, Descartes Univ, Paris, France

Purpose: Clinical trials of patients (pts) who switch between biologic therapies generally assess pts after failure of a prior biologic. At Yr 1 of ATTEST[1] (Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating RA) all pts received abatacept regardless of clinical response or original treatment group. Uniquely, this trial design allowed the assessment of pts who switched from infliximab to abatacept after 1 yr, with various degrees of prior response to infliximab.

Methods: Biologic-naïve pts with RA were randomized to abatacept (~10 mg/kg every 4 weeks), placebo or infliximab (3 mg/kg every 8 weeks), plus MTX. At Mth 6 and Yr 1, placebo- and infliximab-treated pts, respectively, were switched to abatacept. Disease activity was assessed by DAS28 (CRP). High, Moderate and Low Disease Activity States (HDAS, MDAS and LDAS, respectively), and remission were defined as >5.1, >3.2–5.1, □2.6–3.2 and <2.6, respectively. These as-observed *post-hoc* analyses include pts originally randomized to infliximab who entered the long-term extension and had data available at Yr 1 and Yr 2. Data from the original abatacept group are not presented here.

Results: In total, 136 infliximab-treated pts entered the LTE and were eligible for inclusion in these analyses. After switching from infliximab to abatacept at Yr 1, 81.5% (22/27) of pts who were in HDAS improved their disease state by Yr 2. The majority of pts in MDAS and LDAS after 1 yr of infliximab treatment improved their disease state after receiving abatacept for 1 yr (at Yr 2, 60.7 [34/56] and 64.3% [9/14] had improved, respectively). Of the pts who had achieved remission after 1 yr of infliximab treatment, 71.4% maintained their disease state at Yr 2 after switching to abatacept.

Disease status at Yr 1		**Shift in DAS28 status from Yr 1 to Yr 2 after switching from infliximab to abatacept, %**			
	Total, % (n)	**HDAS**	**MDAS***	**LDAS†**	**Remission**
HDAS	21.6 (27)	18.5	55.6	7.4	18.5
MDAS*	44.8 (56)	5.4	33.9	33.9	26.8
LDAS†	11.2 (14)	0	21.4	14.3	64.3
Remission	22.4 (28)	3.6	14.3	10.7	71.4

*But not LDAS/remission; †But not remission

Conclusion: In these *post-hoc* analyses, despite 1 yr of infliximab treatment, the majority of patients improved/maintained their disease status after switching to abatacept regardless of their initial infliximab treatment response. In total, an additional 30% of patients achieved remission after switching to abatacept.

Reference:
1. Schiff M, et al. *Ann Rheum Dis* 2007;**8**:1096–103.

Disclosure: M. Schiff, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 9 ; **M. W. Keiserman**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 9 ; **D. Moniz Reed**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **M. Le Bars**, Bristol-Myers Squibb, 9, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **J. -. C. Becker**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 9 ; **C. Zhao**, Bristol-Myers Squibb, 3 ; **M. Dougados**, Bristol-Myers Squibb, Abbott, Wyeth, Centocor , Roche and Schering Plough, 2, Bristol-Myers Squibb, Abbott, Wyeth, Centocor , Roche and Schering Plough, 5, Bristol-Myers Squibb, Abbott, Roche and Wyeth, 8 .

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An Open-Label, Prospective Study (SUNDIAL) of the Safety of Rituximab in Combination with Disease-Modifying Anti-Rheumatic Drugs in Patients with Active Rheumatoid Arthritis (SUNDIAL). James Loveless[1], E. Olech[2], Charles H. Pritchard[3], A. Chai[4], Ariella Kelman[4] and Micki Klearman[4], [1]Intermountain Orthopedics, Boise, ID, [2]OK Med Research Foundation, Oklahoma City, OK, [3]Willow Grove, PA, [4]Genentech, South San Francisco, CA

Purpose: Rituximab (RTX) in combination with methotrexate (MTX) is an effective and well-tolerated therapy in patients with rheumatoid arthritis (RA). The primary objective is to characterize the safety of RTX when used in combination with DMARDs other than MTX alone in patients with RA.

Method: SUNDIAL is an open-label study of patients with RA who have had an inadequate response to ≥1 DMARD. Patients aged 18-80 years who received a DMARD regimen for ≥12 weeks received RTX (1000 mg IV x 2) plus their current DMARD therapy. Combinations included MTX (7.5–25 mg/wk), leflunomide (10–20 mg/day), sulfasalazine (1000–3000 mg/day), azathioprine (50-200 mg/day), and/or hydroxychloroquine (200–400 mg/day). Other than MTX alone or in combination with LEF, all other DMARDs (or combinations thereof) were permitted. The primary endpoint was the proportion of patients developing a serious adverse event (SAE) within 24 weeks after receiving one course of RTX.

Results: Of 401 patients, the mean (SD) age was 53.3 (11.3) years with 75% Caucasian and 75% female. The mean (SD) RA disease duration was 10.0 (9.3) years and 54% had previously used biologics. Mean (SD) baseline disease activity (DAS28) was 6.2 (1.1). A total of 27 (6.7%) withdrew before/at Week 24, with 3 (0.7%) due to AE. Patients received 15 different DMARD combinations; 54% were on a MTX-containing regimen; 59% were on 2 or more DMARDs. Overall, 26 SAEs in 24 (6.0%) patients were observed for an event rate (95% CI) of 14.39 events/100 pt-yr (9.9, 21.1) (Table). The most common SAEs included chest pain (n=3), pneumonia (n=2), and cellulitis (n=2). One patient died from malignant lung neoplasm considered unrelated to RTX treatment. Seven (1.7%) patients experienced 7 serious infections for a rate (95% CI) of 3.8 events/100 pt-yr (1.8, 8.1). Infusion reactions occurred in 59 (14.7%) patients after the 1st infusion and in 25 (6.2%) patients after the 2nd infusion. One serious infusion reaction (chest pain) occurred with the 1st infusion and none after the 2nd infusion. At Week 24, 15 (3.7%) patients were HACA+. HACA positivity was not related to choice of concomitant DMARD.

Conclusion: The overall safety of a single course of rituximab in combination with multiple non-biologic DMARDs did not reveal any new or unexpected safety concerns. Safety data was consistent with that previously reported for RTX + MTX (Cohen et al; A&R, 2006,54:2793-806, Emery et al; A&R, 2006, 54:1390-400). Further follow-up is ongoing.

Table Safety summary

	No. (%) Patients (N=401)	**No. of Events**	**Event Rate / 100 Patient-years (95% CI) (Total Patient Years =180.6)**
Any SAE	24 (6.0%)	26	14.39 (9.9-21.1)
Any Infection	164 (40.9%)	269	148.9 (132.1-167.8)
Serious Infections*	7 (1.7%)	7	3.8 (1.8-8.1)

*SAE or any infection that was treated with an IV antibiotic

Disclosure: J. Loveless, Genentech Inc, 2 ; **E. Olech**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5, Genentech and Biogen IDEC Inc., 8, UCB, 2, UCB, 5, UCB, 8, Abbott Laboratories, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 8, Centocor, Inc., 2, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Crescendo, 2, Bristol-Myers Squibb, 5 ; **C. H. Pritchard**, Genentech , 9 ; **A. Chai**, Genentech and Biogen IDEC Inc., 3 ; **A. Kelman**, Genentech , 3 ; **M. Klearman**, Genentech , 3 .

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Decreased Expression of the Endothelial Cell Activation Marker HLA-DQ in Skeletal Muscle After Three Months of Adalimumab Treatment in Patients with Rheumatoid Arthritis. Ulf Bergström[1], Cecilia Grundtman[2], Ingrid E. Lundberg[2], Lennart Jacobsson[1], Käth Nilsson[1] and Carl Turesson[1], [1]Malmö University Hospital, Malmö, Sweden, [2]Karolinska Institutet, Stockholm, Sweden

Purpose: Treatment with tumor necrosis factor (TNF) inhibitors for severe rheumatoid arthritis (RA) has been associated with a decreased risk of cardiovascular (CV) disease in observational studies. Previous findings indicate that systemic endothelial expression of HLA-DQ and interleukin-1α (IL-1α) is increased in patients with severe extra-articular RA, indicating that they may be markers of systemic inflammation and increased CV risk. The aim of this study was to investigate these markers in muscle biopsies from patients treated with adalimumab.

Methods: 14 patients with active RA [11 females, 3 males; mean age 63.7 years; median (M) disease duration 9.0 years, interquartile range (IQR) 2.6-11.6; 11 (78 %) RF positive] were started on treatment with adalimumab 40 mg subcutaneously every two weeks. The patients had not been treated with adalimumab previously and had not received other TNF inhibitors within the last three months or glucocorticoids (> 20 mg prednisolon/day) within the last two weeks. 8 patients were on methotrexate (mean dose 18.75 mg/week, range 10-25). None of the patients had clinical signs of myopathy. A structured clinical evaluation was performed and muscle biopsies were taken from the tibial anterior muscle at inclusion and after 3 months treatment. Signs of inflammation and muscle fiber degeneration were evaluated in hematoxylin-eosin stained sections. IL-1α, HLA-DQ, and CD31 expression was investigated by immunohistochemistry. Quantification was based on the total tissue area and performed using blinded digital computerized image analysis.

Results: Disease activity decreased (DAS28 mean 5.6 vs 4.1; p=0.007) from baseline to the 3 month evaluation. A good or moderate EULAR response was seen in 8/14 patients. Muscle biopsies from 11 patients (6 responders/5 non-responders) were available for evaluation. There were no major inflammatory infiltrates within the skeletal muscle. HLA-DQ was mainly expressed in endothelial cells in capillaries, whereas IL-1α was mainly seen in larger vessels. Staining for HLA-DQ decreased significantly after treatment (M 0.073 %, IQR 0.027-0.121 vs M 0.023%, IQR 0.009-0.040; p=0.041). There was a similar trend for IL-1α (mean difference 0.049 %; 95 % confidence interval -0.069-0.168). Capillary density, measured as the proportion of CD31 positive area, also tended to be reduced after adalimumab treatment. Decreased expression of IL-1α was seen in EULAR good/moderate responders, but not in non-responders (mean difference 0.114% vs -0.028%). HLA-DQ expression decreased in both groups (median difference 0.046 % vs 0.036 %).

Conclusion: Treatment with adalimumab was associated with decreased expression of endothelial markers previously associated with severe systemic inflammation in RA. Our findings could indicate reduced systemic endothelial activation in patients treated with anti-TNF drugs, which may contribute to a lower risk of CV co-morbidity.

Disclosure: U. Bergström, None; **C. Grundtman**, None; **I. E. Lundberg**, None; **L. Jacobsson**, None; **K. Nilsson**, None; **C. Turesson**, Abbott Laboratories, 2 .

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Reduced Incidence of Infusion Reactions to Infliximab in Patients Pre-Medicated with Acetaminophen. D. Choquette[1], William G. Bensen[2] and Francois Nantel[3], [1]Montreal, QC, [2]McMaster University, Hamilton, ON, [3]Kirkland, QC, QC

Purpose: Patients treated with infliximab (IFX) sometimes receive premedication in order to reduce the risk of infusion reactions (IR). These pre-medications including anti-histamines, intravenous steroids or acetaminophen either alone or in combination, are sometimes used by physicians in order to prevent the development of allergic reactions.

Methods: RemiTRAC Infusion is an observational registry among 12 Canadian sites where patients receiving IFX are followed prospectively to document pre-medication use, adverse events, infusion reactions and the management of IRs. Seven hundred and fourteen subjects have been enrolled since the registry inception in 2005. A total of 7598 infusions were recorded with a mean of 10.6 ± 7.3 infusions per patient representing 935 years of exposure. The majority of patients (n=366 or 51%) had rheumatoid arthritis whereas 17% (n=120) had ankylosing spondylitis and 6% (n=42) had psoriatic arthritis. The remaining patients were treated for gastroenterological or dermatological diseases.

Results: Among all infusions recorded (n=7598), 161 infusions resulted in an IR (2.1%) and almost all IRs were mild to moderate in severity (151/161 or 94%). Anti-histamines were used in 1591 infusions (21%) compared to steroids and acetaminophen which were used in 1488 (20%) and 1694 (22%) of infusions, respectively. The table below shows the effect of pre-medication on the incidence of IRs.

Premedication	Number of IRs (IR/# of infusions)	Incidence of IRs (%)	p value (vs None group)
None	87/4532	1.9 %	-
Any	74/3066	2.4 %	<0.05
Anti-histamines (AH)	57/1591	3.6%	<0.0001
Steroids (Ster)	45/1488	3.0 %	<0.001
Acetaminophen (Acet)	17/1694	1.0 %	<0.0001
AH alone	19/468	4.0 %	<0.01
Ster alone	10/503	2.0 %	n.s.
Acet alone	4/676	0.6 %	<0.0001
AH + Ster	24/292	8.2 %	<0.0001
Ster + Acet	1/211	0.5 %	<0.05
AH + Acet	4/337	1.2 %	n.s.
AH + Ster + Acet	5/416	1.2 %	n.s.

There was a significantly higher incidence of IRs in infusions that were pre-medicated compared to infusions that had no pre-medication (2.4 % vs 1.9%, $p<0.05$). Most of this increase could be accounted to anti-histamine pre-medication, either alone or in combination with steroids. This elevation in IRs under anti-histamine or steroid pre-medication may result from a selection bias since patients who experienced an IR were more likely to receive pre-medication and to have a subsequent IR. Surprisingly though, infusions in patients receiving acetaminophen, either alone or in combination with steroids, had a significantly reduced incidence of IR.

Conclusion: In a "real-life setting" registry, acetaminophen appears to be a premedication that significantly reduces the incidence of infusion reactions to IFX. The mechanism is unknown but suggests that most infusion reactions might be non-immunogenic in nature.

Disclosure: D. Choquette, None; **W. G. Bensen**, Schering Canada, 5 ; **F. Nantel**, Schering-Plough, 3 .

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Serum Markers Associated with Clinical Response in Methotrexate Naïve Rheumatoid Arthritis Patients Treated with Golimumab, A Human Anti-TNF α Monoclonal Antibody. C. Wagner[1], M. U. Rahman[2], E. C. Hsia[2], P. Emery[3], R.M. Fleischmann[4], M. Mack[1], M. Elashoff[5] and S. Visvanathan[1], [1]Centocor R&D, Inc, Malvern, PA, [2]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [3]University of Leeds, Leeds, United Kingdom, [4]Metroplex Clinical Research Center, Dallas, TX, [5]Elashoff Consulting, Redwood City, CA

Purpose: To identify serum markers that are associated with clinical response in MTX naïve rheumatoid arthritis (RA) patients treated with golimumab (GLM) with and without MTX.

Methods: In the GO-BEFORE study, 637 patients were randomly assigned in a 1:1:1:1 ratio to receive Placebo (PBO) + Methotrexate (MTX): GLM 100 mg+ PBO: GLM 50 mg + MTX:GLM 100 mg + MTX. Sera were collected at wks 0, 4 and 24 from all patients for testing CRP and a subset of 100 - 150 patients for testing select markers of inflammation and bone/cartilage metabolism and protein profiling using multi-analyte profiles. The % change from baseline in markers was compared between the PBO+MTX and combined GLM+MTX group (50 mg + 100 mg) and the GLM+PBO group using ANOVA on the van der Waerden normal scores and t tests. For CRP analyses all GLM groups combined were compared with PBO+MTX. Logistic regression models were used to test for the association of serum markers with clinical endpoints.

Results: Select acute phase (CRP, serum amyloid P) and inflammatory (ICAM-1, MIP1b, MMP-3, ENRAGE and IL-16) markers were significantly decreased at wk 4 and /or wk 24 after treatment with GLM + MTX as compared to PBO + MTX ($p<0.01$). Similar markers

were modulated by GLM + PBO treatment. Further, in the GLM + MTX group, baseline levels of CD40L and osteocalcin were associated (OR 2.04, 2.39, p<0.02) with ACR 50 response at wk 24 and baseline deoxypyridinoline and α1anti-trypsin levels were associated with ACR 20 response (OR 8.74, 0.226, p <0.05) at wk 24. Decreases in MIP1α and ICAM-1 levels at wk 4 were associated with ACR 20 (OR 0.226, 0.113; p<0.05) and DAS 28 (OR 0.231, 0.037; p<0.05) responses at wk 24 in GLM + MTX treated patients. Significant changes in select markers were observed in ACR 20/ACR 50/DAS28 responders as compared to non-responders at wk 24 – including MMP-3, von Willebrand factor, haptoglobin, fibrinogen, ICAM-1, IL-16, serum amyloid P, VEGF, CRP, ENRAGE, IL-6 and bone alkaline phosphatase. A 50% decrease from baseline in CRP level at week 4 was associated with ACR 20 response in patients receiving GLM+/-MTX (OR=1.82; p<0.0026,) but not in patients receiving PBO+MTX (OR=1.42; p=0.367).

Conclusion: Baseline levels and changes at wk 4 in levels of select markers were associated with clinical response to GLM + MTX or GLM + PBO treatment at wk 24 in MTX naïve RA patients. Select markers were significantly changed in clinical responders as compared with non-responders. A 50% decrease from baseline in CRP level 4 wks after first dose of GLM were associated with clinical response at wk 24.

Disclosure: C. Wagner, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor, Inc., 3 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **P. Emery**, Centocor Research and Development, Inc, 9 ; **R. M. Fleischmann**, Centocor Research and Development, Inc ; **M. Mack**, Centocor Research and Development, Inc, 3 ; **M. Elashoff**, Centocor, Inc., 5 ; **S. Visvanathan**, Centocor, Inc., 3 .

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Golimumab Is Efficacious in Anti-TNF Agent Experienced Patients with Active RA Regardless of Type of Agent or Reason for Discontinuation of Prior Anti-TNF Agent: Results From the GO-AFTER Study. J. S. Smolen[1], M. K. Doyle[2], Jonathan Kay[3], E. L. Matteson[4], R. Landewé[5], E. C. Hsia[2], Y. Zhou[6] and M. U. Rahman[2], [1]Medical Univ Vienna, Vienna, Austria, [2]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [3]University of Massachusetts Memorial Medical Center, Worcester, MA, [4]Mayo Clinic, Rochester, MN, [5]U Hosp Maastricht, Maastricht, Netherlands, [6]Centocor R&D, Inc, Malvern, PA

Purpose: To assess efficacy and tolerance of GLM by type, number, or reasons for d/c of prior anti-TNF agent(s).

Method: Pts could have received 1 or more anti-TNF agent(s) and may have d/c'd for any reason(s). Concomitant use of DMARDs, methotrexate, sulfasalazine and hydroxychloroquine was allowed. Subgroup analyses were performed for ACR20 response at wk14 across DMARD use, number of prior anti-TNFs and reason for d/c of prior TNF inhibitor, such that odds ratios and 95% confidence intervals were calculated comparing the proportions of ACR20 responders at wk14 in the combined GLM vs PBO groups. We also examined the subset of pts receiving a single prior anti-TNF agent to assess the impact of the type of TNF inhibitor (P75 receptor-fusion protein vs mAb) on GLM response. Overall incidences of AEs were determined for pt subgroups defined by type and number of prior anti-TNF agents.

Results: Assessed by the proportion of pts achieving an ACR20 at wk14, GLM was effective vs PBO in RA pts previously receiving anti-TNF therapy irrespective of DMARD use (ACR20 40% vs 18%, p<0.001) or the reason for d/c of prior anti-TNF (due to efficacy: 39% vs 18%, p<0.001; all other: 34% vs 20%, p=0.027). This was not the case for pts not receiving DMARDs at baseline (29% vs 19%, p=0.184). A consistent treatment benefit of GLM vs PBO was observed for prior use of 1 (39% vs 20%, p=0.002) or 2 (38% vs 16%, p=0.014) anti-TNF agents; too few pts received 3 prior agents for a meaningful comparison. GLM was also effective regardless of a P75 receptor-fusion protein vs mAb agent. 80% of these subgroup pts received prior anti-TNF therapy for ≥12wks, and 49% received anti-TNF therapy for ≥48wks. The occurrence of AEs through wk24 was similar among pts previously receiving only adalimumab (76.3%), etanercept (70.4%), and infliximab (78.1%), as well as among pts who received 1, 2, & 3 prior anti-TNF agents in both PBO- (74.4%, 77.3%, 71.4%, resp) and GLM- (74.6%, 70.4%, 77.3%, resp.) treated pts. **Table. GLM efficacy among pts who received only 1 prior anti-TNF and discontinued anti-TNF therapy for any reason, by prior anti-TNF agent**

	Adalimumab only	**Etanercept only**	**Infliximab only**
No. of pts	59	81	73
Week 14			
ACR20	19 (32.2%)	33 (40.7%)	30 (41.1%)
ACR50	10 (16.9%)	13 (16.0%)	16 (21.9%)

DAS-CRP responder	33 (55.9%)	45 (55.6%)	49 (67.1%)
DAS-ESR responder	26 (44.1%)	44 (54.3%)	49 (67.1%)
DAS-CRP remission	11 (18.6%)	13 (16.0%)	16 (21.9%)
DAS-ESR remission	5 (8.5%)	9 (11.1%)	8 (11.0%)
Week 24			
ACR20	20 (33.9%)	36 (44.4%)	35 (47.9%)
ACR50	10 (16.9%)	18 (22.2%)	15 (20.5%)
DAS-CRP responder	26 (44.1%)	47 (58.0%)	50 (68.5%)
DAS-ESR responder	25 (42.4%)	46 (56.8%)	48 (65.8%)
DAS-CRP remission	12 (20.3%)	13 (16.0%)	17 (23.3%)
DAS-ESR remission	8 (13.6%)	10 (12.3%)	14 (19.2%)

Conclusion: These data suggest that pts previously treated with adalimumab, etanercept or infliximab responded to, and tolerated GLM regardless of the type, number (although too few pts received 3 prior anti-TNF agents to provide conclusive results) or reason for d/c of prior anti-TNF therapy.

Disclosure: J. S. Smolen, Centocor Research and Development, Inc, 9 ; **M. K. Doyle**, Centocor Research and Development, Inc, 3 ; **J. Kay**, Centocor Research and Development, Inc, 9 ; **E. L. Matteson**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, Centocor Research and Development, Inc ; **R. Landewé**, Centocor Research and Development, Inc, 9 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **Y. Zhou**, Centocor Research and Development, Inc., 3 ; **M. U. Rahman**, Centocor, Inc., 3 .

1665

Rituximab Improved Physical Function and Quality of Life in Patients with Early Rheumatoid Arthritis Who Were Naive to Methotrexate (IMAGE study). W. Rigby[1], G. Ferraccioli[2], M. Greenwald[3], B. Zazueta-Montiel[4], R. Fleischmann[5], S. Wassenberg[6], A. Jahreis[7], L. Burke[8], C. Mela[9] and A. Chen[7], [1]Dartmouth, Lebanon, NH, [2]Catholic Univ of the Sacred Heart, Rome, Italy, [3]Desert Medical Advances, Palm Desert, CA, [4]Inst, Mexico City, Mexico, [5]Univ of Texas, Dallas, TX, [6]Evangelisches Fachkrankenhaus, Ratingen, Germany, [7]Genentech, South San Francisco, CA, [8]Roche, Welwyn Garden City, United Kingdom, [9]Roche, United Kingdom

Purpose: To assess the effect of rituximab (RTX) with methotrexate (MTX) compared to MTX alone on patient (pt) reported outcomes (PRO) of physical function and health-related quality of life (HRQoL) in pts with early active rheumatoid arthritis (RA) who had not previously been treated with MTX.

Methods: Inclusion criteria included no prior exposure to MTX, disease duration ≥8 weeks and ≤4 yrs, swollen and tender joint count ≥8; C-reactive protein ≥1.0 mg/dL, and positive RF or erosive damage. Pts were randomized to placebo + MTX, RTX (2 x 500mg) + MTX, or RTX (2 x 1000 mg) + MTX. MTX in all groups was initiated at 7.5mg/wk and titrated to 20 mg/wk by Wk 8. RTX was given by IV infusion on Days 1 and 15. At Wk 24, pts with DAS28-ESR≥2.6 received a second RTX course. Those with DAS28-ESR<2.6 were retreated if their DAS28-ESR increased to ≥2.6. Physical function was assessed using the Heath Assessment Questionnaire Disability Index (HAQ-DI), and HRQoL with the SF-36, with assessments taken at regular intervals up to 52 wks (primary analysis time point). Minimally clinically important differences (MCID) for HAQ-DI, SF-36 physical component summary (PCS), and mental component summary (MCS) were defined as ≥0.22, >5.42, and >6.33 respectively. Additional PRO endpoints included fatigue (FACIT score), patient global score of disease, and pain (determined using 100mm visual analogue scales).

Results: 748 randomized pts received study drug (intent-to-treat population). Pt characteristics were balanced at baseline with mean RA duration of 0.9 yrs and high disease activity (DAS28 >7). At Wk 52, both RTX groups showed significant changes in HAQ-DI ($p<0.0001$) and also higher proportions of pts achieving MCID compared to MTX alone. Mean change in SF-36 PCS was significant for both dose

groups but only RTX (2 x 1000mg) had higher proportions of pts achieving MCID. Change in SF-36 MCS did not achieve significance for either dose group, however higher proportions of pts receiving RTX (2 x 1000mg) achieved the MCID. Fatigue, pain, and pts global disease score were significantly reduced in RTX groups compared to MTX alone.

Conclusion: RTX at either 2 x 500mg or 2 x 1000mg with MTX was associated with significant improvement in physical function and QoL outcomes compared to MTX alone; however, only RTX 2x1000mg had higher proportions of pts achieving the MCID for SF-36 MCS and PCS.

Table. IMAGE PRO Measures at 52 Weeks

	Placebo + MTX	**RTX (2 x 500mg) + MTX**	**RTX (2 x 1000mg) + MTX**
Mean Change in			
	n=248	n=247	n=249
HAQ-DI	-0.628	-0.905***	-0.916***
	n=244	n=239	n=245
FACIT	6.830	9.362*	10.282***
	n=239	n=236	n=242
PCS	7.237	10.073**	10.763***
	n=239	n=236	n=242
MCS	4.848	6.181	6.662
% Pts with change			
HAQ-DI≥0.22	77.4%	87.4%*	87.6%*
FACIT	67.6%	72.8%	75.1%*
PCS change >5.42	63.2%	69.9%	76.4%**
MCS change >6.33	49.0%	50.8%	57.0%*

**p<0.05, **p<0.001, ***p<0.0001 compared to MTX alone.*

Disclosure: W. Rigby, Roche Pharmaceuticals, 5, Genentech and Biogen IDEC Inc., 5, Genentech and Biogern IDEC Inc., 8 ; **G. Ferraccioli**, None; **M. Greenwald**, Genentech , 2 ; **B. Zazueta-Montiel**, None; **R. Fleischmann**, Amgen, Wyeth, Centocor, Abbott, Genentech, biogen Idec, UCB, Regeneron, Lilly, Pfizer, 2, Amgen, Wyeth, Centocor, Abbott, Genentech, Biogen Idec, UCB, AstraZeneca, Pfizer, Lilly, 5, Amegen, Wyeth, Abbott, 8 ; **S. Wassenberg**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8 ; **A. Jahreis**, Genentech , 1, Genentech , 3 ; **L. Burke**, Roche Pharmaceuticals, 3 ; **C. Mela**, Roche Pharmaceuticals, 3 ; **A. Chen**, Genentech , 1, Genentech , 3 .

1666

The Efficacy of Certolizumab Pegol Added to Methotrexate Is Sustained Over 2 Years in the Treatment of Rheumatoid Arthritis.

Edward C. Keystone[1], Roy Fleischmann[2], J. S. Smolen[3], V. Strand[4], Robert Landewé[5], Bernard Combe[6], Philip J. Mease[7], Zainab Ansari[8], Niti Goel[9] and Désirée M.F.M. van der Heijde[10], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]University of Texas Southwest Medical Center at Dallas, Dallas, TX, [3]Medical University of Vienna, Vienna, Austria, [4]Stanford University, Palo Alto, CA, [5]University Hospital Maastricht, Maastricht, Netherlands, [6]Lapeyronie hospital, Montpellier, [7]Seattle Rheumatology, Seattle, WA, [8]UCB, Slough, United Kingdom, [9]Smyrna, GA, [10]Leiden University Medical Center, Leiden, Netherlands

Purpose: Certolizumab pegol (CZP) 200 or 400 mg Q2W + MTX was found to be significantly more effective than placebo + MTX in the treatment of rheumatoid arthritis (RA) over 1 year (RAPID 1 trial).(1) Here we present the efficacy of CZP + MTX over 2 years.

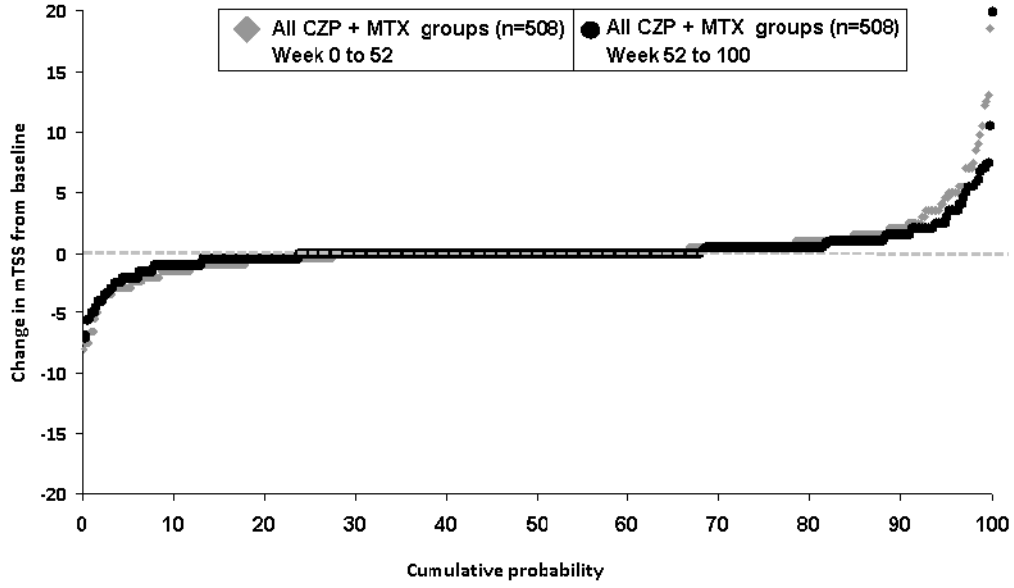
Methods: Patients who completed 52 wks of double-blind treatment in RAPID 1 (completers) or who withdrew at Wk 16 due to lack of ACR20 response (at Wks 12 and 14; withdrawers) were eligible to enter open-label (OL) treatment with CZP 400 mg Q2W + MTX. This analysis focuses on CZP completers who entered the OL study (n=243 for CZP 200 mg + MTX and n=265 for CZP 400 mg + MTX) and had 100 wks (2 years) of CZP exposure from BL. Efficacy analyses included degree of radiographic progression (assessed in hands, wrists, and feet using change from BL in modified total Sharp score [mTSS; linear extrapolation]), ACR20/50/70 responses (nonresponder imputation), ACR core component scores, and DAS28(ESR) (LOCF). Treatment-emergent AEs (AEs after first study drug administration) were assessed in all patients at each visit.

Results: Of all RAPID 1 CZP completers, 95.8% reconsented and received OL CZP. Of these, 91.1% were in the OL study through at least 100 wks. Inhibition of radiographic joint damage progression was maintained throughout 2 years in this patient population (Figure). At 2 years, 72.4% and 77.3% of completers originally in the CZP 200 mg and 400 mg groups were classified as non-progressors (mTSS change ≤0.5 units from BL). ACR20/50/70 responses were also sustained throughout 2 years in CZP completers, as were improvements in ACR core component scores and DAS28 (not shown). Comparable benefits were observed in patients who received CZP 200 or 400 mg through Year 1 based on their original randomization. There were no new safety signals in the OL study.

Conclusion: CZP + MTX provided sustained, long-term inhibition of the progression of radiographic joint damage and improvements in RA signs and symptoms, with no new safety signals, over 2 years.

Reference: 1.Keystone EC, et al. Arthritis Rheum 2008;58:3319-29.

Figure. Cumulative Probability of Change from Baseline in mTSS from Weeks 0-52 and Weeks 52-100



Disclosure: E. C. Keystone, UCB, 5, UCB, 2, UCB, 8 ; **R. Fleischmann**, UCB, 5 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **V. Strand**, UCB, 5, UCB, 8 ; **R. Landewé**, UCB, 5 ; **B. Combe**, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Schering, 5, UCB, 5, Merck Pharmaceuticals, 5 ; **P. J. Mease**, UCB, 5 ; **Z. Ansari**, UCB, 3 ; **N. Goel**, UCB, 3 ; **D. M. F. M. van der Heijde**, UCB, 5, UCB, 2 .

1667

Golimumab in Rheumatoid Arthritis: GO-FORWARD Week 52 Results. Edward C. Keystone[1], M.C. Genovese[2], L. Klareskog[3], E. C. Hsia[4], S. Hall[5], P.C. Miranda[6], J. Pazdur[7], S.C. Bae[8], W. Palmer[9], S. Xu[10] and M. U. Rahman[4], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Stanford U, Palo Alto, CA, [3]Karolinska Institutet, Stockholm, Sweden, [4]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [5]Cabrini Medical Center, Malvern, Victoria, Australia, [6]U of Chile/Hosp San Juan de Dios, Santiago, Chile, [7]Instytut Reumatologii, Warszawa, Poland, [8]Hanyang University Hospital, Seoul, South Korea, [9]Westroads Medical group, Omaha, NE, [10]Centocor R&D, Inc, Malvern, PA

Purpose: To assess efficacy and safety of golimumab (GLM) + MTX vs MTX alone in pts with active RA despite MTX.

Methods: Pts were randomized to PBO + MTX (Grp 1), GLM 100mg + PBO (Grp 2), GLM 50mg + MTX (Grp 3), and GLM 100mg + MTX (Grp 4). At wk16, pts in Grps 1, 2, and 3 who had < 20% improvement in tender and swollen joints entered early escape (EE). At wk 24, pts in Grp 1 crossed over to 50mg + MTX.

Results: Through wk52, 4%, 10%, 12%, and 16% had a sustained clinical response (ACR70 at 6 consecutive monthly visits) in Grps 1 to 4, respectively; sustained remission (DAS 28 remission at 6 consecutive monthly visits), was observed in 15%, 16%, 29%, and 28% of the respective grps. SAEs were reported in 11%, 17%, 14%, and 18% of pts in Grps 1 through 4, respectively & 2%, 6%, 2%, and 8%, respectively, had serious infections. Between wks 24 and 52, 9 serious infections were reported: 2 in Grp1 EE, 4 in Grp2, 1 in Grp3, & 2 in Grp4. During this period 4 pts had malignancies: squamous and basal cell cancer (Grp1), basal cell cancer (Grp4), breast cancer (Grp 3 and Grp 4).

Conclusion: GLM efficacy was sustained through 1 yr with many pts achieving sustained remission and sustained clinical response. More pts in grps receiving GLM 100 mg had SAEs and serious infections.

Table: Wk 52 Efficacy*

Assessment	Group 1: PBO + MTX (wk 0-20) and GLM 50 mg + MTX (wk 24-52)	Group 2: GLM 100 mg + PBO	Group 3: GLM 50 mg+MTX	Group 4: GLM 100 mg+MTX
Pts randomized	133	133	89	89
ACR 20	58(43.6%) [81(62.3%)]	60(45.1%) [75(59.1%)]	57(64.0%) [63(70.8%)]	52(58.4%) [51(58.0%)]
ACR 50	37(27.8%) [49(37.7%)]	38(28.6%) [45(35.2%)]	39(43.8%) [41(46.1%)]	40(44.9%) [39(44.3%)]
ACR 70	20(15.0%) [27(20.8%)]	23(17.3%) [27(21.1%)]	22(24.7%) [22(24.7%)]	30(33.7%) [29(33.0%)]
DAS28 (CRP) Good and Mod responders	72(54.1%) [95(73.1%)]	81(60.9%) [101(78.9%)]	65(73.0%) [76(86.4%)]	70(78.7%) [68(78.2%)]
DAS28 (CRP) remission (< 2.6)	42(31.6%) [52(40.0%)]	38(28.6%) [50(39.1%)]	43(48.3%) [47(53.4%)]	41(46.1%) [41(47.1%)]
Proportion of pts achieving HAQ improvement >0.25	58(43.6%) [69(53.1%)]	57(42.9%) [67(52.3%)]	50(56.2%) [55(61.8%)]	60(67.4%) [59(67.0%)]

* Intent-To-Treat (ITT) analysis [observed analysis] for pts achieving the respective endpoint. ITT analyses considered pts entering EE as non-responders (NR) for categorical endpoints and used LOCF for continuous endpoints. Observed analyses (for Grps 1-3) included all the rules of the ITT analysis except pts entering EE were not considered NR automatically and the observed data at wk 52 were used. Pts

entering EE at wk16 received: Grp 1 (42 pts) GLM 50mg +MTX, Grp 2 (36 pts) GLM 100 mg+MTX, & Grp 3 (15 pts) GLM 100mg+MTX. No EE for Grp4.

Disclosure: E. C. Keystone, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, 5, Centocor Research and Development, Inc, Centocor Research and Development, Inc, 8 ; **M. C. Genovese**, Centocor Research and Development, Inc, Centocor Research and Development, Inc, 5 ; **L. Klareskog**, Centocor Research and Development, Inc ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **S. Hall**, Centocor Research and Development, Inc, 9 ; **P. C. Miranda**, Centocor Research and Development, Inc, 9 ; **J. Pazdur**, Centocor Research and Development, Inc, 9 ; **S. C. Bae**, Centocor Research and Development, Inc, 9 ; **W. Palmer**, Centocor Research and Development, Inc, 9 ; **S. Xu**, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 .

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Incremental Benefit of Open-Label Certolizumab Pegol + MTX in Rheumatoid Arthritis (RA) Patients Following Double-Blind Placebo + MTX Treatment out to 2 Years. Bernard Combe[1], Sergio Schwartzman[2], Elena Massarotti[3], Edward C. Keystone[4], Kristel Luijtens[5] and Désirée M.F.M. van der Heijde[6], [1]Immuno-Rheumatologie, Hospital Lapeyronie, Montpellier, France, [2]Hosp for Special Surgery, New York, NY, [3]Brigham & Women's Hosp, Boston, MA, [4]Professor of Medicine/University of Toronto, Toronto, ON, [5]UCB, Brussels, Belgium, [6]Leiden University Medical Center, Leiden, Netherlands

Purpose: Certolizumab pegol (CZP) 200 or 400 mg Q2W + MTX significantly reduced the signs and symptoms of RA when compared with placebo (PBO) + MTX (RAPID 1 trial).(1) Subjects treated with either PBO + MTX or CZP + MTX who completed the 1-year study were allowed to enter open-label (OL) treatment with CZP 400 mg Q2W + MTX. Data is presented on efficacy outcomes in subjects who completed 1 year of PBO + MTX followed by 1 year of OL CZP + MTX for a total of 2 years' treatment.

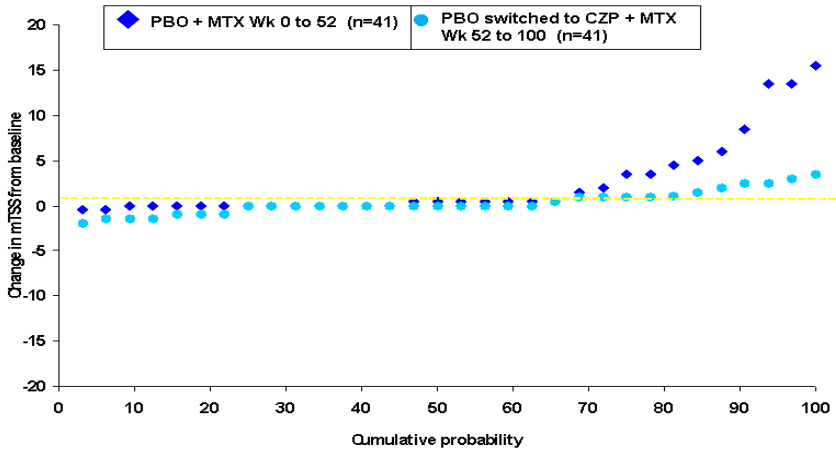
Methods: Analyses included ACR20/50/70 response rates (nonresponder imputation), changes from BL in DAS28(ESR) and HAQ-DI scores (LOCF), and assessment of the inhibition of joint damage progression (assessed in hands, wrists, and feet using change in the modified total Sharp score [mTSS; linear extrapolation] from RAPID 1 BL) over 2 years.

Results: 95.3% of the PBO + MTX RAPID 1 completers reconsented and received OL CZP + MTX. Of these, 92.7% completed a total of 100 wks of observation (52 wks PBO + MTX /48 wks OL + MTX). This patient population experienced reductions in RA signs and symptoms at Wk 52 (ACR20/50/70 responder rates were 63.4%; 39.0%; and 17.1%) that were sustained through to at least Wk 100. The change in mTSS for subjects treated with PBO + MTX was 2.5 U at Wk 52 compared with 2.8 U for subjects completing Wk 100, indicating marked inhibition of radiographic progression (change of only 0.3 from Wk 52 to Wk 100). This difference is demonstrated by the differences in the cumulative probability curves of change in mTSS during double-blind (Wks 0-52) and OL (Wks 52-100) treatment (Figure). Patients also experienced marked improvement in DAS28 and HAQ-DI scores upon switching from PBO + MTX to CZP + MTX that were sustained throughout year 2; changes from BL at Wk 100 were -3.3 and -0.73 for DAS28 and HAQ-DI, respectively.

Conclusion: Radiographic disease progression slowed upon initiation of OL CZP + MTX in subjects who completed 52 wks of double-blind treatment with PBO + MTX. These subjects also experienced sustained improvements in the signs and symptoms of RA throughout 2 years, including marked improvements in DAS28 and HAQ-DI scores upon switching to OL CZP treatment.

Reference: 1.Keystone EC, et al. Arthritis Rheum 2008;58:3319-29.

Figure. Cumulative probability of change in mTSS in PBO Completers Who Entered OL CZP Treatment



Disclosure: B. Combe, UCB, MSD, Roche, Schering,Wyeth, 2, UCB, Abbott, GSK, MSD, Roche, Schering,Wyeth, 5 ; **S. Schwartzman**, Abbott Immunology Pharmaceuticals, 9, Centocor, Inc., 9, Genentech and Biogen IDEC Inc., 9, UCB, 9 ; **E. Massarotti**, EMD Serono, 5, Merck Medco, 5, Pfizer Inc, 5, UCB, 5, Genentech , 5 ; **E. C. Keystone**, Abbott Laboratories, Amgen, AstraZeneca, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc, Novartis Pharmaceutical Corporation, Schering-Plough, UCB, Wyeth Pharmaceuticals, 2, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc., Genentech, Inc., GlaxoSmithKline, Schering-Plough, UCB, Wyeth Pharmaceuticals, 5, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Reserch and Development, Inc., Hoffmann-La Roche, Inc., Genentech, Inc., Schering-Plough, Wyeth Pharmaceuticals, 8 ; **K. Luijtens**, UCB, 3 ; **D. M. F. M. van der Heijde**, Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB, Wyeth, 5 .

1669

Golimumab in Rheumatoid Arthritis Patients Previously Treated with Anti-TNFα Agents (GO-AFTER Study): Week 52 Results. J. S. Smolen[1], Jonathan Kay[2], M. K. Doyle[3], R. Landewé[4], E. L. Matteson[5], J. Wollenhaupt[6], N. B. Gaylis[7], F. T. Murphy[8], J. Neal[9], Y. Zhou[10], S. Visvanathan[10], E. C. Hsia[3] and M. U. Rahman[3], [1]Medical Univ Vienna/Hietzing Hosp, Vienna, Austria, [2]U of Mass Med School, Worcester, MA, [3]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [4]University Hospital Maastricht, Maastricht, Netherlands, [5]Mayo Clinic, Rochester, MN, [6]Klinikum Eilbek, Hamburg, Germany, [7]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [8]Altoona Ctr for Clin Research, Duncansville, PA, [9]Arthritis Center of Lexington, Lexington, KY, [10]Centocor R&D, Inc, Malvern, PA

Purpose: To evaluate the efficacy and safety of golimumab (GLM) in patients (pts) with active rheumatoid arthritis (RA) previously treated with anti-TNFα agent(s).

Methods: Patients in the GO-AFTER study were randomized (1:1:1) to subcutaneous injections of PBO, GLM 50 mg or 100 mg q4wks. Pts could have received ≥1 anti-TNFα agent(s) and discontinued for any reason(s). Pts with <20% improvement in tender and swollen joint counts at wk 16 entered early escape (EE) in a double-blinded fashion: PBO group → GLM 50 mg q4wks, GLM 50 mg → GLM 100 mg q4wks, GLM 100 mg group remained on 100 mg q4wks. At wk 24, PBO pts crossed over to GLM 50 mg and the study was unblinded after the last pt completed the wk 24 visit, and pts on GLM 50 mg could escalate to 100 mg at physician discretion. Wk 24 data presented previously, data through wk 52 are now presented.

Results: The significant improvement in signs and symptoms of RA and physical function observed with GLM at wk 24, as assessed by American College of Rheumatology (ACR) response criteria, Disease Activity Score (DAS) response criteria, and the Health Assessment

Questionnaire (HAQ), was maintained through and at wk 52. In the table below, the 50 → 100 mg column includes pts from the GLM 50 mg group who met EE criteria at wk16 and pts from both PBO and GLM 50 mg groups who were receiving GLM 50 mg q4wks after wk 16 and dose escalated to GLM 100 mg q4wks at the discretion of the investigator after wk 24. These patients may have more refractory disease, but they also had a fairly good response after adjusting their dose of GLM.

Assessment	PBO→50 mg	50 mg only	50→100 mg	100 mg
No. patients	72	64	96	121
Week 52				
ACR 20	52.1%	62.5%	52.6%	60.5%
ACR 50	33.8%	40.6%	18.8%	31.7%
DAS28 responders*	.	.	.	.
CRP	72.1%	81.0%	68.1%	79.1%
ESR	70.4%	79.0%	63.0%	73.0%
HAQ (median improvement from baseline)	0.25	0.25	0.25	0.31
% improvement from baseline in:	.	.	.	.
No. swollen joints	70.0%	61.3%	55.6%	75.0%
No. tender joints	65.9%	81.3%	52.4%	66.7%

* DAS28 Responders (EULAR Moderate-Good)

Through wk 52, 75.6% and 76.4% of pts receiving GLM 50 and 100 mg, respectively, had ≥1 adverse event and 12.9% and 7.7%, respectively, had ≥1 serious adverse event. Serious infections were reported in 3.9% and 3.1%, and injection-site reactions were reported in 1.2% and 2.3%, of pts receiving GLM 50 and 100 mg, respectively.

Conclusion: The efficacy (signs/symptoms/physical function) of GLM was maintained through wk 52 in this population. The GLM safety profile was similar to that reported for other anti-TNFα agents.

Disclosure: J. S. Smolen, Centocor Research and Development, Inc ; **J. Kay**, Centocor Research and Development, Inc, 9 ; **M. K. Doyle**, Centocor Research and Development, Inc, 3 ; **R. Landewé**, Centocor Research and Development, Inc, 9 ; **E. L. Matteson**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, Centocor Research and Development, Inc ; **J. Wollenhaupt**, Centocor Research and Development, Inc , 9 ; **N. B. Gaylis**, Centocor Research and Development, Inc, 9 ; **F. T. Murphy**, Centocor Research and Development, Inc ; **J. Neal**, Centocor Research and Development, Inc, 9 ; **Y. Zhou**, Centocor Research and Development, Inc., 3 ; **S. Visvanathan**, Centocor Research and Development, Inc, 3 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 .

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Impact of Golimumab On Physical Function, Health-Related Quality of Life, Productivity and Employment in Rheumatoid Arthritis Patients: Week 52 Results From GO-FORWARD. M.C. Genovese[1], Edward C. Keystone[2], E. C. Hsia[3], J. Buchanan[4], L. Klareskog[5], F. T. Murphy[6], Z. Wu[7], S. Parasuraman[4] and M. U. Rahman[3], [1]Stanford U, Palo Alto, CA, [2]Professor of Medicine/University of Toronto, Toronto, ON, [3]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [4]Johnson and Johnson Pharmaceutical Services, Malvern, PA, [5]Karolinska Inst & Karolinska Hosp, Stockholm, Sweden, [6]Altoona Ctr for Clin Research, Duncansville, PA, [7]Centocor R&D, Inc, Malvern

Purpose: To evaluate impact of SC golimumab (GLM) on physical function, HRQoL and fatigue.

Methods: 444 pts with active RA (□ 4 TJC and □4 SJC) despite MTX were randomized to PBO+MTX, GLM 100 mg+PBO, GLM 50 mg+MTX, or GLM 100 mg+MTX q4 wks through wk48. At wk16, any pt with <20% improvement from baseline in SJC & TJC entered early escape (EE) in a double-blinded fashion such that PBO+MTX received GLM 50mg+MTX, MTX was added for GLM 100 mg+PBO,

and GLM 50 mg+MTX received GLM 100 mg+MTX; dosing for GLM 100 mg+MTX was unchanged. PBO+MTX crossed over to GLM 50 mg+MTX at wk24. Physical function was assessed using HAQ disability index and SF-36 PCS score. HRQoL was assessed using the PCS and MCS scores of the SF-36. Productivity was assessed on a 10-cm VAS. An ANOVA on van der Waerden normal scores was performed for between-group comparisons at wk24. At wk52, observed efficacy was summarized; no treatment grp comparisons were performed.

Results: Mean baseline HAQ scores indicated moderate functional impairment; PCS scores were lower than US population norm (50±10). GLM+MTX was significantly better than PBO+MTX in improving physical function, HRQoL, productivity, and time lost from work by pt (50 mg only) at wk24 ($p<0.05$). Through wk24, there were no statistically significant improvements in employability, time lost from work by caregiver or healthcare resource consumption. Improvements in HAQ, PCS, MCS, and productivity observed at wk24 were sustained/enhanced through wk52. By wk52, approx 75% of pts receiving GLM 50 or 100 mg+MTX achieved improvement in baseline HAQ ≥ 0.25 and mean changes in productivity ranged from -2.4 to -2.7 across GLM grps. Time lost from work by pts and caregivers decreased from wks24-52.

Conclusion: In pts with active RA despite MTX, GLM 50 mg or 100 mg q4wks + MTX improved physical function, HRQoL, and productivity.

Data are mean±SD or n(%)

	PBO + MTX	GLM 100 mg + PBO	GLM 50 mg + MTX	GLM 100 mg + MTX
Wk24, N	133	133	89	89
HAQ improvement	0.13±0.58	0.24±0.66	0.47 ± 0.55*	0.45±0.52*
HAQ ≥0.25 improvement	38.6%	45.3%	68.2%$^{++}$	72.1%$^{++}$
SF-36 PCS change	2.5±8.1	4.7±8.8	8.3±8.3*	7.0±7.8*
SF-36 MCS change	0.8±9.7	3.4±10.2†	1.8±10.9	4.3±10.7†
Productivity[b] change	-0.45±2.98	-1.08±3.04	-2.0±3.1*	-2.0±2.5*
Time lost from work by pt during past 4 wks (days)[c]	5.7±19.7	1.1±2.2	0.8±3.1†	5.8±12.2
Week 52, N[d]	-	97	74	89
HAQ improvement	-	0.49±0.66	0.61±0.64	0.51±0.56
HAQ ≥0.25 improvement	-	60.9%	76.8%	74.4%
SF-36 PCS change	-	7.2 ±9.7	8.9±9.1	9.5±9.0
SF-36 MCS change	-	3.4±10.2	3.7±9.4	5.5±11.2

*$p<0.001$, $^{\dagger}p<0.05$, $^{++}p<0.0001$

a Pts employable among those not employable due to RA at baseline

b Negative change= improvement

c Among randomized pts <65 yrs and employed full-time at baseline

d For GLM 100 mg+PBO and GLM 50 mg+MTX, includes pts who didn't enter EE. For GLM 100 mg+MTX, includes all randomized pts regardless of whether they entered EE. PBO+MTX pts crossed over to GLM 50mg+MTX at wk24.

Disclosure: M. C. Genovese, Centocor Research and Development, Inc, 9, Centocor Research and Development, Inc, 5 ; **E. C. Keystone**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, 5, Centocor Research and Development, Inc, 9, Centocor Research and Development, Inc, 8 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **J. Buchanan**, JJPS, LLC, 3 ; **L. Klareskog**, Centocor Research and Development, Inc, 9 ; **F. T. Murphy**, Centocor Research and Development, Inc, 9 ; **Z. Wu**, Centocor Research and Development, Inc, 3 ; **S. Parasuraman**, JJPS, LLC, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 .

1671

Six-Month Results From the Collaborative European REgistries for Rituximab in Rheumatoid Arthritis (CERERRA). Efficacy of Rituximab Is Highest in RF-Positive Patients and in Those Who Failed at Most One Prior Anti-TNF. Ronald F. van Vollenhoven[1], K. Chatzidionysiou[1], E. Nasonov[2], G. Lukina[2], M. L. Hetland[3], U. Tarp[3], C. Gabay[4], P. L.C.M. van Riel[5], D. C. Nordström[6], J. J. Gomez-Reino[7], K. Pavelka[8], M. Tomsic[9], E. Lie[10] and T. K. Kvien[10], [1]Karolinska Univ Hosp, Stockholm, Sweden, [2]Institute of Rheumatology, Moscow, Russia, [3]DANBIO, University Hospital, Copenhagen, Denmark, [4]University of Geneva, Geneva, Switzerland, [5]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [6]ROB-FIN Helsinki University Central Hospital, Helsinki, Finland, [7]H. Clinico Universitario de Santiago, Santiago de Compostela, Spain, [8]Charles University, Prague, Czech Republic, [9]University Medical Centre Ljubljana, Ljubljana, Slovenia, [10]Diakonhjemmet Hospital, Oslo, Norway

Purpose: Rituximab is increasingly used in the treatment of RA. Longitudinal cohorts may provide important information on outcomes in clinical practice and predictors of efficacy. The purpose of this study was to analyse the efficacy after 6 months of the first RTX course for RA, based on data from ten large European registries, and to find possible predictors of response.

Method: Ten European registries submitted anonymized datasets with baseline, 3- and 6-month data for patients who had started RTX. These datasets were pooled and analysed. A small number of patients were re-treated before 6 months (6.7%) and were not included in this analysis. Heterogeneity between countries was analysed by ANOVA. Predictors of response and remission were analysed by logistic regression.

Results: 1372 patients were included. The mean (SD) disease duration was 12.3 (8.4) years. 80.4% of patients were female and 85.6% RF positive. They had failed an average of 2.7 DMARDs (range: 0-10). 33% of patients had failed ≥2 anti-TNF agents, 30% had failed one, and 37% of patients were given RTX as their first biologic agent. Significant heterogeneities ($p<0.0001$) were noted between countries for several baseline characteristics including the number of prior biologics. DAS28 decreased from 5.9±1.4 at baseline to 4.1±1.4 at 6 months ($p<0.0001$). These improvements were achieved already at 3 months and remained stable at 6 months. The subset of patients with 0-1 prior anti-TNF had higher baseline DAS28 compared to the group of patients with >1 prior biologics and significantly better responses after 3 and 6 months (table 1). Lower number of prior DMARDs and biologics were found to be prognostic factors for response to treatment ($p<0.0001$ and $p=0.0013$ respectively), as well as positive RF (OR 1.5, 95% CI 0.96-2.0). At the end of 3 and 6 months, 64.4% and 66.2% of patients had achieved EULAR good/moderate response.

Conclusion: In this large observational cohort, RF positivity is a predictor of good response to RTX. Efficacy results were best when RTX was used as first biologic or in patient who failed one anti-TNF.

Table 1. DAS28 at baseline, 3 and 6 months for patients with differentnumbers of prior biologics.

	DAS28 at baseline	DAS28 at 3 m	DAS28 at 6 m
No prior anti-TNF	6.2±1.2	4.2±1.1	4.1±1.3
One prior anti-TNF	6.1±1.3	4.1±1.4	4.1±1.4
>1 prior anti-TNF	5.6±1.4	4.4±1.4	4.3±1.6

Disclosure: R. F. van Vollenhoven, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 ; **K. Chatzidionysiou**, None; **E. Nasonov**, F.Hoffmann-La Roche Ltd, 8 ; **G. Lukina**, F.Hoffmann-La Roche Ltd, 8 ; **M. L. Hetland**, Roche Pharmaceuticals, 2 ; **U. Tarp**, Roche Pharmaceuticals, 5, Abbott Laboratories, 5 ; **C. Gabay**, None; **P. L. C. M. van Riel**, None; **D. C. Nordström**, Abbott Immunology Pharmaceuticals, Roche, 5 ; **J. J. Gomez-Reino**, Roche Pharmaceuticals, Schering Plough, , 5, Roche Pharmaceuticals, Schering Plough, Bristol Meyers Squibb, , 8 ; **K. Pavelka**, None; **M. Tomsic**, None; **E. Lie**, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5 ; **T. K. Kvien**, Roche Pharmaceuticals, Abbot, Wyeth, Schering-Plough, BMS, UCB, 5 .

1672

Rapid Prediction of Low Disease Activity at 1 Year Among RA Patients Treated with Certolizumab Pegol. Jeffrey R. Curtis[1] and Kristel Luijtens[2], [1]UAB, Birmingham, AL, [2]UCB, Brussels, Belgium

Purpose: Rapidly predicting which RA pts will respond to biologics may optimize outcomes.The objective of our analysis was to determine the prognostic significance of data collected early after starting certolizumab pegol (CZP) to predict low disease activity (LDA) at 1 year.

Methods: Wks 4 and 12 data from CZP-treated pts in RAPID 1 were used as variables to predict LDA (DAS28 (ESR) ≤3.2) at Wk 52. Classification and Regression Tree (CART) software (Salford Systems) identified variables, built a prediction model, and tested its performance using a split sample (ie, separate training/testing datasets). The ability of this model (Model 1) to discriminate between pts who did/did not achieve LDA at Wk 52 was assessed using area under the receiver-operator curve (AUC). For pts for whom the prediction of LDA at Wk52 using Wk 4/12 data was suboptimal, Wk 28 data were added. A second prediction model (Model 2) was constructed in which more complex variables (ie, DAS) were replaced with ones more easily measured in clinical practice (ie, Clinical Disease Activity Index).

Results: Of 783 pts randomized to CZP (RAPID 1 ITT pop), 703 were included in this analysis (80 pts who withdrew for safety were excluded); 83% female, mean age 51.7 yrs, disease duration 6.1 yrs, concomitant MTX 13.6 mg/wk, baseline DAS28 6.9. Using Wk 4/12 data, LDA at Wk 52 was predicted with ~71-87% accuracy for 80% of pts. For the remaining 20% of pts, adding Wk 28 data resulted in similar accuracy (Figure below). Model 2 had comparable discrimination and accuracy. Overall results from the testing dataset are shown below; results from the training dataset were somewhat better (not shown).

Figure. Model 1, any variable, Weeks 4 and 12

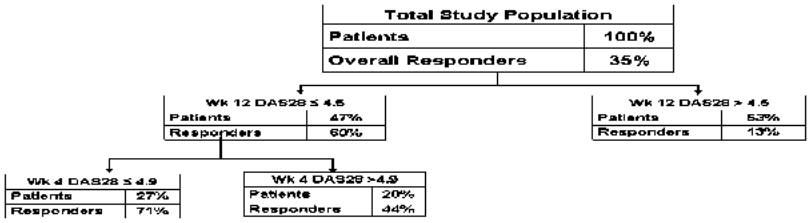

Table: Model discrimination and calibration

Data used from these Wks	AUC	% Correctly Classified
Model 1, Wks 4/12	0.76	74%
Model 1, Wks 4/12/28	0.83	84%
Model 2, Wks 4/12	0.71	76%
Model 2, Wks 4/12/28	0.81	82%

Conclusion: Using CART, we accurately classified ~75% of RA pts as early responders/non-responders within 12 wks of initiating CZP. Wk 28 data improved predictability by an additional 10%. Classification trees may be useful to prospectively guide the management of individual RA pts treated with CZP and perhaps other biologic therapies.

Disclosure: J. R. Curtis, Roche Pharmaceuticals, 8, Roche, UCB, 5, Amgen, Merck, CORRONA, 2 ; **K. Luijtens**, UCB, 3 .

1673

Beneficial Effect of One Year Etanercept Treatment On Lipid Profile in Patients with Rheumatoid Arthritis: ETRA Study. Anna Jamnitski[1], Ingrid M. Visman[1], Mike J.L. Peters[2], Ben A.C. Dijkmans[2], Alexandre E. Voskuyl[2] and Michael T. Nurmohamed[1], [1]Jan van Breemen Institute, Amsterdam, Netherlands, [2]VU Medical Centre, Amsterdam, Netherlands

Purpose: Patients with active rheumatoid arthritis (RA) have an unfavorable lipid profile i.e. a higher TC/HDL cholesterol ratio and Apo B/Apo A-I ratio. Effective anti-inflammatory treatment with TNF blocking agents may improve the lipid profile by increasing HDL cholesterol and Apo A-I levels. Hence, we investigated the influence of long-term etanercept treatment on the lipid profile in RA patients.

Method: Between 2004 and 2008, 292 consecutive patients with active RA (DAS28 > 3.2) and a new etanercept prescription were included in an observational cohort. Disease activity and clinical response variables were assessed at baseline and every three months thereafter. Non fasting lipid samples were collected at baseline (n=149), 16 (n=115) and 52 (n=112) weeks. A paired t-test or the Wilcoxon signed ranks test was used to determine significant changes from baseline, missing values were excluded listwise.

Results: DAS28 score improved significantly (5.2 versus 3.1) reflected by 84% good or moderate responders according to the EULAR response criteria after 1 year of treatment. Changes in the lipid profile are shown in table 1. Apo A-I increased significantly after 1 year of treatment leading to a significant decrease of apo B/apo A-I ratio. When stratified for EULAR response atherogenic index increased significantly (p= 0.027) in non-responders, and did not change in EULAR responders (p = 0.595). Apo A-I levels increased (p= 0.001) and Apo B/Apo A-I ratio decreased further in EULAR responders (p= 0.000) and remained unchanged in EULAR non-responders (p= 0.850).

Conclusion: Treatment with etanercept induced a significant improvement of the Apo B/Apo A-I ratio. Ultimately this may have a beneficial effect on the cardiovascular risk, as we have also demonstrated that etanercept treatment restores the anti-inflammatory properties of HDL-cholesterol (van Eijk IC, et.al. Artrhitis Rheum 2009;60(5))

Table 1. Lipid profile during the one year treatment.

	baseline	16 weeks	P-value	52 weeks	P-value
DAS28	5.21 ± 1.3	3.54 ± 1.5	0.000	3.11 ± 1.3	0.000
ESR	23 (12 - 40)	14 (6 - 26)	0.000	13 (6 - 26)	0.000
CRP	8 (3 - 21)	3 (1 - 8)	0.000	3 (1 - 7)	0.000
Total cholesterol	5.22 ± 1	5.24 ± 1.0	0.492	5.22 ± 0.9	0.777
Triglycerides	1.20 (0.9 - 1.7)	1.27 (0.9 - 1.9)	0.177	1.26 (0.9 - 1.9)	0.000
HDL-cholesterol	1.57 ± 0.5	1.56 ± 0.4	0.137	1.49 ± 0.4	0.166
Totaal chol - HDL chol	3.66 ± 1.0	3.66 ± 0.9	0.135	3.73 ± 0.9	0.294
LDL-cholesterol	3.06 ± 0.9	2.99 ± 0.8	0.178	3.03 ± 0.8	0.889
Atherogenic index	3.65 ± 1.2	3.56 ± 1.1	0.245	3.72 ± 1.1	0.174
Apo A-I	1.53 ± 0.3	1.57 ± 0.3	0.927	1.57 ± 0.3	0.000
Apo B	0.90 ± 0.2	0.85 ± 0.2	0.818	0.88 ± 0.2	0.709
Apo B/Apo A-I ratio	0.61 ± 0.2	0.56 ± 0.2	0.841	0.58 ± 0.2	0.002

*Mean values ± SD, median and interquartile range are shown

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Association of Serum Markers with Clinical Response Measures in Rheumatoid Arthritis Patients Treated with Golimumab, a Human Anti-TNFα Monoclonal Antibody. C. Wagner[1], M. U. Rahman[2], M.C. Genovese[3], E. L. Matteson[4], Jonathan Kay[5], Edward C. Keystone[6], E. C. Hsia[2], M. K. Doyle[2], M. Elashoff[7] and S. Visvanathan[1], [1]Centocor R&D, Inc, Malvern, PA, [2]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [3]Stanford U, Palo Alto, CA, [4]Mayo Clinic, Rochester, MN, [5]University of Massachusetts Memorial Medical Center, Worcester, MA, [6]Professor of Medicine/University of Toronto, Toronto, ON, [7]Elashoff Consulting, Redwood City, CA

Purpose: To examine changes in markers associated with clinical response in 1) active rheumatoid arthritis (RA) patients despite methotrexate (MTX) treated with golimumab (GLM), and 2) RA patients previously treated with TNFα inhibitors.

Methods: Sera were collected at wks 0, 4 and 14 from a subset of the GO-FORWARD (active RA patients despite MTX) and GO-AFTER (active RA patients previously treated with TNF inhibitors) studies. Samples were tested for select markers. The change from baseline in markers was compared between GLM ± MTX and PBO + MTX using ANOVA on the van der Waerden normal scores and t-tests. Logistic regression models were used to test for marker associations with clinical endpoints.

Results: Select inflammatory markers were decreased at wks 4 and 14 after treatment with GLM±MTX as compared to PBO+MTX ($p<0.05$). In a regression analysis including data from both studies, baseline levels of CRP, IL-6, MMP-3, ENRAGE, α2 macroglobulin, insulin, vWF, leptin, apolipoprotein CIII, and bone alkaline phosphatase were associated (OR from 0.59 to 1.19,$p<0.05$) with ACR 20 and ACR 50 response at wk 14 in the GLM ±MTX group. Changes from baseline to wk4 in CRP, IL-6, MMP-3, and ENRAGE plus ICAM-1,VEGF, TIMP-1, TNFRII, IL-1Rα, α1anti trypsin, apolipoprotein C III, serum amyloid P, IL-16, hyaluronic acid and haptoglobin were associated with the same clinical measures at wk14. In GLM ± MTX patients, baseline levels of α2 macroglobulin, apolipoprotein CIII, CRP and MMP-3 were significantly different between ACR 20 and ACR 50 responders and non-responders at wk14($p<0.05$).

Conclusion: GLM impacts multiple proteins associated with the TNFα pathway and RA disease processes. The measurement of select markers in patients with active RA despite MTX and those previously treated with anti-TNF therapy could be used to predict response to GLM.

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Microsomal Prostalglandin E Synthase and Related Enzymes in Rheumatoid Arthritis B Cells and Effects of B Cell Depleting Therapy On Enzyme Expression. Karina R. Gheorghe[1], Rogier M. Thurlings[2], Marie Westman[1], Marina Korotkova[1], Vivianne Malmström[1], Christina Trollmo[1], Per-Johan Jakobsson[1] and Paul P. Tak[3], [1]Karolinska Institute, Stockholm, Sweden, [2]Academic Medical Center/Univ. of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Microsomal prostaglandin E2 synthase 1 (mPGES1) catalyzes the formation of PGE2, which has important contributions to the rheumatoid arthritis (RA) inflammatory process. B cells are essential in promoting immune activation in the rheumatoid synovium. Previously it was reported that activated B lymphocytes form PGE2 through upregulation of cyclooxygenase (COX) 2 enzyme. In this study we aimed to investigate the expression of PGE2 pathway enzymes in RA B cells and to evaluate the effects of B cell depleting therapy on their expression in rheumatoid synovial tissue.

Method: In a first group, synovial fluid and peripheral blood were collected from 9 RA patients and mononuclear cells (MC) were isolated and stimulated overnight with *Stafilococcus aureus* Cowan strain I (SAC) and pokeweed mitogen (PWM). Unstimulated cells were used as controls. Expression of mPGES1, COX1 and COX2 was analyzed by flow cytometry and double immunofluorescense staining identified mPGES1 positive B cells. In a second group, synovial biopsies were obtained from 12 RA patients before starting Rituximab treatment, 4

weeks later and 16 weeks after initiation of therapy. Immunohistochemical analysis of mPGES1, COX1 and COX2 in biopsy sections was performed and the enzyme expression was quantified using computer image analysis.

Results: Unstimulated MC from either rheumatoid arthritis SF or PB did not express mPGES1 or COX2 enzymes, but their expression was significantly upregulated upon stimulation with SAC and PWM ($p < 0.01$). Also, mPGES1 positive B cells were detected after *in vitro* stimulation of SF mononuclear cells using double immunofluorescence, confirming thus the flow cytometry data. Expression of COX1 was not different between control and stimulated cells. In synovial biopsy sections, regardless of the patients' response to treatment as assessed by the change in the 28-joint Disease Activity Score (DAS28), Rituximab therapy resulted in no influence on mPGES1, COX1 or COX2 expression at 4 weeks or 16 weeks after therapy start.

Conclusion: These data demonstrate that RA B lymphocytes are capable of upregulating mPGES1 and COX2 expression in response to activating stimuli. In addition, therapy with B cell depleting agents, although efficient in achieving good clinical response, leaves essentially unaffected the PGE2 pathway in the rheumatoid synovium.

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The Type I IFN Signature Is a Negative Predictor of the Clinical Response to Rituximab Treatment in RA. Rogier M. Thurlings[1], Maartje J. H. Boumans[1], Janneke Tekstra[2], Johannes W.J. Bijlsma[2], Lisa G.M. Van Baarsen[1], Koen Vos[1], Carina Bos[3], K. A. Kirou[4], Mary K. Crow[4], Cornelis L. Verweij[3] and Paul P. Tak[5], [1]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]University Medical Centre Utrecht, Utrecht, Netherlands, [3]VU University Medical Centre, Amsterdam, Netherlands, [4]Hospital for Special Surgery, New York, NY, [5]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Background: In several autoimmune conditions a subset of patients displays type I interferon (IFN) signalling in their peripheral blood; most of these conditions are characterized by auto-antibodies. Type I IFNs may enhance B cell survival.

Purpose: To test whether type I IFN signalling is associated with decreased clinical efficacy of rituximab treatment in RA.

Methods: Twenty RA patients were treated with rituximab (cohort 1). The clinical response was defined as the decrease in DAS28 at week 24 and according to the EULAR response criteria. In peripheral blood mononuclear cells from baseline the presence of an IFN signature was analyzed using polymerase chain reaction on 3 interferon regulated genes. After comparison with healthy controls, patients were qualified as IFN high or IFN low. The data were confirmed in a second independent cohort (n = 30). In this cohort also type I serum IFN bioactivity was analyzed using a reporter assay. The relationship with the clinical response (at week 24) was analyzed using regression analysis.

Results: In cohort 1, the decrease in DAS28 tended to be lower in the IFN high group (n=6) compared to the IFN low group (n=14; -0.67 (±0.9) compared to -1.7 (±1.6); $P = 0.06$). A similar trend was found when analyzing response according to the EULAR criteria in this cohort. In the second, validation cohort IFN high patients (n = 18) experienced a significantly lower decrease in DAS28 at week 24 compared to IFN low patients (n = 13; mean (±SD) -0.98 (±1.6) compared to -2.3 (±1.3); $P = 0.022$). Less patients obtained a EULAR response in the IFN high compared to the IFN low group ($P = 0.05$). Serum type I IFN bioactivity at baseline negatively predicted the decrease in DAS28 at week 24 ($R^2 = 0.13$, $P = 0.046$). The pooled data of the 2 cohorts also showed a significant lower decrease in DAS28 in the IFN high patients (n=24) at week 24 compared to the IFN low group (n=27; mean (±SD) -0.90 (±1.5) compared to -2.0 (±1.4); $P = 0.012$) and less patients obtained a EULAR response in the IFN high compared to the IFN low group when the data are pooled ($P = 0.032$).

Conclusion: The type I IFN signature negatively predicts the clinical response to rituximab treatment in RA. These data support the notion that type I IFN signalling plays a role in RA immunopathology.

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Radiographic Progression of Cervical Lesions in Patients with Rheumatoid Arthritis Receiving Infliximab Treatment. Yasuhide Kanayama, Toshihisa Kojima, Tomone Shioura, Masatoshi Hayashi, Koji Funahashi and Naoki Ishiguro, Nagoya Univeristy GraduateSchool & Faculty of Medicine, Showa, Nagoya, Japan

Purpose: Cervical lesions are known to occur at high frequency as a complication of rheumatoid arthritis (RA). Treatment with Anti-TNFα agents are more clinically effective than the disease-modifying antirheumatic drugs (DMARDs) that were in use previously, in particular, with their efficacy in suppressing joint destruction having been emphasized. However, most clinical studies on the efficacy of biological agents in suppressing joint destruction in the hands and feet, and no studies have been carried out on efficacy against cervical lesions. Therefore, we carried out the present study, which was a prospective investigation in patients receiving infliximab, in order to elucidate the efficacy of infliximab for inhibiting the radiographic progression of RA cervical lesions .

Method: This study was carried out with 47 patients with active RA who received continuous infliximab treatment for at least 1 year. Infliximab treatment was initiated between November 2003 and December 2007. The infliximab dose was 3 mg/kg. The first three doses were administered at Week 0, 2 and 6, and the fourth and later doses were administered every 8 weeks up to Week 54. For evaluation of cervical lesions, the atlanto-dental interval (ADI), the space available for the spinal cord (SAC), and the Ranawat value were measured by plain lateral radiographs in the flexion position, at baseline and Week 54.

Results: When progression was defined as a change of 1 mm or more in one of the radiographic cervical lesion parameters for a period of 1 year, the numbers of patients, of a total of 47, who showed progression in ADI, SAC and Ranewat value were 16 (34%), 15 (32%), and 10 (21%), respectively, and the number who showed progression in at least one of these three parameters was 20 (43%).With respect to MMP3, the non-progressive group showed marked and significant alleviation in 1 year, from 423.6 ± 389.4 to 165.5 ± 150.8 ng/ml ($p < 0.001$), whereas the change in the progressive group was from 305.2 ± 222.7 to 224.4 ± 109.5 ng/ml ($p = 0.136$), which was not significant. At Week 54, the responses to infliximab on the basis of the EULAR response criteria were good and moderate in 23 patients (49%) and 24 patients (51%), respectively. Whereas cervical lesion progression was suppressed in 19 of 23 good-response patients (83%), progression occurred in 16 of 24 moderate-response patients (67%), and this difference was shown to be significant by the Fisher's exact test ($p = 0.002$). In the good-response patients ($n = 23$) and moderate-response patients ($n = 24$), the respective changes in cervical lesion parameters in 1 year were as follows: ADI: 0.17 ± 0.49 and 0.54 ± 0.58 mm ($p = 0.013$); SAC: −0.17 ± 0.49 and −0.54 ± 0.59 mm ($p = 0.025$); and Ranawat value: −0.09 ± 0.29 and −0.42 ± 0.65 mm ($p = 0.032$).

Conclusion: Infliximab treatment can be used to suppress the progression of RA cervical lesions, as well as hand and foot joints lesions. It is possible that response to infliximab and MMP3 improvement could be used to predict the progression of RA cervical lesions.

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BLyS Promoter Polymorphism and Response to Rituximab in Rheumatoid Arthritis (RA) Patients Positive or Negative for the Rheumatoid Factor. Martina Fabris[1], Luca Quartuccio[1], Marta Saracco[2], Raffaele Pellerito[2], Fabiola Atzeni[3], Piercarlo Sarzi-Puttini[4], Marco A. Cimmino[5], Maurizio Benucci[6], Cinzia Fabro[1], Pia Morassi[7], Martina Bolzan[1], Fabio Fischetti[7], Elio Tonutti[8] and Salvatore De Vita[9], [1]University of Udine, Udine, Italy, [2]Ospedale Mauriziano, Torino, Italy, [3]L.Sacco University Hospital, Milano, Italy, [4]L. Sacco University Hospital, Milano, Italy, [5]University of Genova, Genova, Italy, [6]Ospedale San Giovanni di Dio, Firenze, Italy, [7]Ospedali Riuniti of Trieste, Trieste, Italy, [8]Azienda Ospedaliero-Universitaria of Udine, Udine, Italy, [9]University of Udine, Italy

Purpose: To analyse the relationship between the -871C/T BLyS promoter polymorphism and the response to therapy in a large series of RA patients treated with rituximab (RTX), distinguishing also rheumatoid factor (RF)-positive and negative cases.

Method: One hundred and twenty (120) consecutive RA patients (mean age 61.6±12.8 yrs; mean disease duration 14.4±10.8 yrs) from 6 different Rheumatologic Centres of Italy were enrolled in the study. Patients fulfilled the ACR criteria for the classification of RA and were 82.5% RF-positive. The patients previously failed several DMARDs (3.4±1.5) and/or anti-TNF agents (1.2±0.9) and presented a high disease activity at baseline (DAS28 6.3±0.9). RTX therapy was administered at the standard dose regimen, and the ACR criteria were used to assess the response 6 months after RTX first infusion (mo. +6). BLyS promoter polymorphism was analysed by PCR-RFLP following previously reported methods (Novak et al, J Clin Oncol 2006). BLyS serum levels were analysed in all the available serum samples by ELISA using commercial kits (R&D Systems).

Results: At mo. +6 we found 15.8% non responders (NR) and 17.5% ACR20, 46.7% ACR50 and 20% ACR70/90 responder patients. BLyS serum levels at baseline were significantly more elevated in cases carrying the BLyS promoter genotypes CT/TT than in the those carrying the CC genotype, both at baseline (1.33±0.61 ng/ml versus 0.91±0.24 ng/ml; p=0.032), and in the follow-up (4.92±2.06 versus 3.58±1.10 ng/ml; p=0.083, at mo. +6). A response to RTX ≥ACR50 was found in 23/27 (85.2%) of the low BLyS producers CC patients compared to 57/93 (61.3%) of the high BLyS producers CT/TT patients [OR:3.63; CI95%:1.16-11.37; p=0.0215]. No NR patients were found among the CC patients. The presence of the RF, as previously reported (Quartuccio et al, Reumatismo 2008), was significantly associated with a response ≥ACR50 to RTX (OR:3.38; 95%CI:1.28-8.91; p=0.02). Patients carrying the CC genotype presented an elevated degree of response either in RF-positive (19/23, 82.6%) and in RF-negative (4/4, 100%; p=ns) cases. In contrast, CT/TT patients disclosed a significant increase of poor/non responder cases (ACR20/NR) in RF-negative (12/17, 70.6%) compared to RF-positive patients (23/75, 30.7%; OR:5.43, 95%CI:1.71-17.19, p=0.0045).

Conclusion: RF-negative RA patients carrying the CT/TT genotype present the highest risk of unfavourable outcome with RTX therapy. The analysis of the -871C/T BLyS polymorphism, influencing BLyS serum levels, may then deserve further attention to optimize the treatment of RA with RTX.

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Long-Term Impact of Adalimumab Plus Methotrexate On Radiographic, Clinical, and Functional Progression of Rheumatoid Arthritis. Edward C. Keystone[1], Arthur Kavanaugh[2], Désirée M.F.M. van der Heijde[3], Sandra Sinisi[4], Jesse Hall[4] and Benoît Guerette[5], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]University of California San Diego, La Jolla, CA, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Abbott Laboratories, Abbott Park, IL, [5]Abbott Laboratories, Rungis, France

Purpose: Assessing long-term efficacy is important when tailoring treatment. We describe the long-term (8-yr) impact of adalimumab (ADA) plus methotrexate (MTX) on radiographic, clinical, and functional parameters in patients (pts) with rheumatoid arthritis (RA).

Methods: In the DE019 study, pts with RA were randomized to double-blind (DB) MTX (n=200), ADA 40 mg every other week (eow) plus MTX (n=207), or ADA 20 mg weekly plus MTX (n=212) for 1 yr.[1] Pts completing DB therapy received open-label ADA 40 mg eow plus MTX for an additional 7 yrs. Observed data analyses were performed using the intention-to treat population (all pts who received ≥1 dose of study drug with data at each visit). American College of Rheumatology (ACR) responses and swollen (SJC66) and tender joint counts (TJC68) were used to assess clinical response. Remission was defined using 28-joint Disease Activity Score (DAS28)<2.6, SJC66=0, and TJC68=0. The Health Assessment Questionnaire (HAQ) was used to assess physical function. Two experts blinded to sequence and order read radiographic films from baseline and Yrs 5, 6, and 8. Radiographic changes were determined using the modified total Sharp score (mTSS); nonprogression was defined as a change in mTSS<0.5.

Results: After 8 yrs, 81%, 62%, 46%, and 19% of ADA+MTX pts (n=185) achieved ACR20, 50, 70, and 90, respectively. Mean SJC decreased from 26 to 4 and mean TJC decreased from 20 to 4. DAS28<2.6, SJC=0, and TJC=0 were achieved by 60%, 42%, and 40% of pts, respectively. Mean HAQ decreased from 1.33 to 0.65 (n=186). Radiographic nonprogression occurred in 55% of pts (table).

Mean Changes in Radiographic Endpoints From Baseline to 8 Yrs

Original Treatment Group	□mTSS	□JES	□JSN	□mTSS<0.5, %
MTX (n=65)	5.12	1.74	3.38	37
ADA 20 mg weekly+MTX (n=90)	1.85	0.53	1.32	45
ADA 40 mg eow+MTX (n=96)	0.57	–0.21	0.78	55

JES=joint-erosion score; JSN=joint-space narrowing.

Conclusion: After 8 yrs of therapy, ADA+MTX provided sustained improvements in clinical efficacy; remission occurred in 60% of pts. Radiographic nonprogression was achieved by 55% of pts. Pts treated with MTX, for whom ADA 40 mg eow therapy was delayed 1 yr, experienced a 29% relative increase in the percentage of pts with radiographic progression. Overall, 8 yrs of ADA 40 mg eow+MTX prevented radiographic progression and provided the best outcomes.

Reference: [1]Keystone EC, et al. *Arthritis Rheum.* 2004;50:1400–11.

Disclosure: E. C. Keystone, Abbott Laboratories, 2, Abbott Laboratories, 5, Centocor, Inc., 2, Centocor, Inc., 5, Amgen, 2, Amgen, 5 ; **A. Kavanaugh**, Abbott Laboratories ; **D. M. F. M. van der Heijde**, Abbott Laboratories, 5, Amgen, 5, Aventis Pharmaceuticals, 5, Bristol Meyers Squibb, 5, Centocor, Inc., 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCB, 5, Wyeth Pharmaceuticals, 5 ; **S. Sinisi**, Abbott Laboratories, 3 ; **J. Hall**, Abbott Laboratories, 3 ; **B. Guerette**, Abbott Laboratories, 3 .

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Identification of Biomarkers for Enhanced Benefit to Rituximab in Rheumatoid Arthritis: Role of Autoantibodies and Inflammatory Markers. G. J. Silverman[1], Sergio Schwartzman[2], M. Townsend[3], Z. Su[3], C. Holweg[3], S. Read[4], D. Yocum[3] and P. Lal[3], [1]UCSD, La Jolla, CA, [2]Hosp for Special Surgery, New York, NY, [3]Genentech, South San Francisco, CA, [4]Roche, United Kingdom

Purpose: Rituximab has been shown to significantly improve the signs and symptoms of rheumatoid arthritis (RA) as well as slow the progression of joint damage. The purpose of this analysis was to examine serologic markers in randomized clinical trials (RCT) and identify biomarkers that best distinguish patient subsets with high hurdle clinical responses (ACR 50 at 24 weeks) to rituximab therapy.

Methods: With baseline samples from the REFLEX trial of 517 RA patients with previous inadequate response to TNF inhibitors, a threshold sensitivity method was used to identify candidate biomarkers that enriched for placebo corrected ACR50 response at 24 weeks, and which represented at least 20% of subjects. Of 19 serological markers and 9 clinical features examined, we identified the best four biomarkers, which included levels of IgA isotype of rheumatoid factor (RF), sCD25, and IgG anti-CCP3 antibodies, as determined by ELISA, and of C-reactive protein (CRP), as determined by nephelometry. These biomarkers and five of their two-biomarker combinations as well as levels of IgM and IgG isotypes of RF were then further investigated following a pre-specified diagnostic plan using data from the SERENE RCT of 501 RA patients with an inadequate response to methotrexate. We then also calculated odds ratios for achieving an ACR50 response at 24 weeks compared to placebo, as well as additional summary statistics for biomarker positive/negative subgroups (Table1).

Results: In discovery studies we found that, compared to seronegative patients, seropositivity for any isotypes of RF or IgG anti-CCP antibodies was associated with a higher rate of placebo controlled ACR50 responses at 24 weeks. Patients with elevated levels of CRP also demonstrated more frequent clinical benefit. These findings were independently reiterated in the SERENE patient populations. The greatest enhancement was seen in patients with both elevated baseline CRP (>2.9 mg/dL) and positivity for RF of any isotypes or IgG anti-CCP. These patients had better clinical responses across a spectrum of clinical outcome measures (ACR responses, delta DAS, and EULAR response).

Conclusion: In the REFLEX and SERENE RCT, the presence of autoantibodies and elevated CRP identified a subgroup of RA patients with an enhanced benefit to rituximab. However, these findings need to be verified in large independent data sets.

Table Efficacy difference (95% CI) between Rituximab and placebo treated patients at Week 24 in the SERENE trial.

	□ **ACR50***	**ACR50 O.R.**	□ **ACR20**	□ **EULAR good/moderate**	□ **mean DAS change from baseline**
Biomarker(+) CRP>2.9 mg/dL & RF IgA**>25 U/ml 22% population	34% (20%, 48%)	10.4 (2.9, 37.2)	44% (28%, 60%)	55% (39%, 71%)	-1.54 (-2.00 , -1.08)

Biomarker(-) 78% population	13% (6%, 20%)	2.7 (1.4, 5.2)	26% (16%, 36%)	25% (15%, 35%)	-0.82 (-1.11, -0.53)

*□ is between active and placebo. Permutation p-value=0.02, unadjusted for the number of biomarkers considered.

**Similar enhanced benefit to rituximab in the biomarker (+) group was observed when any other isotype of RF or Total RF was substituted for RF IgA.

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Three-Year Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis with and without History of Other Tumor Necrosis Factor Antagonist Therapies. G. Burmester[1], Sonja Kary[2], Kristina Unnebrink[2], Benoît Guerette[3], Uemit Oezer[2] and Hartmut Kupper[2], [1]Charité-University Medicine, Berlin, Germany, [2]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [3]Abbott Laboratories, Rungis, France

Purpose: For treatment of patients (pts) with rheumatoid arthritis (RA), switching to another tumor necrosis factor (TNF) antagonist is effective after failure with or intolerance of a prior anti-TNF therapy.[1] However, data on the maintenance of effectiveness are rare. We compared the effectiveness of adalimumab (ADA) for pts with and without history of anti-TNF therapy who continued ADA in an ongoing, 5-yr observational study (ReAlise) after completion of a multinational, uncontrolled, Phase IIIb study (ReAct), during which pts received ADA therapy for ≥12 weeks.

Methods: Data were analyzed from the first 3 years (yrs) after the first ADA injection in ReAct. Treatment effectiveness was measured by 28-joint Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ) score, and American College of Rheumatology (ACR) responses (ACR20 and ACR50). Scores for pts with and without prior anti-TNF treatment were compared. Outcomes for pts with prior anti-TNF therapy were analyzed by reason for anti-TNF therapy discontinuation.

Results: Data were available for 3,433 ReAlise pts, including 408 (12%) with prior anti-TNF therapy. At ReAct baseline, mean DAS28 and HAQ scores were greater for pts with vs. without prior anti-TNF therapy (table). After 3 months (M), treatment responses were marked in all pt groups and were sustained after 1 and 3 yrs of therapy. Pts with prior anti-TNF therapy achieved quite similar improvement.

Outcomes for RA Pts Treated With ADA by History of Prior Anti-TNF Therapy

		No Prior Anti-TNF Therapy	**Prior Anti-TNF Therapy**	**Reason for Discontinuation of Prior Anti-TNF Therapy**		
				Lack of Response	**Loss of Response**	**Intolerance**
N at BL[a]		3025	408	76	142	87
N at M 3[b]		2998	402	75	140	86
N at M 12[b]		2487	349	63	117	78
N at M 36[b]		1815	227	39	78	46
DAS28, mean (SD)	BL[a]	5.9 (1.1)	6.3 (1.1)	6.4 (1.1)	6.3 (1.1)	6.3 (1.2)
	M 3	3.6 (1.4)	4.1 (1.4)	4.4 (1.4)	4.2 (1.2)	3.8 (1.4)
	M 12	3.2 (1.3)	3.8 (1.4)	3.9 (1.2)	3.9 (1.4)	3.6 (1.5)
	M 36	3.0 (1.3)	3.5 (1.4)	3.3 (1.0)	3.6 (1.4)	3.3 (1.5)
HAQ, mean (SD)	BL[a]	1.58 (0.67)	1.83 (0.67)	1.94 (0.63)	1.89 (0.68)	1.71 (0.74)

	M 3	0.97 (0.74)	1.31 (0.74)	1.44 (0.69)	1.39 (0.72)	1.10 (0.73)
	M 12	0.88 (0.74)	1.23 (0.74)	1.34 (0.67)	1.27 (0.74)	1.03 (0.79)
	M 36	0.81 (0.71)	1.14 (0.76)	1.26 (0.80)	1.25 (0.76)	1.01 (0.77)
	M 3	76	65	54	69	75
ACR20, %	M 12	82	77	80	81	80
	M 36	84	77	76	77	79
	M 3	47	37	28	35	44
ACR50, %	M 12	59	47	49	50	51
	M 36	67	53	55	50	54

[a]BL= ReAct baseline; [b]Pts with DAS28 data available.

Conclusion: ADA was effective in pts with or without history of prior anti-TNF therapy, and irrespective of the reason for discontinuation or type of anti-TNF therapy received. Effectiveness was sustained for 3 yrs.

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Golimumab and Cardiovascular Disease in Inflammatory Arthritides. J. Bathon[1], M. C. Wasko[2], E. C. Hsia[3], B. Kirkham[4], Roy Fleischmann[5], M.C. Genovese[6], E. L. Matteson[7], H. Liu[8] and M. U. Rahman[3], [1]Johns Hopkins Univ Sch of Med, Baltimore, MD, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [4]Guy's and St. Thomas' Hosp, London, England, [5]Metroplex Clinical Research Center, Dallas, TX, [6]Stanford U, Palo Alto, CA, [7]Mayo Clinic, Rochester, MN, [8]Centocor R&D, Inc, Malvern, PA

Purpose: To assess the effect of golimumab (GLM) +/- MTX on serum lipid profile and inflammatory markers associated with cardiovascular disease (CVD), and on cardiovascular (CV) events.

Methods: Serum lipids and inflammatory CV markers (eg. hsCRP, VEGF, ICAM-1 SAA, fibrinogen, IL-6) were assessed in 2 phase 3 GLM trials in pts with rheumatoid (RA): MTX-naïve (GO-BEFORE); MTX inadequate responders (IR) (GO-FORWARD). Changes from baseline (BL) to wk14 or 24 were compared between PBO+MTX (N=293) and combined GLM 50 and 100 mg + MTX (N=496) groups (grps). CV events (not adjudicated) from these & another phase 3 trial in anti-TNF experienced RA pts (GO-AFTER; N=461) were summarized.

Results: The changes in lipid profile & a CV inflammatory marker are shown in the table. In the GO-FORWARD study, total cholesterol (TC), HDL and LDL levels all increased in the GLM+MTX compared to PBO+MTX grp whereas atherogenic ratios (TC/HDL, LDL/HDL, ApoB1/A1) were not substantially changed. Favorable changes in the LDL subfraction (increase in large and decrease in small LDL) were seen in GLM groups. In the GO-BEFORE study (with MTX-naïve pts), similar changes were seen in both the MTX and GLM groups. Most inflammatory CV markers improved significantly with GLM+MTX compared to PBO+MTX in both studies (1 shown in Table as representative data). During the PBO-controlled period, 7 of 449 pts (1.6%) in the PBO+/-MTX & 10 of 1088 pts (1%) (p=0.275) in the GLM+/-MTX grps had CV events. Through June 2, 2008 (all pts had completed ≥1 yr), CV events per 100 pt-yrs (95% CI) were 2.72 (1.09, 5.6) for PBO+/-MTX & 0.8 (0.45, 1.32) for GLM+/-MTX grps (p=0.35).

Conclusion: This is the first demonstration of favorable changes in LDL sub-fractions in response to anti-TNF therapy. Despite increase in TC & LDL, the atherogenic indices remained stable and CV-related inflammatory markers improved. A suggestion of lower incidence of CV events (not adjudicated) was noted in GLM+MTX treated pts.

Table: Data are median value or median % change.

	Pbo+MTX		GLM 50 & 100 mg +MTX Combined		Median % change from baseline	
	BL	Wk 14/24	BL	Wk 14/24	Pbo+ MTX	GLM (50 &100) + MTX
GO-FORWARD (MTX-IR)						
LIPID MARKERS (mg/dL)						
Triglycerides	103.5	108.0	108.0	113.0	1.9	3.7
Total cholesterol	194.0	199.0	198.5	213.0###	1.0	8.4***
HDL	61.0	59.0	60.5	62.0###	0.0	5.4**
T chol/HDL	3.17	3.26	3.35	3.37#	1.90	2.78
LDL	107.5	111.0	112.0	121.0##	3.3	11.6***
LDL subfractions						
Mean LDL size (nM)	21.3	21.2	21.2	21.6###	0.0	1.0***
Large LDLs (mmol/L)	465.5	465.0	457.0	537.0###	3.4	21.5**
Small LDLs (mmol/L)	543.0	641.0	648.0	484.0##	4.3	-10.5***
ApoB/A1	0.52	0.54	0.57	0.54	-1.08	-3.78
INFLAMMATORY MARKERS						
High sensitivity CRP (mg/dL)	7.0	6.0	9.7	2.1###	-10.4	-70.7***
GO-BEFORE (MTX-naïve)						
LIPID MARKERS (mg/dL)						
Triglycerides	114.0	113.5	107.0	114.0	-2.0	4.1
Total cholesterol	193.0	199.0##	191.0	202.0###	4.0	4.1
HDL	58.0	56.0	57.0	59.0##	0.6	2.5
T chol/HDL	3.28	3.56#	3.37	3.34	4.8	0.79
LDL	109.0	116.0###	108.0	115.5###	6.3	2.7
LDL subfractions						
Mean LDL size (nM)	21.2	21.4##	21.2	21.5###	0.5	0.9
Large LDLs (mmol/L)	406.0	479.0##	464.5	544.0###	11.8	8.0
Small LDLs (mmol/L)	679.0	538.0	644.5	516.0###	-10.4	-16.9
ApoB/A1	0.56	0.59##	0.58	0.53###	-2.0	-3.84
INFLAMMATORY MARKERS						
High sensitivity CRP (mg/L)	13.4	4.5###	12.4	2.1##	-49.6	-71.7***

#, ##, ###p ≤0.05, 0.01, 0.001, resp., for within-group change from baseline.
*, **, ***p ≤0.05, 0.01, 0.001, resp., GLM+MTX vs Pbo+MTX

Disclosure: J. Bathon, Centocor Research and Development, Inc, 9 ; **M. C. Wasko**, Centocor Research and Development, Inc, 9 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **B. Kirkham**, Centocor Research and Development, Inc, 9 ; **R. Fleischmann**, Centocor Research and Development, Inc ; **M. C. Genovese**, Centocor Research and Development, Inc, Centocor Research and Development, Inc, 5 ; **E. L. Matteson**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, Centocor Research and Development, Inc ; **H. Liu**, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor Research and Development, Inc, 3 .

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Multiple Courses of Rituximab (RTX) Produce Sustained Efficacy in Patients (pts) with Rheumatoid Arthritis (RA) with An Inadequate Response (IR) to One or More TNF Inhibitors. Edward C. Keystone[1], Roy Fleischmann[2], Paul Emery[3], Maxime Dougados[4], Andrew R. Baldassare[5], Gillian K. Armstrong[6], Matthew D. Linnik[7], Mark Reynard[6] and Helen Tyrrell[6], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]University of Texas Southwest Medical Center at Dallas, Dallas, TX, [3]Leeds General Infirmary, Leeds, United Kingdom, [4]Hôpital Cochin, Paris, France, [5]St Louis University, St Louis, MO, [6]Roche Products Ltd, Welwyn Garden City, United Kingdom, [7]Biogen Idec, San Diego, CA

Purpose: To assess the effect of repeat courses of RTX in pts with a prior inadequate response to TNF inhibitors (TNF-IR).

Methods: RA pts recruited into Phase II or III studies with RTX and who had previously had an IR to a TNF inhibitor were permitted to receive further courses of RTX in open-label extensions. Eligibility for retreatment included a response to the initial course (at least 20% reduction in swollen and tender joint counts [SJC/TJC]) with courses no more frequently than every 4 months. Criteria for retreatment included active disease defined as either ≥8 SJC and TJC or DAS28≥2.6 (depending on the study). Each course (C) consisted of 2 x 1000mg given as IV infusions 2 weeks (wks) apart. Efficacy was determined 24 wks following each course of RTX with outcomes assessed relative to the pts pre-RTX treatment baseline. Analyses were performed using observed data on all pts, and on all pts with efficacy data at 24 wks following each of their first 4 courses of RTX, the within pt, within visit (WW) population.

Results: 500 RA TNF-IR pts had been exposed to at least 1 course of RTX and had efficacy data at Week 24, with 146 evaluable at 24 wks following each course (WW population). Observed efficacy in all pts show higher responses for C2 onwards compared with C1. However, retreatment criteria cause this analysis to become enriched for RTX responders as pts were required to achieve a response to C1. The same maintained or improved responses were seen in the WW population (Table). From C1 to C4, the proportion of pts in the WW population achieving DAS28 low disease activity (LDA) or remission doubled. Safety over repeat courses did not show any unexpected findings with rates of infection, including serious infection unchanged.

Table:

	All patients				**Within pt, within visit**			
	C1	**C2**	**C3**	**C4**	**C1**	**C2**	**C3**	**C4**
ACR responses (n)	500	355	264	178	146	146	146	146
ACR20 (%)	61.0	70.4	70.5	64.0	69.2	74.0	71.9	65.8
ACR50 (%)	30.2	40.6	46.6	41.6	36.3	42.5	45.9	43.8
ACR70 (%)	12.0	18.6	24.6	21.3	15.8	17.8	21.2	21.9
EULAR responses (n)	489	350	264	171	139	139	139	139
Good response (%)	15.7	24.9	33.0	27.5	12.2	21.6	27.3	25.2
DAS28 LDA (%)	16.2	25.1	33.0	27.5	12.9	21.6	27.3	25.2
DAS28 remission (%)	8.4	13.7	17.4	17.5	7.9	8.6	12.9	16.5
Change in DAS28	-2.15	-2.63	-2.97	-2.85	-2.35	-2.64	-2.90	-2.88
Mean change	1.43	1.43	1.47	1.62	1.34	1.39	1.45	1.60
SD								

LDA =DAS28≤3.2; remission = DAS28<2.6

Conclusion: In TNF-IR pts with an initial response to RTX repeated courses of RTX were associated with sustained levels of efficacy.

Disclosure: E. C. Keystone, Abbott Laboratories, 2, Centocor, 2, Amgen, 2, Abbott Laboratories, 5, Centocor, Inc., 5, Amgen, 5 ; **R. Fleischmann**, Abbott Laboratories, 1, Merck Pharmaceuticals, 1, Proctor and Gamble, 1, Amgen, 2, Wyeth Pharmaceuticals, 2, Abbott Laboratories, 2, Centocor, Inc., 2, UCB, 2, Genentech and Biogen IDEC Inc., 2, Roche Pharmaceuticals, 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2, Bristol Myers Squibb, 2, Regeneron, 2, XDx, 2, Amgen, 5, Wyeth Pharmaceuticals, 5, Abbott Laboratories, 5, Centocor, Inc., 5, UCB, 5, Genentech and Biogen IDEC Inc., 5, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Amgen, 8, Wyeth Pharmaceuticals, 5, Abbott Laboratories, 8 ; **P. Emery**, Roche Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Roche Pharmaceuticals ; **M. Dougados**, Roche Pharmaceuticals, 2, Wyeth Pharmaceuticals, 2, Bristol-Myers Squibb, 2, Abbott Laboratories, 2, UCB, 2, Roche Pharmaceuticals, 5, Wyeth Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Abbott Laboratories, 5, UCB, 5 ; **A. R. Baldassare**, None; **G. K. Armstrong**, Roche , 3 ; **M. D. Linnik**, Biogen Idec, 1, Biogen Idec, 3 ; **M. Reynard**, Roche Pharmaceuticals, 1, GlaxoSmithKline, 1, Roche Pharmaceuticals, 3 ; **H. Tyrrell**, Roche Pharmaceuticals, 3 .

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The Relationship Between Synovial Lymphocyte Aggregates and the Clinical Response to Infliximab in Rheumatoid Arthritis: a Prospective Study. Ruth Klaasen, Rogier M. Thurlings, Carla A. Wijbrandts, Arno W.R. van Kuijk, Dominique L. Baeten, Danielle M. Gerlag and Paul P. Tak, Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: The extent and pattern of lymphocyte infiltration in the inflamed synovial tissue is widely variable among rheumatoid arthritis (RA) patients. In some tissues a diffuse or scarce infiltration of T cells is present while in others B, T, and plasma cells are organized in aggregates exhibiting germinal center-like features. Our previous work has suggested that the clinical response to anti tumour necrosis factor (TNF) antibody treatment is related to pre-treatment synovial tissue inflammation (1) and that the presence of synovial lymphocyte aggregates is a secondary phenomenon due to chronic inflammation (2). Therefore, we hypothesized that the presence of synovial lymphocyte aggregates at baseline could in part predict clinical response to TNF blockade and that their presence is reversible after anti-TNF treatment.

Methods: Synovial tissue biopsies were obtained from 97 patients with active RA before initiation of infliximab treatment. Aggregates were counted and graded according to size (0-3). Grade 2 and 3 aggregates were termed ‘large' lymphocyte aggregates and grade 1 aggregates ‘small' lymphocyte aggregates. We determined the responder status by the reduction in disease activity score (DAS28) of at least 1.2 after 16 weeks of therapy. Serial synovial biopsies were obtained before and 28 days after initiation of TNF blockade to evaluate the effects of TNF blockade on lymphocyte aggregates in 15 RA and 9 psoriatic arthritis (PsA) patients.

Results: Good treatment response was found in 75% of patients. Of 97 patients 43% had diffuse synovial inflammation, 25% had only small lymphocyte aggregates and 32% had large and small lymphocyte aggregates. At baseline lymphocyte aggregates were found in 67% of clinical responders compared to 38% of non-responders and their presence was a highly significant predictor of the clinical response to anti-TNF treatment ($R^2 = 0.08$, $P = 0.007$). Separate analysis of large aggregates suggested a relationship with response (NS). Positivity for lymphocyte aggregates increased the prediction of clinical response to $R^2 = 0.29$ in a model including DAS28, anti-CCP positivity and synovial TNFa expression. There was reduction of lymphocyte aggregates after anti-TNF antibody therapy in both RA and PsA.

Conclusion: RA patients with synovial lymphocyte aggregates have on average a better response to infliximab treatment than those with only diffuse leukocyte infiltration. Moreover the presence of lymphocyte aggregates is reversible after TNF antibody treatment.

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Body Surface Area, Erythrocyte Sedimentation Rate, Methotrexate and Antibodies to Infliximab Influence the Pharmacokinetics of Infliximab in Rheumatoid Arthritis. Emilie Ducourau[1], David Ternant[1], Anca Corondan[2], Benoit Legoff[3], Aleth Perdriger[4], Valérie Devauchelle[5], Elisabeth Solau-Gervais[6], Philippe Goupille[1], Gilles Paintaud[1] and Denis Mulleman[1], [1]Université François Rabelais de Tours; CNRS, UMR 6239; CHRU de Tours, Tours, France, [2]CHR d'Orléans, Orléans, France, [3]CHU de Nantes, Nantes, France, [4]CHU de Rennes, Rennes, France, [5]CHU Brest, Brest, France, [6]University Hospital of Poitiers, Poitiers, France

Purpose: Infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor alpha**,** is used in rheumatoid arthritis (RA) but around 1/3 of patients are non responders. Serum trough concentrations are variable between individuals and are related to clinical response (1). To date, no detailed analysis of infliximab pharmacokinetic (PK) has been reported in RA. Our objective was to describe infliximab PK in RA and to quantify the influence of its sources of interindividual variability.

Method: Forty-three RA patients treated with infliximab for at least 14 weeks were studied. They had a stable dose of infliximab, prednisone and methotrexate (MTX) since the last infusion. Infliximab concentrations were measured by enzyme-linked immunosorbent assay (2) before the infusion, 2 hours, 1 week, 4 weeks after the infusion and immediately before the next infusion. Infliximab PK was studied using a population approach. Influences of sex, body surface area (BSA), age, cotreatment, disease activity score on 28 joints (DAS 28), erythrocyte sedimentation rate (ESR), and presence of antibodies toward infliximab (ATI), on pharmacokinetic parameters were studied.

Results: A two-compartment model with first-order distribution and elimination constants allowed a satisfactory description of infliximab PK. Population estimates were obtained from the final covariate model as follow: clearance = 0.01 L/h, volume of the central compartment = 2.1 L, intercompartment clearance = 0.02 L/h, and volume of the peripheral compartment = 1.7 L. Volume of distribution of the central compartment increased with BSA. Clearance was lower in presence of MTX and higher in the presence of ATI and increased with ESR. Mean elimination half-life was 9 days without MTX, 12 days with MTX and 2.6 days with MTX and ATI.

Conclusion: This detailed description of infliximab PK in RA allowed to quantify influence of individual sources of variability. For a given dose, infliximab concentrations were higher during MTX cotreatment and lower in the presence of ATI. Exposure to infliximab decreased when BSA and ESR increased.

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Early Changes in Serum Levels of Cytokines and Chemokines Are Predictive of the Response to Rituximab Treatment in Rheumatoid Arthritis. Rogier M. Thurlings[1], Maartje J. H. Boumans[1], Koen Vos[1], Wilco de Jager[2], B. Prakken[3], Danielle M. Gerlag[1] and Paul P. Tak[4], [1]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]University Medical Center, Utrecht, Netherlands, [4]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Background: Rituximab induces a rapid decrease in B cells in peripheral blood, but the mechanism by which B cell depletion leads to clinical improvement is not completely understood.

Purpose: We used a multiplex assay to analyze the early changes in mediators of inflammation in serial serum samples after initiation of rituximab treatment in rheumatoid arthritis (RA) patients and aimed to identify soluble biomarkers of response.

Method: Twenty-eight rheumatoid factor positive and/or ACPA positive RA patients were treated with rituximab. Methylprednisolone pre-medication was omitted to study the specific effects of rituximab. Clinical response was assessed at baseline and monthly after initiation of treatment using the DAS28. A clinical response was defined as the decrease in DAS28 at week 24 and according to the EULAR response criteria. Serum cytokines, chemokines, soluble adhesion molecules and growth factors were measured using multiplex analysis before, 4 and 16 weeks after treatment. Changes were analyzed using the Wilcoxon's signed rank test.

Results: The DAS28 decreased significantly from 8 weeks after treatment ($P < 0.001$). At week 4, before any change in the DAS28, we found a decrease in serum levels of IL-22 ($P = 0.002$), IL-23 ($P = 0.03$) and CCL19 ($P = 0.04$). In the clinical responders (defined at week 24), there was also a statistically significant decrease in serum levels of IL-6, IL-15, IFNγ, TNFα, CXCL3, CCL22 and OPG at week 4. Thus, the changes in several cytokines and chemokines at week 4 were predictive of the clinical response at week 24. At week 16 most cytokines and chemokines were decreased.

Conclusion: We identified several mediators of inflammation (including those associated with the Th1 and Th17 adaptive immune response) that appear predictive of the response to rituximab treatment in RA. Rituximab-induced B cell depletion may cause a decrease in the activation state of T cell subsets, contributing to clinical improvement.

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Effectiveness of Rituximab (RTX) + Methotrexate (MTX) in Patients (pts) with Early Active Rheumatoid Arthritis (RA) and Disease Characteristics Associated with Poor Outcomes. Xavier Mariette[1], Alan Kivitz[2], John D. Isaacs[3], William Stohl[4], Paul P. Tak[5], Richard E. Jones[6], Angelika Jahreis[7], Gillian K. Armstrong[8] and Tim M. Shaw[8], [1]Hospital Bicêtre, Kremlin-Bicêtre, France, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Newcastle University, Newcastle Upon Tyne, United Kingdom, [4]Univ Southern California, Los Angeles, CA, [5]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [6]Clinic for Rheumatic Diseases, Tuscaloosa, AL, [7]Genentech, South San Francisco, CA, [8]Roche Products Ltd, Welwyn Garden City, United Kingdom

Purpose: To determine if RTX plus MTX is effective in pts with early RA in reducing the rate of joint damage and achieving clinical responses in subgroups known to be associated with poor prognoses.

Methods: IMAGE is a randomized active controlled study of RTX plus MTX compared with MTX + placebo (Plc) in MTX-naive pts with RA [1]. Pts were randomized to either Plc + MTX, RTX (2 x 500 mg) + MTX, or RTX (2 x 1000 mg) + MTX. MTX in all groups was initiated at 7.5 mg/wk and titrated to 20 mg/wk by Week 8 as tolerated. RTX was given by IV infusion with a 24-week repeat treatment schedule based on DAS28 >2.6 [1]. Radiographic (Genant modified Sharp score [mTSS]) and clinical outcomes were assessed at Week 52 and explored by baseline subgroups including pts with high DAS28 (7.5-8.3), high CRP (4th quartile) and autoantibody presence (seropositive [sero+ve] for rheumatoid factor [RF] or anti-cyclic citrullinated peptide antibodies [aCCP] or seronegative [sero–ve] for both).

Results: At Week 52 only RTX (2 x 1000mg) + MTX significantly reduced the rate of joint damage [1]; consequently data are only presented for this dose. In patients with high DAS or high CRP receiving RTX + MTX, superior clinical outcomes were observed compared with matched pts treated with Plc + MTX. In sero+ve pts receiving RTX + MTX, superior outcomes were observed compared with sero+ve pts treated with Plc + MTX (Table). Although limited by low numbers and lower radiographic progression compared with sero+ve pts, outcomes in sero–ve patients receiving RTX + MTX or Plc + MTX were similar.

Conclusion: Efficacy was demonstrated in RTX + MTX-treated MTX-naïve pts with baseline characteristics associated with poor prognosis. The presence of RF and/or aCCP may indicate a subset of MTX-naïve RA patients with more aggressive disease more likely to benefit from treatment with RTX + MTX compared with MTX alone.

	Sero+ve		**Sero–ve**	
	Plc + MTX	**RTX 2 x 1000 mg + MTX**	**Plc + MTX**	**RTX 2 x 1000 mg + MTX**
Radiographic outcomes				
N	211	218	21	24
Mean change in mTSS at Wk 52	1.148	0.354*	0.387	0.352
% with change in mTSS≤0 at Wk52	53.6%	62.4%	52.4%	79.2%
Odds ratio		1.438		3.455
95% CI		(0.979, 2.114)		(0.936, 12.743)
Clinical outcomes				
N	227	224	22	24
ACR50 response (%)	40.5%	66.5%	54.5%	54.2%
Odds ratio		2.915		0.985

95% CI		(1.986, 4.278)		(0.308, 3.146)
ACR70 response (%)	25.1%	49.6%	22.7%	25.0%
Mean change in DAS28 (SD)	-2.6	-3.64	-2.95	-3.08
	(1.529)	(1.518)	(2.073)	(1.743)
DAS28 remission (%)	12.0%	31.4%	18.2%	25.0%

*p<0.001

References:

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Disclosure: X. Mariette, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 6, Wyeth Pharmaceuticals, 6, UCB, 6 ; **A. Kivitz**, Novartis Pharmaceutical Corporation, 8, Roche Pharmaceuticals, 8, Takeda, 8, Amgen, 8 ; **J. D. Isaacs**, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8 ; **W. Stohl**, Genentech and Biogen IDEC Inc., 9 ; **P. P. Tak**, Roche Pharmaceuticals, 2, Merck-Serono, 2, Roche Pharmaceuticals, 5, Genentech and Biogen IDEC Inc., 5 ; **R. E. Jones**, Genentech and Biogen IDEC Inc., 8, Abbott Laboratories, 8, Novartis Pharmaceutical Corporation, 8, Takeda, 8, Pfizer Inc, 8 ; **A. Jahreis**, Genentech and Biogen IDEC Inc., 1, Genentech and Biogen IDEC Inc., 3 ; **G. K. Armstrong**, Roche Pharmaceuticals, 3 ; **T. M. Shaw**, Roche Pharmaceuticals, 1, Roche Pharmaceuticals, 3 .

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Patients with Early RA Treated with Abatacept Plus MTX Have a Higher Likelihood of Increasing or Maintaining Initial Improvements in Signs and Symptoms and Physical Function Over Time Than Those Treated with MTX Alone. Y. Yazici[1], D. Moniz Reed[2], A. Covucci[2], J. C. Becker[2] and R. Westhovens[3], [1]NYU Hospital for Joint Diseases, New York, NY, [2]Bristol-Myers Squibb, Princeton, NJ, [3]UZ Gasthuisberg, KU Leuven, Leuven, Belgium

Purpose: EULAR/ACR recommendations stress the importance of reporting the sustainability of treatment responses in patients (pts) with RA[1]. Here we assess the likelihood of maintaining/improving initial improvements in the signs/symptoms of RA and physical function with abatacept over 1 year (yr), in MTX-naive pts with early RA and poor prognostic factors.

Methods: In the 12-month (mth) double-blind period of AGREE (Abatacept study to Gauge Remission and joint damage progression in MTX-naïve pts with Early Erosive RA)[2], pts with RA ≤2 yrs received abatacept (~10 mg/kg) + MTX or MTX alone. In these *post-hoc* analyses, shifts in ACR response and Health Assessment Questionnaire-Disability Index (HAQ-DI) status from Mth 3 to 12 were evaluated in pts who completed the DB period (as-observed). Discrete ACR categories were defined as ACR non-responders (NR; those not achieving ACR 20), ACR 20, 50 and 70 responders; and HAQ-DI status categories as >1.5 (high), >0.8–1.5 (moderate), >0.5–0.8 (low) and ≤0.5 (normalized function)[3].

Results: In total, 232 and 227 pts were eligible for these analyses in the abatacept + MTX and MTX alone groups; baseline characteristics were comparable[2]. Shifts in ACR responses are shown (Table); between Mths 3 and 12, ACR responses deteriorated in 33.3% of MTX alone pts, compared with only 17.7% of abatacept + MTX pts. For abatacept + MTX pts with high HAQ-DI and moderate HAQ-DI at Mth 3, 50.0 and 41.3%, respectively, improved their status by Mth 12. Of the abatacept + MTX pts with low HAQ-DI at Mth 3, 65.5% achieved normalized HAQ-DI at Mth 12. For those abatacept + MTX pts who achieved normalized HAQ at Mth 3, 89.6% retained their status at Mth 12. Similar patterns of maintenance were seen for the MTX alone active comparator group; 76.9% of MTX alone pts achieved normalized HAQ-DI at Mth 3 and retained their status at Mth 12.

Proportion with ACR response at Mth 3	**Shift in ACR response from Mth 3 to 12 (%)**			
	ACR 20 NR	**ACR 20**	**ACR 50**	**ACR 70**
Abatacept + MTX				
ACR 20 NR, 35.9%	46.7	27.2	12.0	14.1
ACR 20, 24.2%	21.0	22.6	27.4	29.0

ACR 50, 21.1%	7.4	14.8	14.8	63.0
ACR 70, 18.8 %	2.1	2.1	4.2	91.7
MTX alone				
ACR 20 NR, 46.6%	49.2	20.3	13.6	16.9
ACR 20, 30.8%	33.3	28.2	19.2	19.2
ACR 50, 12.6%	15.6	3.1	12.5	68.8
ACR 70, 9.9%	28.0	12.0	12.0	48.0

Conclusion: At Yr 1, the majority of abatacept-treated pts with early RA demonstrated improvement/maintenance in signs/symptoms and physical function. Pts treated with abatacept + MTX had a higher likelihood of maintaining or improving ACR responses over time than those treated with MTX alone. These data demonstrate the sustained efficacy of abatacept in early RA.

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Abatacept Demonstrates Consistent Safety and Sustained Improvements in Efficacy through 4 Years of Open-Label Treatment in Patients with An Inadequate Response to Anti-TNF Therapy. M. C. Genovese[1], M. Schiff[2], M. E. Luggen[3], M. Le Bars[4], J. C. Becker[5], R. Aranda[5], A. Elegbe[5], R. Cohen[5] and M. Dougados[6], [1]Stanford University, Palo Alto, CA, [2]Univ of Colorado, Denver, CO, [3]University of Cincinnati Medical Center, Cincinnati, OH, [4]Bristol-Myers Squibb, Rueil-Malmaison, France, [5]Bristol-Myers Squibb, Princeton, NJ, [6]Hospital Cochin, Descartes Univ, Paris, France

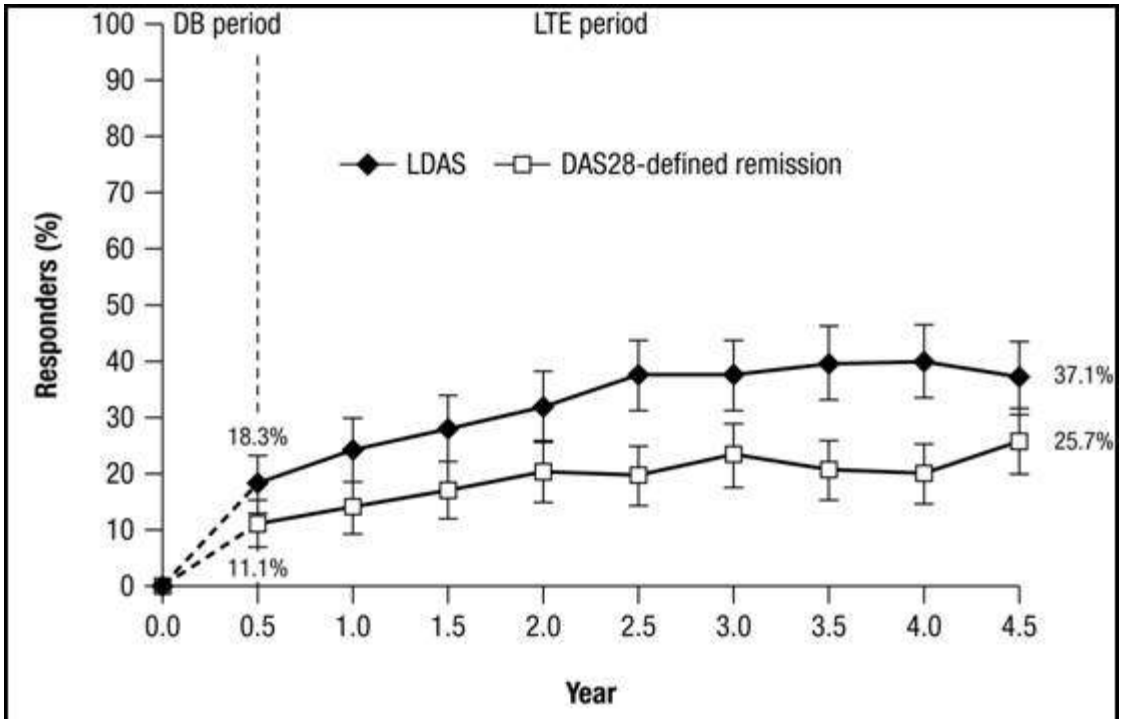
Purpose: Abatacept has demonstrated sustained efficacy and consistent safety over 3 years in patients with RA and an inadequate response to anti-TNF therapy in the ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) trial[1]. Here we evaluate the long-term safety and efficacy of abatacept over 4 years of the open-label (OL) long-term extension (LTE) of this trial.

Methods: Patients completing the 6-month double-blind (DB) period were eligible for the LTE (abatacept ~10 mg/kg, every 4 wks plus DMARDs). Here we present interim as-observed analyses of long-term safety and efficacy. Safety was assessed monthly for all patients who received ≥1 dose of abatacept during the LTE.

Clinical efficacy (ACR 20, 50 and 70 responders), disease activity status (DAS28 [CRP]-defined remission [DAS28<2.6] and Low Disease Activity State [LDAS; DAS28 ≤3.2]) were evaluated quarterly to Year 3, and biannually thereafter, for patients originally randomized to abatacept.

Results: In total, 258 and 133 patients were randomized and treated with abatacept or placebo in the DB period; 218 and 99 entered the LTE, respectively. At the time of reporting, 6 months of DB and 4 years of LTE efficacy data were available, while safety analyses were reported up to Nov 2008 (mean abatacept exposure during the DB period plus LTE=42.2 months [range=3.7–65.5]). Up to Nov 2008, 165 (52.1%) patients discontinued from the LTE. In the DB period vs the LTE, incidence rates for serious adverse events were 25.98 vs 19.55/100 patient–years (pt–yrs), and for serious infections were 5.28 vs 3.40/100 pt–yrs. There were no cases of TB or opportunistic infections in the LTE. Rates of malignancies were 3.51 vs 2.17/100 pt–yrs in the DB vs LTE period. Rates of autoimmune events were 1.75 vs 1.53/100 pt–yrs in the DB vs LTE period. There was a sustained improvement over 4 years of OL abatacept treatment in ACR 20 responders (Month 6=60.1% [95% CI: 53.6, 66.6] vs Year 4.5=80.9% [75.7, 86.1]). A similar pattern was observed for ACR 50 and 70 responders (Month

6=23.9% [18.2, 29.6] and 11.8% [7.5, 16.1] vs Year 4.5=45.0% [38.4, 51.7] and 23.2% [17.6, 28.8]), and for patients achieving LDAS and DAS28-defined remission (Figure).



	Year 0.5 (n)	Year 1.0 (n)	Year 1.5 (n)	Year 2.0 (n)	Year 2.5 (n)	Year 3.0 (n)	Year 3.5 (n)	Year 4.0 (n)	Year 4.5 (n)
LDAS/remission	208	194	164	153	133	133	126	115	105

Conclusion: In this trial of patients with RA and an inadequate response to anti-TNF therapy, the safety of abatacept over 4 years of the LTE was consistent with the DB period. Sustained clinical efficacy was observed in patients initially randomized to abatacept, supporting long-term use of abatacept in this patient population with refractory disease.

Reference: 1. Kremer, JM. *Arthritis Rheum* 2007;**56**(Suppl 9):S300. Abstract 699.

Disclosure: M. C. Genovese, Bristol-Myers Squibb, 8, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2 ; **M. Schiff**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 9 ; **M. E. Luggen**, Bristol-Myers Squibb, 2, Centocor, Inc., 2, Genentech, 2, Roche Pharmaceuticals, 2, BiogenIDEC, 2 ; **M. Le Bars**, Bristol-Myers Squibb, 9, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **J. C. Becker**, Bristol-Myers Squibb, 9, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1 ; **R. Aranda**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **A. Elegbe**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 9 ; **R. Cohen**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3 ; **M. Dougados**, Bristol-Myers Squibb, 8, Schering Plough, 5, Roche , 5, Centocor, Inc., 5, Wyeth, 5, Abbott, 5, Bristol-Myers Squibb, 5, Schering Plough, 2, Roche Pharmaceuticals, 2, Centocor, 2, Wyeth Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 2, Abbott, 8, Roche, 8, Wyeth, 8 .

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Abatacept Reduces Osteitis and Inhibits Bone Erosion in Anti-CCP2 Positive Patients with Synovitis at High Risk of Developing RA.

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Purpose: Osteitis on magnetic resonance imaging (MRI) is a strong predictor of radiographic progression in patients with RA[1]. Here, for the first time, we assess the impact of T-cell co-stimulation modulation with abatacept on MRI osteitis score in very early arthritis in patients with synovitis and anti-CCP antibodies, who are at a high risk of developing RA.

Methods: ADJUST (Abatacept study to Determine the effectiveness in preventing the development of RA in patients with Undifferentiated inflammatory arthritis and to evaluate Safety and Tolerability) was a randomized, double-blind, Phase II, placebo-controlled exploratory study of patients with undifferentiated arthritis, symptomatic clinical synovitis of ≥2 joints and anti-CCP2 positivity; the primary endpoint was proportion of patients who developed RA by ACR criteria. A total of 56 patients with mean symptom duration of 7.9 months were randomized 1:1 to abatacept (~10 mg/kg) or placebo for up to 6 months, after which treatment was stopped. Patients who developed RA were discontinued. In this substudy, 21 patients had gadolinium-enhanced MRI of one hand/wrist within 2 weeks prior to initiating study drug and repeated at Month 6 and Year 1. MRI images were scored using the OMERACT 6 method[2].

Results: At Month 6, osteitis scores had improved from baseline with abatacept, but increased with placebo (Table). For patients who completed Year 1, 6 months after stopping therapy there was little progression in osteitis in the abatacept group but worsening in the placebo group (Table). MRI erosion and synovitis scores showed a similar trend; at Month 6, mean changes from baseline were 0.45 and 0.27, respectively, in the abatacept group and 1.20 and 1.60 in the placebo group. By Year 1, mean change from baseline in erosion and synovitis scores were 0 and 0.22, respectively, in the abatacept group versus 5.00 and 2.33 in the placebo group.

Osteitis scores	**Abatacept**	**Placebo**
Month 6	**n=11**	**n=10**
Baseline (SD)	2.36 (5.28)	3.40 (8.42)
Month 6 (SD)	0.73 (1.10)	4.80 (7.84)
Change (95% CI)	–1.64 (–4.94, 1.67)	1.40 (–2.19, 4.99)
Month 12	**n=9**	**n=6**
Baseline (SD)	0.56 (1.01)	0.67 (1.63)
Year 1 (SD)	0.78 (1.30)	7.33 (11.52)
Change (95% CI)	0.22 (–0.92, 1.36)	6.67 (–4.19, 17.53)
SD=standard deviation; CI=confidence interval		

Conclusion: This small substudy in anti-CCP2 positive patients with early arthritis suggests that administration of abatacept reduces osteitis and synovitis, and inhibits bone erosion on MRI. This inhibition was maintained to Year 1, demonstrating a sustained benefit that persisted after therapy cessation.

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Disclosure: C. Peterfy, Synarc, Inc., 3, Synarc, Inc., 4 ; **P. Durez**, Bristol-Myers Squibb, 8, Board member of the UEMS and the Royal Belgian Society of Rheumatology , 6, Bristol-Myers Squibb, Roche, Centocor, Abbott, Wyeth , 5 ; **J. DiCarlo**, Synarc, Inc., 3 ; **J. C. Becker**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, Bristol-Myers Squibb ; **G. Vratsanos**, Bristol-Myers Squibb, 3 ; **S. Overfield**, None; **K. Qi**, Bristol-Myers Squibb, 3 ; **P. Mitra**, Bristol-Myers Squibb, 3 ; **H. K. Genant**, BMS, Roche, Genentech, Pfizer, Amgen, Merck, Servier, BiogenIdec, Lilly, 2, BMS, Roche, Merck, Lilly, Genentch, Amgen, Servier, Synarc, 5 ; **P. Emery**, Amgen, Schering-Plough, Centocor, Bristol-Myers Squibb, Roche, 5 .

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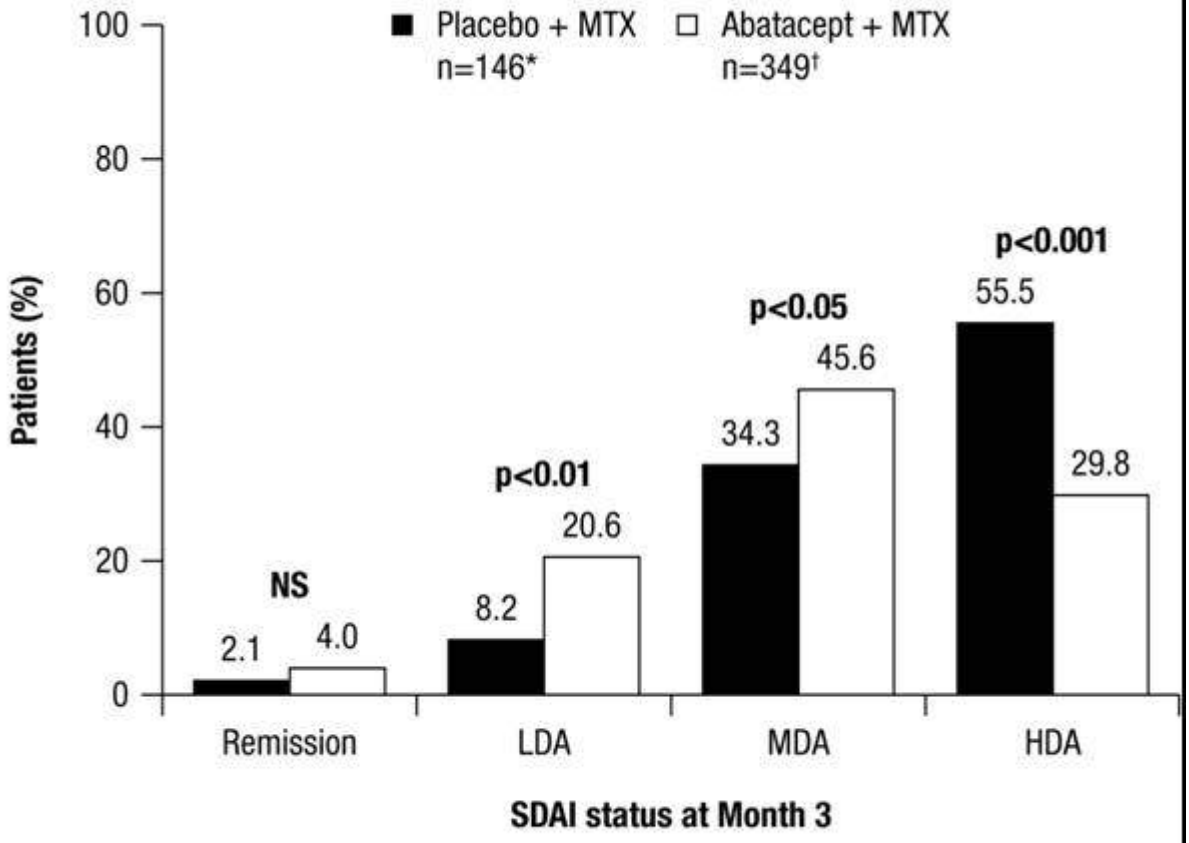
A Significant Proportion of Patients with RA Achieve Simplified Disease Activity Index (SDAI)-Defined Low Disease Activity or Remission with Abatacept Vs Placebo, and SDAI Remission Is Associated with Reduced Radiographic Progression. J. S. Smolen[1], D. Aletaha[1], M. Le Bars[2], C. Poncet[3], M. Schiff[4], J. M. Kremer[5], Y. Yazici[6], P. Emery[7], R. Westhovens[8] and M. Dougados[9], [1]Medical Univ Vienna, Vienna, Austria, [2]Bristol-Myers Squibb, Rueil-Malmaison, France, [3]Docs International, Issy-les-Moulineaux, France, [4]Univ of Colorado, Denver, CO, [5]Albany Medical College, Albany, NY, [6]NYU Hospital for Joint Diseases, New York, NY, [7]Univ Leeds, Leeds, United Kingdom, [8]UZ Gasthuisberg, KU Leuven, Leuven, Belgium, [9]Hospital Cochin, Descartes Univ, Paris, France

Purpose: The SDAI composite disease activity index is a stringent measure of remission[1], and good correlation between SDAI states and changes in radiographic progression have been reported[2]. Analyses were performed to assess SDAI disease activity status and to determine the correlation between SDAI status and radiographic progression in patients (pts) with RA and an inadequate response to MTX.

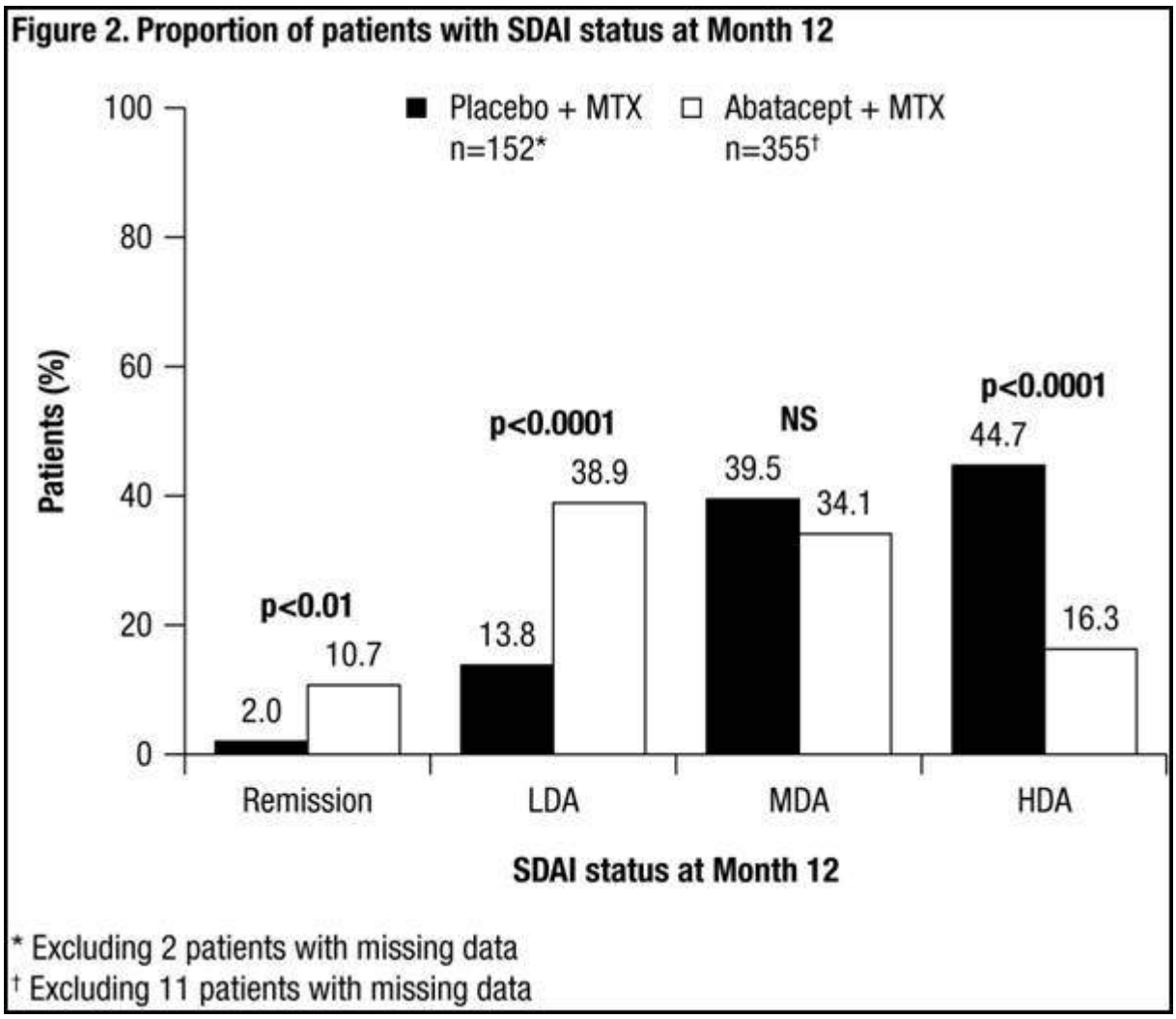
Methods: Pts who completed the 1-yr, randomized, double-blind period of the AIM (Abatacept in Inadequate Responders to MTX) trial (abatacept ~10 mg/kg or placebo, plus MTX)[3] and had radiographs at baseline and Yr 1 were eligible for analysis (*post hoc*, as observed). SDAI states were assessed at Mths 3 and 12, defined as High Disease Activity (HDA; >26), Moderate Disease Activity (MDA; >11–26), Low Disease Activity (LDA; >3.3–11) or remission (≤3.3). Changes from baseline to Mth 12 in Genant-modifed Sharp total score (TS) were analysed by SDAI status attained at Mth 3.

Results: 366 abatacept and 154 placebo pts were eligible for analysis. Baseline demographics were comparable between treatment groups[3]. At Mth 3, significantly more abatacept than placebo pts had achieved LDA; at Mth 12, the proportions of abatacept pts in LDA and remission had increased ~twofold and differences between treatment groups were statistically significant for both measures (Figs). The proportion of abatacept pts in HDA was reduced by ~45% from Mth 3 to 12; levels were significantly lower vs placebo at both time points (Figs). In the radiographic analysis, the smallest change in TS from baseline to Mth 12 was observed in abatacept pts who achieved remission at Mth 3 (change in TS: –0.2 [n=14]); mean changes in TS were 0.63 (72), 1.1 (159) and 1.97 (104) for LDA, MDA and HDA, respectively. For placebo pts mean changes in TS were 0.73 (3), 2.75 (12), 2.26 (50) and 2.9 (81) for remission, LDA, MDA and HDA, respectively. Changes in TS, especially in the remission and LDA groups, were numerically smaller in abatacept vs placebo pts.

Figure 1. Proportion of patients with SDAI status at Month 3



* Excluding 17 patients with missing data
† Excluding 8 patients with missing data



Conclusion: A significant proportion of abatacept pts achieved LDA or remission vs placebo over 1 yr according to the stringent SDAI criteria. SDAI remission and LDA at Mth 3 were associated with low levels of radiographic progression at Mth 12, in particular with abatacept compared with placebo, suggesting that these states are predictive of a reduction in radiographic progression, as observed with other biologics[4].

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Disclosure: J. S. Smolen, Bristol-Myers Squibb, 8, Bristol-Myers Squibb, 5 ; **D. Aletaha**, Abbott, Bristol-Myers Squibb, 5, Abbott, Roche, Shering-Plough, Bristol-Myers Squibb, 8 ; **M. Le Bars**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 9 ; **C. Poncet**, None; **M. Schiff**, Bristol-Myers Squibb, 9, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2 ; **J. M. Kremer**, Abbott Immunology Pharmaceuticals, 2, Amgen, 2, Bristol-Myers Squibb, 2, Centocor, Inc., 2, Genentech, 2, Merck , 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 5, Amgen, 5, Bristol-Myers Squibb, 5, Genentech, 5, Centocor, 5, Merck, 5, Pfizer Inc, 5, Roche, 5 ; **Y. Yazici**, Bristol-Myers Squibb, Celgene, Roche, Centocor, Genentech, UCB, 5, Bristol-Myers Squibb, Pfizer, 8 ; **P. Emery**, Amgen, Shering-Plough, Centocor, Bristol-Myers Squibb, Roche, 5 ; **R. Westhovens**, Bristol-Myers Squibb, 8, Bristol-

Myers Squibb, Schering-Plough, Centocor, Roche, 5, UCB , 2 ; **M. Dougados**, Bristol-Myers Squibb, Abbott, Roche, Wyeth, 8, Bristol-Myers Squibb, Abbott, Wyeth, Centocor, Roche, Schering Plough, 2, Bristol-Myers Squibb, Abbott, Wyeth, Centocor, Roche, Schering Plough, 5 .

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Immunogenicity Is Not Increased with Subcutaneous Administration of Abatacept with and without Methotrexate in Patients with Rheumatoid Arthritis: Results From a Phase III Study. P. Nash[1], S. Nayiager[2], M. Genovese[3], A. Kivitz[4], K. Oelke[5], C. Ludivico[6], W. Palmer[7], C. Rodriguez[8], I. Dalaet[8], S. Overfield[8], A. Elegbe[8] and M. Corbo[8], [1]University of Queensland, Brisbane, Australia, [2]St Augustine's Hospital, Durban, South Africa, [3]Stanford University, Palo Alto, CA, [4]Altoona Center for Clinical Research, Duncansville, PA, [5]Rheumatic Disease Center, Glendale, WI, [6]East Penn Rheumatology Associates, Bethlehem, PA, [7]Westroads Medical group, Omaha, NE, [8]Bristol-Myers Squibb, Princeton, NJ

Purpose: Abatacept (ABA), a selective co-stimulation modulator, is approved for IV use in rheumatoid arthritis (RA). Subcutaneous (SC) administration may provide further dosing flexibility. The use of some biologics requires background methotrexate (MTX) to suppress immunogenicity[1]. We present data from a phase III study in RA patients (pts) examining the immunogenicity and safety of SC ABA with or without background MTX in the absence of an initial IV loading dose of ABA.

Method: In this multi-center, 4-month, parallel-cohort, open-label trial, RA pts were stratified to SC ABA + MTX or SC ABA only. SC ABA was self-administered once weekly at a fixed dose of 125 mg in a ready-to-use prefilled syringe. The primary endpoint was the proportion of pts seropositive by ELISA for anti-ABA or anti-CTLA4 antibodies at Day 113. Antibodies were also assessed by electrochemiluminescence meso-scale discovery (MSD) method. Safety was monitored throughout. Clinical efficacy and pharmacokinetics were secondary endpoints.

Results: One hundred pts (mean age, 54.0 yrs; mean weight, 83.1 kg; mean disease duration, 10.1 yrs) were treated with SC ABA + MTX (n = 51) or SC ABA only (n = 49). ELISA detected no antibody response to ABA or CTLA-4 at Day 113, giving an immunogenicity rate of 0%. Prior to Day 85, 2 pts (1, anti-ABA; 1, anti-CTLA4) in the SC ABA + MTX group (3.9%) and 1 pt (anti-CTLA4) in the SC ABA only group (2.0%) developed antibodies. MSD method confirmed the low immunogenicity rate observed with ELISA. No neutralizing antibodies were detected. Treatment-related AE rates were similar between SC ABA + MTX (27.5%) and SC ABA only (24.5%) with 1 serious AE considered drug-related in each group. Injection site reactions were mostly mild and similar between SC ABA + MTX (5.9%) and SC ABA only (8.2%). No malignancies, autoimmune disorders or deaths were reported. Improvements in Disease Activity Score (DAS) 28 from baseline to Day 113 were seen in both arms. Immunogenicity was transient; it did not affect efficacy or serum ABA Cmin, nor did it increase injection site reactions.

Conclusion: Weekly SC ABA resulted in low immunogenicity after repeat dosing regardless of the presence or absence of background MTX or an initial IV loading dose of ABA. SC ABA was well tolerated with no new safety signals observed. These results are consistent with previous experience with IV ABA[2] and support the continued development of SC ABA with and without background MTX.

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A Safety Analysis of Oral Prednisone as a Pre-Treatment for Rituximab in Rheumatoid Arthritis. John D. Carter[1], Anthony I. Sebba[2], Nancy L. Albritton[1], Angie H. Osorio[1], Ginger L. Pfeiffer[2], Joanne Valeriano[1] and Frank B. Vasey[1], [1]University of South Florida, Tampa, FL, [2]Palm Harbor, FL

Purpose: The administration of 100mg of methylprednisolone intravenously (IV) ½ hour prior to rituximab decreases the incidence and severity of acute infusion reactions (AIRs). However, the recommended pretreatment with IV methylprednisolone adds considerable time to the medication administration protocol; it also conveys potential risk. We present preliminary results of an assessment of oral prednisone as a pretreatment to rituximab.

Methods: This is a 6-month open-label assessment of 40mg of oral prednisone given ½ hour prior to rituximab as a prophylaxis against acute infusion reactions in patients with rheumatoid arthritis (RA). Subjects are ages 18-80 and are either methotrexate (MTX) or TNF-antagonist inadequate responders. All subjects have to be on concomitant methotrexate. Standard safety and laboratory exclusions applied. All subjects were treated with 40mg of oral prednisone ½ hour prior to their rituximab infusions. Rituximab was administered as per the standard RA protocol; i.e. 1000mg IV twice at days #1 and #15. The primary endpoint is AIRs in the first 24 hours after the initiation of their day #1 infusion. The severity, timing, and treatment (including rituximab dose modifications) of any AIRs are also recorded. Secondary endpoints include AIRs during the 24 hours following the day #15 infusion and any adverse events experienced during the 6 month study; efficacy measures (DAS-28 and HAQ-DI) were also followed as secondary endpoints.

Results: 32 subjects have been screened and 27 subjects qualified. Baseline demographics include 25 females and 2 males, with 22/27 (81%) Caucasians, 4 (15%) Hispanics, and 1 other. The subjects mean age was 52.9 years (range 29-80) and disease duration was 10.7 years (range 1-40). The average MTX dose is 15.1mg weekly and 16/27 (59%) have failed previous anti-TNF therapy (average number of TNF-antagonists used was 1.5). 12/27 (44%) subjects were on glucocorticoids at baseline with an average dose of 6.3mg prednisone daily; 18/27 (67%) subjects were seropositive. The mean DAS28 at screening was 5.48 and their HAQ-DI was 1.38. Regarding the primary endpoint, 7/27 (26%) of the subjects had AIRs within 24 hours of their day #1 infusion; 6 were mild in severity and 1 was moderate. There were only 3 (11%) AIRs within 24 hours of their day #15 infusion; all were mild. None of the AIRs required drug discontinuation. Of the 13 subjects who have completed the entire 6 months of the study, 8 (62%) experienced an AE at some point during the trial. There were 2 SAE's (a-fib and asthma) deemed not to be study-drug related. The DAS28 and HAQ-DI all improved significantly at weeks 8, 16, and 26 compared to baseline.

Conclusion: Historical controls demonstrate that 27-33% of RA subjects experience AIRs with their first rituximab infusion. Our data suggest a smaller dose of oral prednisone is an effective alternative to IV methylprednisolone as a pretreatment for rituximab in patients with RA.

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Single Infusion of Infliximab Reduced Excessive Bone Resorption in Patients with Rheumatoid Arthritis. Masao Nawata, Kazuyoshi Saito, Kentaro Hanami and Yoshiya Tanaka, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background: Bone disorders associated with rheumatoid arthritis (RA) are classified mainly into joint destruction due to spread of synovitis, abnormal periarticular and systemic bone metabolism. However, a growing body of evidence including ATTRACT study has emphasized suppressive effects of tumor necrosis factor (TNF)-α inhibitor infliximab on joint destruction at one year, precise mechanisms of infliximab for bone metabolism in RA patients remain to be clarified. We here addressed the involvement of TNF-α in bone destruction in RA, by observing how infliximab effects on bone metabolism in RA patients from 2 to 54 weeks.

Purpose: The aim of this study is to investigate the short and long term effect of infliximab on bone metabolism and to elucidate the mechanism of suppressive effect of infliximab on bone destruction by infliximab in RA.

Method: 105 active RA patients were enrolled. Among them, 90 patients were refractory to MTX and were treated with infliximab (3 mg/kg, administered every 8 week) and 15 patients were treated with MTX alone as the control group. Clinical disease activity was determined using DAS28 and bone mineral density (BMD), urinary crosslinked N-terminal telopeptide of type I collagen (u-NTx) and serum bone alkaline phosphate (BAP) were measured at a baseline and week 2, 22 and 54 after the treatment.

Results: The enrolled RA patients showed a high disease activity (DAS28 5.3±0.91) and corresponding levels to the age of BMD (L2-4; 0.89±0.18 g/cm^2, hip; 0.67±0.14 g/cm^2). Serum BAP were within normal levels (26.9±10.5 U/I), whereas u-NTx levels (76.9±74.1 nmol/mmol CRE) were markedly increased at baseline. No significant difference was observed between infliximab and MTX group

regarding background. BMD did not change for 54 weeks in both groups. MTX alone did not change u-NTx and BAP levels during 54 weeks. It is noteworthy that treatment with infliximab significantly decreased u-NTx to 59.5±43.7 ($p<0.05$) with in only 2 weeks and this decrease of u-NTx levels was maintained with 55.4±29.7 ($p<0.05$) and 47.8±26.5 ($p<0.05$) at the week 22, and 54, respectively. The rate of change in u-NTx at 2 week was significantly correlated with the rate of u-NTx at 54 week by the multivariate analysis ($r=0.529$, $p<0.0001$). In contrast, serum BAP levels increased significantly at week 22 (31.6±11.5 ; $p<0.05$) and 54 (31.8±11.6 ; $p<0.05$) but not at week 2 (24.3±7.4; ns) by infliximab.

Conclusion: Although bone resorption was markedly enhanced in RA, single infusion of infliximab significantly reduced excessive the bone resorption within 2 weeks, implying rapid and strong suppression of bone resorption or joint destruction by infliximab. This reduction of bone resorption was maintained for 52 weeks. Thus, the complete inhibition of yearly progression of Total Sharp Score might be due to such a rapid and marked reduction of bone resorption within 2 weeks after infliximab infusion.

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Effectiveness of Treatment with Rituximab Depends On Autoantibody Status – Results From 2 Years of Experience in the German Biologics Register RABBIT. Anja Strangfeld[1], Maria Eveslage[1], Joern Kekow[2], Anett Gräßler[3], Jörg Kaufmann[4], Joachim Listing[5] and Angela Zink[1], [1]German Rheumatism Research Center, Berlin, Germany, [2]Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany, [3]Rheumatologist in Private Practice, Pirna, Germany, [4]Rheumatologist in Private Pactice, Ludwigsfelde, Germany, [5]DRFZ, Berlin, Germany

Purpose: To investigate the effectiveness of treatment with Rituximab (RTX) over the first six to twelve months in daily rheumatologic care.

Methods: The German biologics register RABBIT is a prospective cohort study observing all licensed biologic agents. Since 2006, patients with a first or repeat treatment cycle of RTX have been enrolled. They will be followed up for at least 5 years. Regular assessments include clinical status as well as therapy.

Results: Of a total of 661 patients enrolled at start of RTX therapy, 424 patients (78% female) were observed for at least six months. Their median disease duration was 11 years. 16.3% of the patients achieved a EULAR good response, 44.7% a moderate response and 39.0% no response after six months. There was no difference in the proportion of moderate or good responses between patients who received RTX for the first time or a repeat cycle or between patients who received RTX in combination with methotrexate and those on RTX monotherapy.

	Treatment RTX		Rheumat. factor		anti-CCP	
	+ MTX	Mono ther.	Neg.	Positive	Neg.	Positive
n	229	120	75	348	82	342
DAS28 month 0	5.5	5.7	5.3	5.6	5.2	5.6
DAS28 month 6	4.5	4.3	4.7	4.3	4.4	4.4
% EULAR response #	56.8	64.2	45.3	64.4	54.9	62.6
OR EULAR response *	Refer.	1.38	Refer.	2.01	Refer.	1.26
CI 95% of OR		[0.86; 2.21]		[1.2; 3.4]		[0.76; 2.07]

* odds ratio adjusted for baseline status of DAS28, # DAS28 good or moderate response

Rheumatoid factor (RF) positive patients had a significantly better response than seronegative ones ($p=0.003$). Taking the baseline status into account this difference corresponds to an adjusted odds ratio of 2.0 (95%CI: 1.2 - 3.4). A similar, albeit insignificant, difference was observed for anti-CCP antibodies. Among 265 patients observed for at least 12 months, 180 (68%) had a second cycle of RTX after a mean duration of 8.7 months. After six months, 9% of the patients had already received their second cycle.

Conclusion: The data show effectiveness of RTX in a majority of unselected real-life RA patients. The higher improvement in rheumatoid factor and/or anti-CCP antibody positive patients might indicate that B-cell depletions is more effective in autoantibody positive patients.

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Efficacy of Golimumab, a Human Anti-TNFα Antibody, by Baseline CRP Level in Patients with Rheumatoid Arthritis: Results From Three Phase 3, Randomized, Double-Blind, Placebo-Controlled Studies. P. Emery[1], M.C. Genovese[2], R.M. Fleischmann[3], E. L. Matteson[4], E. C. Hsia[5], S. Xu[6], M. K. Doyle[5] and M. U. Rahman[5], [1]Leeds Gen Infirmary, Leeds, United Kingdom, [2]Stanford University, Palo Alto, CA, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Mayo Clinic, Rochester, MN, [5]Centocor R&D, Inc/U of Penn School of Med, Malvern, PA, [6]Centocor R&D, Inc, Malvern, PA

Purpose: To assess GLM efficacy by baseline disease severity as measured by CRP level in three Phase 3 RA clinical trials (GO-BEFORE, GO-FORWARD, and GO-AFTER).

Methods: Adult pts with active RA were randomized to placebo (PBO)+/- methotrexate (MTX) or GLM (50 or 100 mg)+/-MTX across the three studies. Study agent was administered subcutaneously q4wks. The studies enrolled pts who were MTX-naive (n=637; GO-BEFORE), responded inadequately to MTX (n=444; GO-FORWARD), and who were previously treated with a biologic anti-TNFalpha agent (n=459; GO-AFTER). ACR20, ACR50 and DAS28-CRP (good or moderate) responses at wk 24 were assessed by baseline disease severity, as determined by baseline CRP quartiles. The baseline CRP quartiles (Q1-Q4) were ≤0.5, >0.5-≤1.3, >1.3-≤3.4, >3.4 mg/dL for GO-BEFORE; ≤0.4, >0.4-≤ 0.9, >0.9-≤ 2.3, >2.3 mg/dL for GO-FORWARD; ≤0.3, >0.3-≤0.8, >0.8-≤2.3, >2.3 mg/dL for GO-AFTER.

Results: GLM +/- MTX demonstrated efficacy in three distinct RA populations in all 4 quartiles of baseline serum CRP levels, although statistical significance vs PBO was not reached for all efficacy parameters in all subgroups (Table). In MTX-naïve pts, GLM was effective, with comparable ACR 20, ACR50 and DAS28-CRP responses at wk 24 across CRP quartiles. In pts with inadequate response to MTX, GLM was effective across CRP quartiles, with pts in the 2nd and 3rd quartiles achieving the highest ACR and DAS-CRP response rates at wk24. In pts with prior biologic anti- TNFalpha agent experience, benefit was observed across all CRP quartiles, including in the highest quartile.

Table:

Summary of Results

Baseline CRP quartile (Q)	**PBO(+/-MTX)**	**GLM 50mg (+/-MTX)**	**GLM 100mg (+/-MTX)**
GO-BEFORE			
1Q, N, ACR20/50/DAS	40, 48%, 15%, 53%	41, 61%, 27%, 76%*	52, 48%, 27%, 62%
2Q, N, ACR20/50/DAS	38, 63%, 37%, 74%	40, 63%, 48%, 78%	30, 67%, 33%, 83%
3Q, N, ACR20/50/DAS	43, 42%, 35%, 61%	43, 56%, 40%, 70%	38, 68%*, 50%, 79%
4Q, N, ACR20/50/DAS	39, 46%, 31%, 56%	35, 69%, 49%, 80%*	39, 69%*, 39%, 85%*
GO-FORWARD			
1Q, N, ACR20/50/DAS	42, 29%, 14%, 48%	24, 50%, 33%, 71%	24, 46%, 13%, 71%
2Q, N, ACR20/50/DAS	29, 24%, 14%, 52%	20, 55%*, 45%*, 80%	21, 71%**, 43%*, 95%

3Q, N, ACR20/50/DAS	34, 29%, 9%, 35%	21, 71%*, 33%*, 81%*	21, 67%*, 33%*, 76%*
4Q, N, ACR20/50/DAS	28, 29%, 18%, 54%	24, 63%*, 38%, 67%	23, 57%*, 44%*, 74%*
GO-AFTER 1Q, N, ACR20/50/DAS	43, 21%, 12%, 30%	40, 20%, 15%, 38%	52, 37%, 19%, 62%*
2Q, N, ACR20/50/DAS	29, 21%, 0%, 17%	37, 49%*, 19%*, 62%**	30, 37%, 17%*, 57%*
3Q, N, ACR20/50/DAS	48, 15%, 4%, 21%	34, 38%*, 18%*, 53%*	33, 46%*, 18%*, 61%**
4Q, N, ACR20/50/DAS	35, 11%, 3%, 23%	41, 32%*, 22%*, 44%*	37,60%**, 27%*, 78%**

**p<0.05, **p<0.001 vs PBO*

Conclusion: GLM was efficacious in active RA pts, including those who were MTX-naïve, with inadequate response to MTX, and who were previously treated with anti-TNFalpha agent(s), regardless of baseline disease activity as assessed by serum CRP level.

Disclosure: P. Emery, Centocor Research and Development, Inc, 9 ; **M. C. Genovese**, JNJ, 2, JNJ, 5, Centocor Research and Development, Inc, 8 ; **R. M. Fleischmann**, Centocor Research and Development, Inc, 9 ; **E. L. Matteson**, Centocor Research and Development, Inc, 2, Centocor Research and Development, Inc, 9, Centocor Research and Development, Inc, 9 ; **E. C. Hsia**, Centocor Research and Development, Inc, 3 ; **S. Xu**, Centocor Research and Development, Inc, 3 ; **M. K. Doyle**, Centocor Research and Development, Inc, 3 ; **M. U. Rahman**, Centocor, Inc., 3 .

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Open-Label Certolizumab Pegol Is Effective in Patients Who Withdrew From Double-Blind Treatment Due to Non-Response.

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Purpose: The RAPID 1 trial demonstrated that double-blind treatment with certolizumab pegol (CZP) 200 or 400 mg Q2W + MTX significantly reduces RA signs and symptoms and inhibits radiograph progression compared with placebo (PBO) + MTX.(1) Here we present the efficacy of open-label (OL) CZP + MTX in patients who withdrew from double-blind treatment with either CZP or PBO.

Methods: Of the 199, 393 and 390 patients treated with PBO, CZP 200 mg and CZP 400 mg, respectively, in RAPID 1, 137, 91, and 74 withdrew at Wk 16 due to ACR20 non-response at Wks 12 and 14 (as per protocol). 287 (95.0%) patients reconsented and were enrolled in the OL study. Efficacy assessments included ACR20/50/70 responder rates (using non-responder imputation based on enrollment in the OL portion of the trial), DAS28(ESR) and HAQ-DI (LOCF).

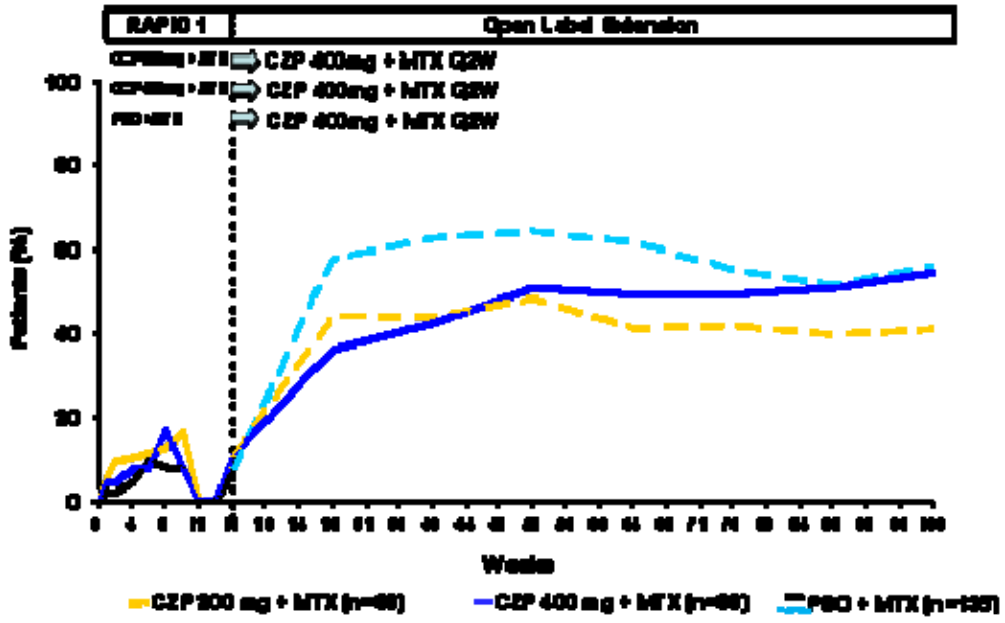
Results: Of the patients who withdrew at Wk 16 due to ACR20 non-response, 8% of PBO-treated patients and 16% of CZP-treated patients demonstrated ACR20 responses at Wk 8 that were transient (Figure). Upon receiving OL CZP treatment, patients rapidly achieved ACR20 responses, which reached 63% in PBO withdrawers switched to OL CZP and 54% in CZP withdrawers (400 mg) switched to OL CZP, and were comparable to response rates in the double-blind trial. Responses were sustained through to at least Wk 100. Similar trends for both the PBO and CZP withdrawers were observed for ACR50 and 70 response rates, HAQ-DI scores and DAS28 (data not shown). Comparable benefits were observed in patients who received either CZP 200 mg or 400 mg for the first 16 weeks.

Conclusion: A subset of patients with ongoing active disease that failed to respond to CZP or PBO in the double-blind phase rapidly responded to CZP upon receiving OL therapy. These data suggest that response to CZP + MTX, and perhaps other study drugs, may be underestimated in a double-blind trial, and supports the use of an early escape to OL treatment in clinical trials. These results may also

contribute to the understanding as to how both patient and physician perceptions are influenced by the possibility of receiving placebo versus active treatment.

References: 1.Keystone EC, et al. Arthritis Rheum 2008;58:3319–3329.

Figure. ACR20 responder rate in CZP and PBO withdrawers



Disclosure: E. C. Keystone, UCB, 5, UCB, 2, UCB, 8 ; **D. M. F. M. van der Heijde**, UCB, 5, UCB, 2 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **D. E. Furst**, UCB, 2, UCB, 5, UCB, 8 ; **M. E. Weinblatt**, UCB, 5 ; **T. K. Kvien**, UCB, 2, UCB, 5 ; **V. Strand**, UCB, 5, UCB, 8 ; **Z. Ansari**, UCB, 3 ; **N. Goel**, UCB, 3 ; **B. Combe**, UCB, 2, UCB, 5 .

1698

Certolizumab Pegol (CZP) Added to Methotrexate (MTX) Provides Lasting Improvements in Patient-Reported Outcomes (PROs) Over 2 Years. V. Strand[1], R. Fleischmann[2], Tore K. Kvien[3], A. Kavanaugh[4], J. S. Smolen[5], Alvin F. Wells[6], E. Nikaï[7], G. Coteur[7] and B. Combe[8], [1]Stanford University, Palo Alto, CA, [2]Univ of Texas, Dallas, TX, [3]Diakonhjemmet Hospital, Oslo, [4]UCSD, San Diego, CA, [5]Medical Univ Vienna, Vienna, Austria, [6]Rheum & Immunotherapy Center, Oak Creek, WI, [7]UCB, Brussels, Belgium, [8]Immuno-Rheumatology, Montpellier, France

Purpose: CZP 200 or 400 mg Q2W+MTX provided rapid, sustained, and clinically meaningful improvements in physical function and HRQoL, as well as reductions in arthritis pain and fatigue over 1 year (RAPID 1 trial). Here we present the impact of CZP+MTX on these PROs over 2 years.

Methods: This analysis focuses on patients who completed 52 wks of double-blind CZP treatment (completers) and then continued with open-label CZP+MTX; patients had at least 100 wks (2 yrs) of CZP exposure from BL. PROs included physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), pain (Visual Analog Scale [VAS; 0-100 mm]), fatigue (Fatigue Assessment Scale [FAS, 0-10]), and HRQoL (SF-36). Changes from RAPID 1 BL and % of patients achieving Minimum Clinically Important Differences (MCIDs) were assessed. MCIDs are ≥0.22 for HAQ-DI, ≥10 for pain VAS, ≥1 for FAS, ≥5 points for the 8 SF-36 domains (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) and ≥2.5 points for SF-36 physical and mental component summaries [PCS, MCS]).

Results: Clinically-meaningful improvements in physical function and reductions in pain and fatigue were reported at Wk 1 with CZP; HRQoL improvements were reported at Wk 12 (first post-BL assessment). Improvements in all PROs were sustained through at least Wk 100 (Table). At Wk 100, physical function (HAQ-DI) was improved on average by 0.79 points for completers originally treated with CZP 200 mg+MTX; pain relief averaged 39.5 points, and fatigue relief averaged 3.2 points. Patients originally receiving CZP 200 mg+MTX had mean improvements of 10.1 and 7.7 points for the PCS and MCS, respectively (Wk 100). HRQoL levels approached US population norms in the Vitality and Mental Health domains. Comparable benefits were observed in completers who received CZP 400 mg+MTX in RAPID 1.

Table. HAQ-DI, Pain, Fatigue, and HRQoL Change from Baseline and % of Patients Achieving MCID at Wk 100

	CZP Dose in RAPID 1	HAQ-DI	Pain VAS	FAS	SF-36 PCS	SF-36 MCS
Change from baseline	200 mg+MTX	-0.79	-39.5	-3.2	10.1	7.7
	400 mg+MTX	-0.78	-40.6	-3.0	10.5	7.1
%MCID	200 mg+MTX	64.1%	66.7%	63.3%	56.6%	48.4%
	400 mg+MTX	61.8%	67.6%	61.5%	59.0%	42.6%

Conclusion: Over 2 yrs, CZP+MTX provided lasting and clinically meaningful improvements in physical function and HRQoL, as well as relief from pain and fatigue, with improvements maintained at average levels at least 3 times higher than the thresholds for meaningful improvement.

Disclosure: V. Strand, Abbott, Allergan, Amgen, AstraZeneca, BiogenIdec, Centocor, Genentech, Novartis, Pfizer, Roche, Sanofi-Aventis, Schering Plough, UCB, Wyeth , 5 ; **R. Fleischmann**, Amgen, Wyeth, Centocor, Abbott, Genentech, biogen Idec, UCB, Regeneron, Lilly, Pfizer, 2, Amgen, Wyeth, Centocor, Abbott, Genentech, Biogen Idec, UCB, AstraZeneca, Pfizer, Lilly, 5, Amegen, Wyeth, Abbott, 8 ; **T. K. Kvien**, UCB, Abbott, BMS, Roche, Schering-Plough, Wyeth, MSD, 2, UCB, Abbott, BMS, Roche, Schering-Plough, Wyeth, MSD, Pfizer, 5, Abbott, Roche, Wyeth, MSD, Pfizer, 8 ; **A. Kavanaugh**, UCB, 2, UCB, 5 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **A. F. Wells**, UCB, Amgen, Abbott, Centocor, BMS, Pfizer, GSK, Wyeth, Takeda, 5 ; **E. Nikaï**, UCB, 3 ; **G. Coteur**, UCB, 3 ; **B. Combe**, UCB, MSD, Roche, Shering, Wyeth, 2, UCB, Abbott, GSK, MSD, Roche, Schering, Wyeth, 5 .

1699

Safety Update On Certolizumab Pegol (CZP) in Patients with Active Rheumatoid Arthritis (RA). Ronald F. van Vollenhoven[1], J. S. Smolen[2], M. Schiff[3], Roy Fleischmann[4], B. Combe[5], N. Goel[6], C. Desai[7], Jeffrey R. Curtis[8] and Edward C. Keystone[9], [1]Karolinska Univ Hosp, Stockholm, Sweden, [2]Medical Univ Vienna, Vienna, Austria, [3]Univ of Colorado School of Medicine, Greenwood Village, CO, [4]Metroplex Clinical Research Center, Dallas, TX, [5]Immuno-Rheumatology, Montpellier, France, [6]Smyrna, GA, [7]UCB, Slough, United Kingdom, [8]Univ of Alabama at Birmingham, Birmingham, AL, [9]Professor of Medicine/University of Toronto, Toronto, ON

Purpose: To update the safety profile of CZP in RA clinical trials and open-label extensions (OLEs).

Methods: Adverse event (AE) data were pooled from Phase 1 and 2 studies as well as the Phase 3 studies RAPID 1, RAPID 2, FAST4WARD and 014 (and their OLEs). Analyses were performed using cut-off dates of Jan 31, 2007 (initial) and Aug 31, 2007 (update). These analyses are presented by incidence (AEs/100 patient-years [pt-yrs]; data were censored per pt at first occurrence of the AE or serious AE [SAE]) and by proportion of pts experiencing each AE. Malignancy data are presented as standardized incidence ratios (SIRs) vs the GLOBOCAN database (excluding non-melanoma skin cancers and cancers within 30 days of first study drug injection).

Results: As of Aug 2007, 2367 CZP-treated RA pts with 4065 pt-yrs of exposure were available for safety analyses. Most AEs were mild/moderate (Table). The most common AEs were infections: 55.5% and 61.2% (70.6 vs 65.8/100 pt-yrs) in Jan and Aug 2007, respectively. The most frequently reported serious infections were respiratory tract infections and tuberculosis (TB). Most TB cases occurred in countries with a high prevalence of latent TB; no cases of TB were reported in the US. Opportunistic infections included 3 fungal esophagitis cases and 1 case each of geotrichosis and *Pneumocystis*. 1 patient had gastrointestinal perforation. In Jan and Aug 2007, the malignancy SIRs were 1.06 (95% CI:0.65-1.61) and 1.22 (95% CI:0.82-1.74), respectively; the lymphoma SIRs were 4.97 (95% CI:1.03-14.54) and 4.10 (95% CI:0.84-11.97). The standardized mortality ratios were 1.02 (95% CI:0.67-1.49) and 0.96 (95% CI:0.65-1.36), respectively. The % of pts with injection site reactions and pain was 7.9% and 1.8%.

Table. AEs (safety population)

	All CZP doses		**All CZP doses**	
	N=2367		N=2367	
Cut-off date	**Jan 31, 2007**		**Aug 31, 2007**	
Exposure (pt-yrs)	3218.0		4065.2	
	Incidence/100 pt-yrs	**%**	**Incidence/100 pt-yrs**	**%**
Any AE	199.5	81.7	183.1	86.1
SAE	17.9	22.1	17.0	26.0
AE leading to death	1.15	1.2	1.27	1.4
AEs leading to withdrawal	7.0	10.0	6.5	12.2
Serious infections	5.4	7.3	5.3	8.9
Lower respiratory tract and lung	1.2	1.6	1.3	2.2
TB	0.7	1.0	0.7	1.3
Cardiac disorders	4.7	6.3	4.3	7.3
Ischemic coronary artery disorders	1.3	1.7	1.1	1.9
Rate and rhythm disorders	1.2	1.7	1.1	1.9

Conclusion: The incidence rate of AEs and SAEs and the overall safety profile of CZP remained similar to previous reports with the addition of 850 pt-yrs of CZP exposure. These data support the favorable benefit/risk balance for CZP in RA.

Disclosure: R. F. van Vollenhoven, UCB Pharma, 2, UCB Pharma, 5 ; **J. S. Smolen**, UCB, 2, UCB, 5 ; **M. Schiff**, UCB, 2, UCB, 5 ; **R. Fleischmann**, Amgen, Wyeth, Centocor, Abbott, Genentech, BiogenIdec, UCB, Regeneron, Lilly, Pfizer, 2, Amgen, Wyeth, Centocor, Abbott, Genentech, Biogen Idec, UCB, AstraZeneca, Pfizer, Lilly, 5, Amgen, Wyeth, Abbott, 8 ; **B. Combe**, UCB, MSD, Roche, Shering, Wyeth, 2, UCB, Abbott, GSK, MSD, Roche, Schering, Wyeth, 5 ; **N. Goel**, UCB, 3 ; **C. Desai**, UCB, 3 ; **J. R. Curtis**, Amgen, Merck, CORRONA, 2, Roche, UCB, 5, Roche Pharmaceuticals, 8 ; **E. C. Keystone**, UCB, 5, UCB, 2, UCB, 8 .

1700

Infliximab Concentration Monitoring Improves the Control of Disease Activity in Rheumatoid Arthritis. Jean-Camille Méric[1], Denis Mulleman[2], Gilles Paintaud[2], Emilie Ducourau[2], Charlotte Magdelaine-Beuzelin[2], Jean-Pierre Valat[1] and Philippe Goupille[3], [1]CHRU de Tours, Tours, France, [2]Université François Rabelais de Tours; CNRS, UMR 6239; CHRU de Tours, Tours, France, [3]Université François Rabelais de Tours, CNRS, UMR 6239; CHRU de Tours, Tours, France

Purpose: To study if measurement of infliximab serum concentration in RA modifies the therapeutic strategy and improves the control of disease activity.

Method: RA patients routinely treated with infliximab were included in an observational open label study. On visit 1 (V1), according to the patient's disease activity, a preliminary therapeutic decision was selected among four scheduled therapeutic options and a blood sample was collected to measure infliximab trough serum concentration. The final therapeutic decision was chosen and applied on the following infusion (V2), by taking into account both disease activity and infliximab serum concentration assessed on V1. Clinical and biological evaluations were performed on V3 and V4 and compared with those of V1.

Results: Twenty-four patients were studied. No patient had high infliximab concentration, 17 patients (71%) had medium infliximab concentrations and 7 (29%) had low infliximab concentration. The final therapeutic decision differed from the preliminary therapeutic decision for 12 patients (50%). In patients who had an increase of their infliximab dosage on V2, mean DAS28 decreased of about 20% on V3 or V4 as compared with V1 (see *figure1*). Decrease in DAS28 was correlated with increase in infliximab serum concentration ($p < 0.02$).

Conclusion: The measurement of infliximab trough concentration modifies the therapeutic strategy for RA patients and lead to an improved control of disease activity. Pharmacological drug monitoring of infliximab in RA may be useful for individual dosage adjustment to improve the control of disease activity

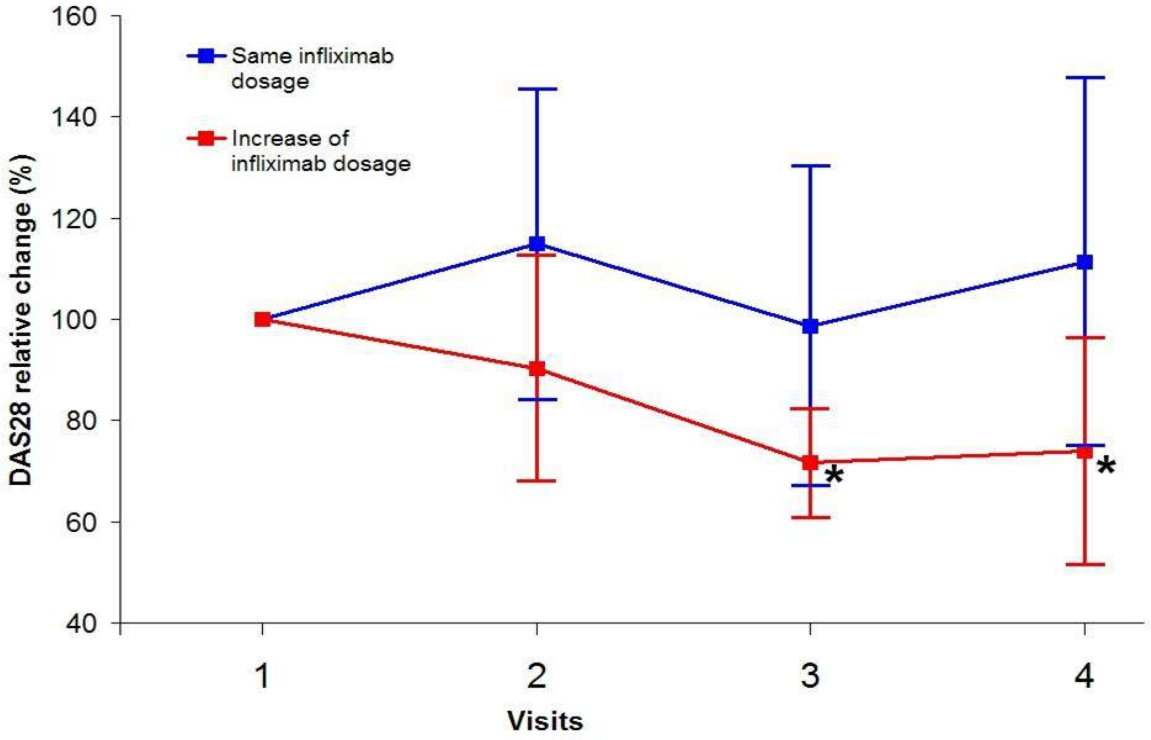


Figure 1: Relative changes in mean DAS28 according to final therapeutic decision.

** p< 0.05*

Disclosure: J. C. Méric, None; **D. Mulleman**, None; **G. Paintaud**, Innate Pharma, 2, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, LFB, 5 ; **E. Ducourau**, None; **C. Magdelaine-Beuzelin**, Abbott Laboratories, 5 ; **J. P. Valat**, None; **P. Goupille**, Abbott Laboratories, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2 .

1701

Reasons for Different Infliximab Survival Time Among Patients with Rheumatoid Arthritis and Spondyloarthritis. Enrique Calvo, Carlos M. Gonzalez, Irene Díez-Merchán, Elena Becerra, Carmen Martínez-Porras, Delia Gerona, Francisco Aramburu, Carolina Marín, María Montoro, Laura Cebrián, Indalecio Monteagudo, Francisco J. López-Longo and Luis Carreño, HGU Gregorio Marañón, Madrid, Spain

Purpose: To know the reasons of the different infliximab survival time observed among patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA).

Method: All patients treated with infliximab in our hospital were included in this prospective, observational study. Data concerning patient's demographics and drug efficacy, tolerability, concomitant therapy, adverse events, and drug discontinuation were recorded. Survival was studied with Kaplan-Meier method and variables analyzed using Cox proportional-hazards regression model.

Results: 183 patients with RA and 170 with SpA (63.5% ankylosing spondylitis, 18.2% psoriatic arthritis, 10% undifferentiated spondyloarthritis and 8.2% arthritis associated with inflammatory bowel disease) were included in the study and followed for a total of 874.1 patient-years (p-y). Infliximab was the first anti-TNF used in 335/353 (95%) patients. Infliximab survival time in SpA patients was

significantly higher than in RA patients. Median survival time (months): SpA 26.1; RA: 19.1. The unadjusted hazard ratio (HR) for infliximab discontinuation in SpA compared with RA was 0.45 (95% confidence interval [CI] 0.32-0.63). 138/353 (39.1%) patients discontinued infliximab due to lack of efficacy, infusion reaction or adverse events. Lack of efficacy: 3.64/100 p-y SpA vs 7.80/100 p-y RA; HR 0,46, 95% CI: 0.25-0.83. Infusion reaction: 3.87/100 p-y SpA vs 7.12/100 p-y RA; HR 0.54, 95% CI: 0.30-0.98. Adverse events: 2.05/100 p-y SpA vs 7.12/100 p-y RA; HR: 0.29, 95% CI: 0.14-0.61 (all HR unadjusted). When adverse event discontinuation was adjusted by diagnosis, age at infliximab start, gender and concomitant treatment, the only significant variable was age at the beginning of infliximab treatment: HR 1.07, 95% CI: 1.04-1.1 per year. SpA or RA diagnosis was not significant for adverse event discontinuation. When infusion reaction discontinuation was compared between all SpA patients and RA patients with methotrexate (MTX) as concomitant treatment there was no significant difference between both groups: 3.87/100p-y vs 4.60/100 p-y; NS.

Conclusion: Long term treatment with Infliximab is a good and safe therapeutic option for both RA or SpA patients. Infliximab survival time is better in SpA patients. Adverse event discontinuation is related to age at infliximab star but not to diagnosis. RA patients concomitantly treated with MTX had no significant difference in infusion reaction discontinuation than SpA patients.

Disclosure: E. Calvo, None; **C. M. Gonzalez**, Roche Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5 ; **I. Díez-Merchán**, None; **E. Becerra**, None; **C. Martínez-Porras**, None; **D. Gerona**, None; **F. Aramburu**, None; **C. Marín**, None; **M. Montoro**, None; **L. Cebrián**, None; **I. Monteagudo**, Abbott Laboratories, 5 ; **F. J. López-Longo**, Roche Pharmaceuticals, 5, Schering-Plough, 5 ; **L. Carreño**, Roche Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5 .

1702

Adalimumab Dose Escalation Induces Durable Remissions and Is Safe in Minorities with Moderate to Severe Rheumatoid Arthritis (RA). George A. Karpouzas[1], Alexander Broumand[1], Shirin Bagheri[1], Leila Sayed[1], James S. Louie[2], Daniel E. Furst[2] and Dilrukshie Cooray[1], [1]Harbor-UCLA Medical Center, Torrance, CA, [2]UCLA, Los Angeles, CA

Purpose: Patients (pts) with RA and partial response to disease modifying drugs (DMARDs) are treated with Tumor Necrosis Factor-Alpha inhibitors (TNFi) with good results. Adalimumab (ADA) is a human monoclonal antibody that inhibits TNFa, approved for use in RA at 40mg SQ every other week (QOW) or every week (QW). We investigated whether dose escalation to QW renders additional clinical benefit, whether the responses are sustained, and if this regimen is safe.

Methods: We studied 65 pts fulfilling 1987 criteria for RA and given ADA 40mg QOW. All had follow-up in a single academic center, where ADA is the recommended formulary drug. Subjects were largely minorities, indigent, and part of an assistance program. All had Disease Activity Scores (DAS28-3v-ESR) recorded every 3 months (mo). Good EULAR response (GER) was the primary outcome. Partial responders were given ADA 40mg QW. Flares were defined as: DAS28>3.2 and increase in DAS28>0.6 (from the initial good response) and/ or addition of a new drug. Intra-articular injections and/or 1 dose of intramuscular steroid were allowed. Response and flare data was analyzed with paired t-tests and Fisher's exact tests. Adverse events were reported as n/100-PY.

Results: Twenty two of 65 pts (33.8%) achieved GER in 5.3±3.9 mo and remained on QOW ADA for 23.5±17.8 mo. Forty three pts (66.2%) did not and received ADA 40mg QW for 17.2±12 mo. Twenty four of 43 (56%) achieved new GER within 7.5±5.9 mo, that lasted over 12±9.6 mo. Eleven of 24 (46%) had a flare within 11.7±10.2 mo, and 4/11 (36.4%) resolved without change in regimen over 4.5±3 mo. More flares occurred in the group on QW vs. on QOW ADA (OR=3.6, CI=0.9-13.9, p=0.07). GER persisted in 17/24 (71%) of the QW ADA group to the end of observation. Serious infections were 5.5 /100-PY in the QW group, not different from 4.9/100-PY in the QOW group. No cases of Tuberculosis (TB) or opportunistic infections were noted.

Conclusion: ADA dose escalation to 40 mg QW in partial responders induced new and durable GER. It was well tolerated with serious infections within the expected range for pts with RA.

Table 1: Patient Characteristics

	QOW	**QW**	*p*					
n	22	43	*ns*					
Females (%)	77.3	88.4	*ns*					
Age (M±SD)	51.5±10	52.5±9.9	*ns*					

Duration		8.1±6.1	9.8±7.6	*ns*					
Hispanic (%)		73	93	*ns*					
AA (%)		5	7	*ns*					
RF + (%)		89.5	97	*ns*					
a-CCP + (%)		87.5	88	*ns*					
Erosions (%)		58	71	*ns*					
ESR (mm/hr)		41±19	43±24	*ns*					
% on pred		31.6	59.5	*ns*					
% on DMARDs		100	100	*ns*					
n-DMARD (M±SD)		2±1.1	2±0.9	*ns*					
			Time Quarters (3 mo)						
DAS28	**QOW**	**QW**	**1**	**2**	**4**	**6**	**8**	**10**	**12**
All	5±0.1								
QOW pt	4.6±0.2		3±0.2*	2.8±0.2*	2.8±0.2*	2.7±0.3*	3±0.2*	2.4±0.4†	2.1
QW pts	5.2±0.2	4.6±0.1*	3.6±0.2*	3.2±0.2*	3.17±0.2*	3±0.2*	2.9±0.3*	3.3±0.3µ	3±0.5µ
Safety			**QOW**	**QW**					
All Infections (n/100-PY)			17.1	20.2					
Non-serious (n/100-PY)			12.2	14.7					
Serious (n/100-PY)			***4.95***	***5.5***					
Pneumonia			2	0					
Cellulitis/ abscess			2	3					
TB			0	0					
Opportunistic			0	0					

*<0.001, †<0.01, µ<0.05

Disclosure: G. A. Karpouzas, Centocor, Inc., 8, Abbott Immunology Pharmaceuticals, 8, Actelion Pharmaceuticals US, 8, Actelion Pharmaceuticals, 2 ; **A. Broumand**, None; **S. Bagheri**, None; **L. Sayed**, None; **J. S. Louie**, None; **D. E. Furst**, abbott,actelion,amgen,bms,genentech,gilead,gsk,nitec,novartis,roche,ucb,wyeth,xoma, 2, Abbott,actelion,amgen,bms,biogenIdec,centocor,genentech,gilead,gsk,merck,nitec,novartis,ucb,wyeth,xoma, 5, Abbott,actelion,amgen,bms,biogenIdec,centocor,genentech,gilead,merck,nitec, 9, Abbott,actelion,ucb, 9 ; **D. Cooray**, None.

1703

Predictive Risk Factors of Severe Infections in RA Patients Treated with Rituximab in Real Life: Results From the AIR Registry.

Jacques-Eric Gottenberg[1], Xavier Mariette[2] and For the scientific committee members of AIR registry, [1]University Hospital of Strasbourg, Strasbourg, France, [2]Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France

Purpose: We investigated the rate and predicting factors of severe infections in patients with rheumatoid arthritis treated with rituximab (RTX) in daily practice.

Method: AIR is an independent registry promoted by the French society for Rheumatology.Standardized information are prospectively collected every 6 months during 5 years, by trained clinical nurses in each center. Central reviewing of charts of patients with SAEs is performed by the two coordinators of the study. Only severe infections occurring during the year following last infusion of RTX were analyzed. Statistical models included patients for whom all studied variables were available.

Results: -Baseline characteristics and comorbidities

1681 patients (1690 patients/year) were included in 85 centers. 712 patients had been retreated with RTX (2 cycles: 466; 3 cycles: 176; 4 cycles: 45; ≥5 cycles: 25). 13.7% of patients had a record of cancer, 28.7% a record of severe infection, including 40 previous tuberculosis infections, 11.8% had chronic cardiac or lung disease.

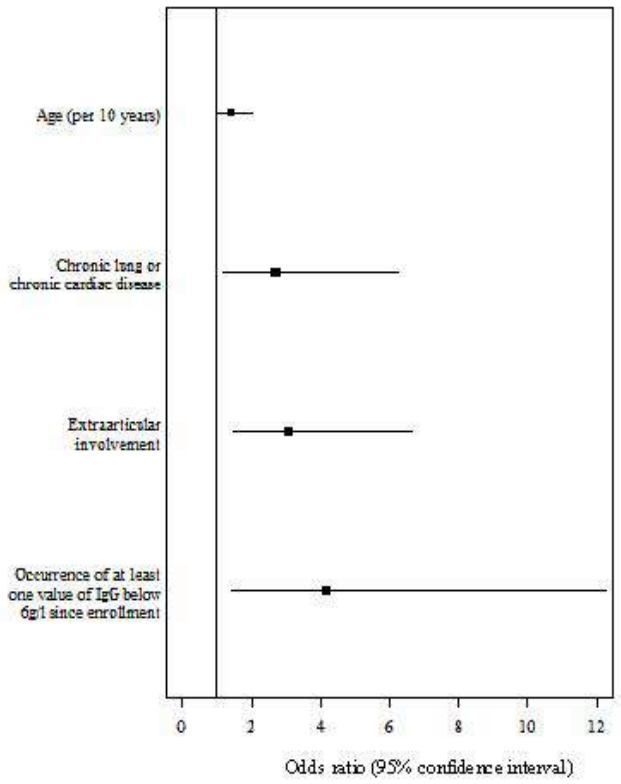
-Rate and description of severe infections

82 severe infections (4.9 severe infections/100 patients/year) were observed, resulting in 4 deaths. Bronchopulmonar, skin/soft tissue, urinary, digestive, osteo-articular, ENT and septicaemia represented 41.5%, 15.9%, 13.4%, 13.4%, 12.2, 2.4 and 1.2% of severe infections, respectively. Only 1 opportunistic infection was observed (a fungal septic arthritis). No tuberculosis reactivation was observed. 56 infections occurred after the 1st cycle, 22 after the 2d cycle, 3 after the 3d cycle, 1 after the 4th cycle. 79% of the severe infections occurred in the 6 months (50.6% before 3 months, 28.4% between 3 and 6 months) following RTX infusion.

998 patients had a follow-up duration longer or equal to 3 months and were included in the analysis of predicting factors of severe infections. On univariate analysis, age, chronic lung or cardiac disease, record of or current smoking, diabetes, a lower number of previous anti-TNF, extraarticular involvement, initial corticosteroid dosage, existence of at least one value of gammaglobulins or IgG below 6g/l since enrollment were associated with a higher risk of severe infections. On multivariate analysis, an older age (OR = 1.43 [1.02 ; 2.01], p=0.0382), chronic lung or cardiac disease(OR = 2.70 [1.17 ; 6.26], p=0.0205), extraarticular involvement (OR = 3.10 [1.45 ; 6.65,], p=0.0035), and occurrence of at least one value of IgG below 6g/l since enrollment (OR = 4.18 [1.42 ; 12.25], p=0.0092 were associated with an increased risk of severe infection (Figure 1).

Conclusion: In AIR registry, the rate of severe infections is similar in unselected patients as that reported in clinical trials. Interestingly, severe infections are time-dependent and occur in the first months following RTX infusion. Predicting factors of severe infections include age, comorbidities, extraarticular involvement, and hypoIgG. This suggests to monitor IgG levels before retreating patients with RTX and discuss the individual benefice/risk balance of RTX in patients with hypoIgG.

Figure 1. Multivariate analysis of the risk of severe infections in patients with RA treated with RTX



Disclosure: J. E. Gottenberg, None; **X. Mariette**, None.

ACR/ARHP Poster Session C

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1743

Genetic Variation at the IRF7/PHRF1 Locus Is Associated with Autoantibody Profile and Serum Interferon Alpha Activity in Lupus Patients. Rafah Salloum[1], Beverly S. Franek[1], Silvia N. Kariuki[1], Lesley Rhee[1], Rachel A. Mikolaitis[2], Meenakshi Jolly[2], Tammy O. Utset[1] and Timothy B. Niewold[1], [1]University of Chicago, Chicago, IL, [2]Rush University Medical Center, Chicago, IL

Purpose: Interferon alpha (IFN-α) is a heritable risk factor for systemic lupus erythematosus (SLE). Studies have implicated genetic variation near interferon regulatory factor 7 (IRF7) in SLE susceptibility. SLE-associated autoantibodies can stimulate IFN-α production through the Toll-like receptor/IRF7 pathway. We hypothesized that variants of IRF7 may cause risk of SLE by increasing IFN-α production, and that autoantibodies may be important to this phenomenon.

Methods: 511 SLE patients were studied: 255 African-American, 162 European-American, and 94 Hispanic-American. Serum IFN-α was measured using a reporter cell assay. The rs4963128, rs12286521, rs702966, and rs2246614 SNPs in the IRF7/PHRF1 locus were genotyped.

Results: In European-American subjects, rs702966C was associated with anti-dsDNA antibodies (OR=1.81, p=0.030). The rs702966C allele was only associated with higher serum IFN-α in European-American and Hispanic-American patients with anti-dsDNA antibodies (p=0.0024 and p=0.0014 respectively). In African-American subjects, anti-Sm antibodies were associated with the rs4963128 SNP downstream of IRF7 (OR=1.92, p=0.0019). African-American patients with anti-Sm antibodies showed a dose-response effect between rs4963128T and higher IFN-α (p=0.0021). In African-American patients lacking anti-Sm antibodies, the anti-dsDNA/rs702966C interaction upon serum IFN-α was observed, similar to the other ancestral backgrounds. In European-American and Hispanic-American patients, an SLE-risk variant of interferon regulatory factor 5 (rs2004640T) showed an additive effect with rs702966C upon IFN-α in patients with anti-dsDNA antibodies.

Conclusion: These data suggest that IRF7/PHRF1 variants cooperate with SLE-associated autoantibodies to result in higher serum IFN-α, providing a biologic relevance for this locus at the protein level in SLE in vivo.

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1744

A Polymorphic Microsatellite in the Fli1 Promoter Is Associated with Nephritis and Serositis in the Carolina Lupus (CLU) Cohort.

John L. Svenson, Paul Nietert, GS Gilkeson and Tamara K. Nowling, Medical University of South Carolina, Charleston, SC

Purpose: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Fli1 levels are elevated in lymphocytes from lupus mouse models and patients. Lowering the levels of Fli1 in two lupus mouse models significantly improved disease and prolonged survival. We identified a polymorphic GA microsatellite in the mouse Fli1 promoter that is shorter in lupus prone mouse strains compared to control mouse strains and demonstrated that the length is inversely proportional to expression in T cells. The microsatellite is conserved between mouse and human. To determine whether microsatellite length is associated with disease or disease characteristics in lupus patients and to analyze the role of the microsatellite in the human gene in T cells.

Methods: The promoter region containing the microsatellite was amplified from over 1100 patients and unaffected controls enrolled in the Carolina Lupus (CLU), SLE in Gullah Health (SLEIGH) and MUSC lupus clinic cohorts and genotyped. Fli1 message levels were measured by real-time RTPCR in 50 lupus patient RNA samples. The length of the microsatellite and message levels were analyzed for correlation/association with disease and disease characteristics. The promoter region of the human gene was cloned from four unaffected controls and role of the microsatellite analyzed by transient transfection in a T cell line.

Results: We identified 23 alleles spanning 13-39 repeats of the GA microsatellite. The length of the microsatellite was inversely correlated with activity of the human promoter in a T cell line. There was significant association of microsatellite length of 22 repeats with disease in the CLU cohort and specifically with nephritis in the CLU patients. A microsatellite length of 26 repeats was associated with serositis in the CLU patients and inversely associated with serositis in the SLEIGH patients. Interestingly, Fli1 message levels were significantly higher in patients with serositis.

Conclusion: Although there is a correlation between length of the Fli1 promoter GA microsatellite and Fli1 expression in a T cell line, a specific microsatellite length of 22 repeats was associated with disease, specifically with nephritis, in the CLU cohort. Additionally, a microsatellite length of 26 repeats was associated with serositis in the CLU patients whereas the same length appears to be protective in the SLEIGH patients and higher Fli1 transcript levels correlated with serositis. Together these results suggest that a specific lengths of the microsatellite may serve as markers for disease, specifically nephritis and serositis. It will be of interest to determine how the microsatellite functions in regulating Fli1 expression and how Fli1 levels specifically impact nephritis and serositis.

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1745

Two Single Nucleotide Polymorphisms (SNPS) in the Endothelial Protein C Receptor (EPCR) Gene Are Associated with Lower Soluble EPCR (sEPCR). Low Complement C4 and Thrombotic Risk in Patients with Lupus (SLE). J. T. Merrill[1], Robert M. Clancy[2], Stan Kamp[3], Kenaz Thomas[3], Barry Woodhams[4] and Naomi L. Esmon[3], [1]OMRF, Oklahoma City, OK, [2]NYU School of Medicine, New York, NY, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]92600 Asbueres, France

Purpose: Patients (pts) with SLE develop widespread vascular inflammation and life threatening thrombotic events which are not completely explained by typical antiphospholipid antibodies. Since EPCR is a critical regulator at a crossroads of inflammation and thrombosis, two SNPs were evaluated in 199 active SLE pts to determine if genotype has an impact on circulating sEPCR, autoantibodies to EPCR, and thrombotic risk.

Methods: Genotyping was performed by RTPCR with TaqMan primers for rs6936 A-G (serine to glycine) and rs7014 G-C (3' UTR). Circulating sEPCR was quantified by the ASSERACHROM sEPCR ELISA (Stago). Antibodies to EPCR were measured by a novel ELISA, calibrated against sera from 60 healthy individuals. Medical history and disease activity scores were obtained at the time of sampling.

Results: Mean pt age was 39.1, 89.9% female, 62.3% Caucasian, 25.6% African descent and 12.1% Asian. There was no demographic bias in rs6936 genotypes, but most African descent pts were homozygous for G at rs7014 (40/51 vs 46/148 in others, $p < 0.001$). Lupus activity (by BILAG) was the same between groups with overall mean (SD) score of 6.9 (4.3), suggesting moderate vascular inflammation throughout the population. In pts with the genotype rs6936 AA, median sEPCR was 145 ng/ml vs 317 ng/ml in non-AA ($p < 0.001$). There was also a difference between genotypes at rs7014: 130 ng/ml in CC pts vs 164 in non-CC ($p=0.005$). Median sEPCR of 37 pts who carried both of the low sEPCR genotypes was 130 ng/ml vs 317 ng/ml in the rest of the population ($p<0.001$). Low C4 complement was unevenly distributed in rs7014 genotypes, found in 25% of GG, 41.6% of GC and 33.3% of CC, ($p=0.041$, GG vs GC).

More women with rs6936 AA had a history of pregnancy loss and/or pre-eclampsia (23.6% vs 8% of those with G alleles in that gene, $p=0.054$) and the same for rs7014 (37.8% CC vs 17% with G alleles, $p=0.011$). Overall pts with a history of pregnancy complications, arterial and/or venous thromboses were also increased in rs6396 AA, 32.9% vs 15% in non-AA ($p=0.06$) and rs7014 CC, 37.8% vs 26.7% in non-CC (p=ns). Combining genotypes in assessing thrombotic risk, AA/CC women had a high rate of pregnancy complications (14/35 or 40% vs 3/35 or 8.57% of non-AA/non-CC ($p=0.004$). Pts with any type of thrombotic event included 14/37 (37.8%) of AA/CC vs 6/38 (15.7%) of non-AA or CC ($p=0.039$). 38 pts had autoantibodies to EPCR, more common in rs6936 AA than in pts with the G allele (32/162 vs 6/38 (p=ns) and more common in rs7014 pts with G allele than CC (34/163 vs 4/37) (p=ns). There were no pts with both 6936 AA and a G allele in 7014 even though each genotype represents about 19% of the population.

Conclusion: These data suggest that genetic variants influence sEPCR levels in active lupus and may increase complement consumption, autoantibody formation and thrombotic complications in these patients.

Disclosure: J. T. Merrill, None; **R. M. Clancy**, None; **S. Kamp**, None; **K. Thomas**, None; **B. Woodhams**, Stago, 3 ; **N. L. Esmon**, None.

1746

Patients with C1q Deficiency Have Elevated Serum Interferon-Alpha and IP-10 Associated with Defective Suppression of Immune Complex Stimulation of Plasmacytoid Dendritic Cells. Deanna M. Santer[1], Peter D. Arkwright[2] and Keith B. Elkon[1], [1]University of Washington, Seattle, WA, [2]University of Manchester, Manchester, England

Purpose: Patients with Systemic Lupus Erythematosus (SLE) have an 'IFN-signature' which correlates with disease severity. Deficiency of C1q (C1qD) has the highest penetrance for susceptibility to SLE (>90%). Although the mechanism(s) responsible for this strong association is not clear, there is evidence to suggest that defective clearance of apoptotic cells and/or immune complexes (ICs) may, in part, be responsible. We recently demonstrated that normal human serum (NHS) contains potent inhibitors of IFN-α induced by SLE ICs. Since we observed that heat inactivation of NHS almost completely abrogated its inhibitory activity, we asked whether C1q played a critical role in inhibiting IC stimulation of IFN-α by pDC.

Method: NHS selectively depleted of C1q or C2 was obtained commercially. Serum was obtained from a family where there are four C1qD (C1q <10U/ml) and one unaffected (normal C1q levels) sibling. In addition, cerebrospinal fluid (CSF) was available from one C1qD patient who had neuropsychiatric symptoms. IFN-α and IP-10 levels in serum and CSF were quantified by a multiplex protein array. To stimulate IFN-α, SLE ICs were formed by SLE serum and necrotic cell extract and added to normal donor PBMCs in the presence or absence of the

inhibitor being tested. IFN-α was quantified by ELISA in culture supernatants 20 h later. In certain experiments, monocytes were depleted from PBMCs using CD14-magnetic beads (<0.2% remaining) or pDCs were isolated by negative selection (>95% pure).

Results: With respect to IFN-α inhibition, C1q depleted, but not C2 depleted serum was significantly less inhibitory compared to NHS ($p<0.01$). To verify that C1q was an important inhibitor in serum, we tested sera from C1qD affected and unaffected siblings. C1qD patient sera were also unable to inhibit IFN-α induction by SLE ICs such that higher concentrations of IFN-α were induced by IC when C1q was absent. With all C1qD sera tested, add back of purified C1q protein completely restored inhibition of IFN-α to normal levels. 3 of 4 C1qD patients had elevated serum levels of IFN-α, which strongly correlated with levels of the IFN inducible chemokine IP-10 ($r= 0.98$, $p=0.004$). Levels of IFN-α in the CSF from the C1qD patient with neuropsychiatric symptoms were also markedly elevated (79 vs 1 pg/ml control CSF). Addition of purified C1q protein to SLE IC led to a dose dependent inhibition of IFN-α, which further illustrates the role of C1q itself as an inhibitor of IFN-α. Surprisingly, C1q could not directly inhibit purified pDCs and instead required the presence of monocytes for the full inhibitory effect.

Conclusion: *Ex vivo* detection of high serum concentrations of IFN-α and IP-10 in patients with C1q deficiency coupled with the impaired ability of C1qD sera to suppress IFN-α responses to IC, suggest a new mechanism to explain the susceptibility of C1qD individuals to develop SLE.

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1747

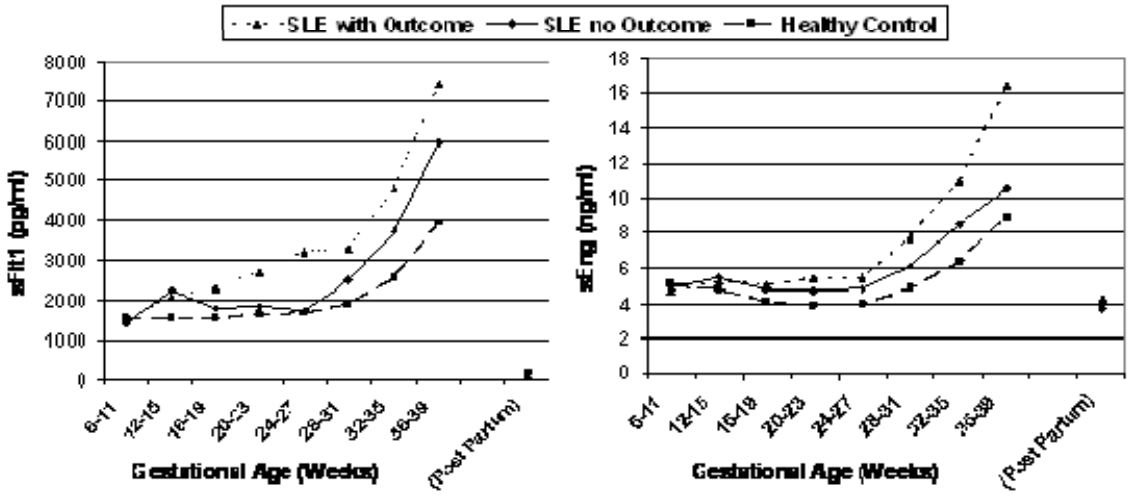
Angiogenic Factor Imbalance in Pregnant SLE Patients May Explain Increased Risk for Complications. Jane E. Salmon[1], Mimi Y. Kim[2], Sarosh Rana[3], Marta Guerra[1], Michael D. Lockshin[1], D. Ware Branch[4], Carl A. Laskin[5], Michelle Petri[6], Allen D. Sawitzke[4], Joan T. Merrill[7], Jill P. Buyon[8] and S. Ananth Karumanchi[3], [1]Hospital for Special Surgery, New York, NY, [2]Albert Einstein Coll Medicine, Bronx, NY, [3]Beth Israel Deaconess Med Ctr, Boston, MA, [4]Univ of Utah, Salt Lake City, UT, [5]Mt. Sinai Hosp, Toronto, ON, [6]Johns Hopkins Univ, Baltimore, MD, [7]Oklahoma Med Res Found, Oklahoma City, OK, [8]NYU School of Medicine, New York, NY

Purpose: Pregnant women with lupus are at increased risk for complications characterized by insufficient placental vascularization, such as preeclampsia and intrauterine growth restriction. Elevated levels of circulating antiangiogenic factors (sFlt-1 and sEng) and increased rates of increase of these factors through pregnancy predict such complications in healthy women and contribute to disease pathogenesis. Angiogenic imbalance can be triggered by complement activation. We hypothesized that pregnant patients with SLE have altered regulation of anti-angiogenic factors providing a basis for their increased risk for complications.

Methods: We performed a nested case-control study of SLE patients within the PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus). Poor pregnancy outcome was defined as: fetal death >12 wks; neonatal death; preeclampsia; preterm delivery <36 wks due to placental insufficiency; or intrauterine growth restriction. We studied 23 SLE patients with poor pregnancy outcomes (SLE/outcome) and 100 SLE patients with uncomplicated pregnancies (SLE/no outcome) matched by age, race/ethnicity to 98 pregnant healthy controls (HC). Subjects were evaluated and blood collected monthly beginning at <12 wks gestation. Mean levels of angiogenic factors were compared between groups at each time point using analysis of variance models. In addition, linear mixed effects models were fit to the data to estimate and compare rates of change in these factors over the entire gestational period.

Results: The rates of increase in sFlt-1 and sEng through pregnancy were significantly higher in SLE/no outcome patients than HC ($p=0.01$ and $p=0.03$, respectively). The rates of rise in sFlt-1 and sEng were also higher in SLE/outcome compared to SLE/no outcome and HC ($p < 0.0001$). Levels of sFlt-1 and sEng were significantly increased in SLE/outcome compared to HC as early as 20 and 16 wks gestation, respectively, and these differences persisted through 39 wks.

Conclusion: Angiogenic dysregulation occurs in pregnant SLE patients and may increase their vulnerability to placental insufficiency. Inflammatory mediators associated with SLE, such as complement products and interferon α, create an anti-angiogenic milieu. They may amplify the rates of rise of sFlt-1 and sEng through pregnancy and thereby increase risk for poor placental development and decrease threshold for complications like preeclampsia. We have identified predictors of risk; defining the mediators of angiogenic imbalance will identify targets to treat at-risk patients.



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Altered Balance Between the Effector and Regulatory T Cell Pathways in Systemic Lupus Erythematosus and Decreased Regulatory T Cell Levels in Active Lupus Nephritis. Danilo Mesquita[1], Wilson M. Cruvinel[2], Julio A. P. Araujo[1], Esper G. Kallas[3] and Luis Eduardo C. Andrade[1], [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Catolica de Goias, Goiania, Brazil, [3]Universidade de Sao Paulo, Sao Paulo, Brazil

Purpose: Deficiency in $CD4^+CD25^+$ regulatory T cells (TREG) has been related to the pathogenesis of human and experimental autoimmune diseases. Controversy in published data on TREG frequency in systemic lupus erythematosus (SLE) is partially due to heterogeneity in phenotype TREG markers and in patient selection. We aimed to quantify TREG and effector T cells (TEFF) based on the CD25, CD127 and FoxP3 expression in active and inactive systemic lupus erythematosus (A-SLE & I-SLE).

Method: Thirty-one patients with A-SLE (SLEDAI>6) and 32 patients with I-SLE (SLEDAI=0) fulfilling the ACR criteria were sequentially retrieved from the University Hospital outpatient clinic. Kidney involvement was defined according to the ACR criteria. Twenty-six HC were recruited among staff personnel. Peripheral blood mononuclear cells (PBMC) were analyzed by multicolor flow cytometry (FACSCANTO) and data analyzed using FlowJo software.

Results: The frequency of $CD25^{high}$ cells was increased in A-SLE (5.2±5.7%) as compared to I-SLE (3.4±3.4) and HC (1.73±0.8%) (P=0.007). However, this did not represent an increase in TREG subset in A-SLE since the frequency of $CD25^+CD127^{low}$ cells was equivalent in A-SLE (1.4±0.8), I-SLE (1.37±1.0) and HC (1.13±0.59) (P=0.42). In fact the percentage of $FoxP3^+$ cells in the $CD25^{high}$ subset was decreased in A-SLE (24.6±16.4%) as compared to I-SLE (33.7±16) and HC (45±25.1%) (P<0.01). This was possibly due to an increased frequency of TEFF cells ($CD25^{high}CD127^+FoxP3^{neg}$) in A-SLE (10.7±7.3%) as compared to I-SLE (8.5±6.5) and HC (6.1±1.8%) (P=0.02). Interestingly we observed a lower frequency of TREG cells ($CD25^+CD127^{low}FoxP3^+$) in renal A-SLE patients (0.8±0.4) as compared to non-renal A-SLE patients (2.19±1) (p<0.001).

Conclusion: The high degree of T cell activation in SLE hampers the use of CD25 as a marker for TREG since A-SLE samples present increased levels of $CD25^+$ and $CD25^{high}$ effector T cells not related to TREG. There seems to be an altered balance between the effector and regulatory pathways in active SLE patients, especially in those with kidney involvement, and this imbalance may favor high effector T cell activity and thus contribute to the pathophysiology of this disease.

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1749

CD4+ T Cells in Systemic Lupus Erythematosus Secrete IL17 After Antigenic Challenge. Sandra Schneider[1], Arne Sattler[1], Tobias Alexander[1], Sarah Meier[2], Udo Schneider[1], Regina Stark[2], Michael Mahler[3], Andreas Radbruch[4], Andreas Thiel[2], Gerd-R. Burmester[1] and Falk Hiepe[1], [1]Charité, Rheumatology and Clinical Immunology, Berlin, Germany, [2]BCRT, Regenerative Immunology and Aging, Berlin, Germany, [3]Dr. Fooke Laboratorien, Neuss, Germany, [4]DRFZ, Berlin, Germany

Background: $CD4^+$ Interleukin (IL)17 secreting cells (Th17 cells) seem to contribute to inflammation in autoimmune disease such as rheumatoid arthritis or Crohn's disease. Also in systemic lupus erythematosus (SLE) there is growing evidence for a pathogenic relevance of IL17.

Purpose: Since viral and bacterial infections have the potential to trigger lupus flares our aim was to further investigate IL17 compared to interferon gamma (IFNg) secretion in $CD4^+$ cells after antigen stimulation ex vivo in SLE patients and healthy controls (HC).

Method: We stimulated full blood samples from 8 SLE patients and 7 HC in the presence of CD28 and brefeldin A for 6 hours with *staphylococcus* enterotoxin B (SEB), with a peptide mixture of the cytomegalo virus (CMV) protein pp65, with a peptide mixture of the hexon protein of adenovirus 5 (AdV5) and with a protein mixture of the RNP/Sm complex (a nuclear target of autoantibodies in lupus). After erythrocyte lysis and permeabilization samples were stained for multicolor FACS analysis with antibodies against CD3 and CD4 to gate on $CD4^+$ T cells and with CD14 and CD19 to gate out B cells and monocytes. Frequencies of activated cytokine producing $CD4^+$ T cells were determined by intracellular staining of IL17 and IFNg together with the activation marker CD40 ligand (CD40L).

Results: After SEB stimulation we found frequencies of IFNg/CD40L double positive cells in $CD4^+$ cells from 1.51 to 4.65% in SLE patients vs. 0.87 to 2.80% in HC and frequencies of IL17/CD40L double positive cells from 0.21 to 1.24% in lupus vs. 0.04 to 0.22% in HC. Whereas for the IFNg production no significant difference in between groups could be seen, Mann Whitney test showed significantly higher IL17 levels ($p = 0.02$) as well as significantly higher IL17/IFNg ratios ($p = 0.04$) in the SLE group. After CMV stimulation the highest detectable frequency for IFNg/CD40L was 1.72% in patients vs. 0.22% in HC, for IL17/CD40L 0.06% in a lupus patient and 0.01% in a HC with no significant differences detectable. In AdV5 stimulated probes only very low frequencies of cytokine producing $CD4^+$ cells could be observed: for IFNg up to 0.10 vs. up to 0.16% in lupus vs. HC and for IL17 up to 0.04 and up to 0.02%, respectively. Towards the autoantigen stimulation with RNP/Sm neither in patients nor in HC any clear IFNg reaction was detectable, but in one of 8 patients we found a weak IL17 reaction with a frequency of 0.06%.

Conclusion: We found a significantly increased frequency of Th17 cells but not of IFNg secreting Th cells after ex vivo stimulation with SEB in SLE patients compared to HC. We also could detect low frequencies of IL17 secreting $CD4^+$ cells after viral and - in one patient - after autoantigenic challenge. Our data provide further affirmation for a disease related role of IL17 in SLE.

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1750

Silencing of Endogenous Retrovirus Is Impaired in B Cells From Systemic Lupus Erythematosus. Yves Renaudineau[1], Christelle Le Dantec[1], Sandrine Jousse-Joulin[2], Soizic Garaud[1] and Pierre Youinou[1], [1]Brest University Medical School Hospital, Brest, France, [2]CHU Brest, Brest, France

Purpose: Systemic Lupus Erythematosus (SLE) is a heterogenous autoimmune disease of unknown origin. Both genetic and epigenetic factors have been implicated in its pathogenesis. A defect in DNA methylation has been demonstrated in T cells and more recently in B cells from SLE patients. The aim of the study was to analyse several promoters known to be methylation-sensitive in B cells from SLE patients.

Method: Samples were B cell-enriched from the blood of 7 patients with SLE and 6 healthy controls (HCs). Seven methylation-sensitive promoters were tested (CD21, CD70, Pax5, Syk, HRES-1, CD5-E1A and HERV-CD5) using methylation-specific PCR assays and bisulfite sequencing following or not BCR engagement. B-cells were stimulated in vitro with anti-IgM antibodies, or incubated with DNMTs inhibitors (procainamide, 5-azacytidine and PD98059).

Results: In SLE and HCs, at basal level all promoter tested were hypomethylated. However, in HCs, BCR engagement with an anti-IgM increased DNA methylation in the two endogenous retrovirus derived promoters (HRES-1 and HERV-CD5). In contrast, promoters from anti-IgM stimulated SLE B cells remains demethylated. Demethylation of HERV-CD5 increases CD5-E1B expression in lupus B cells and B cells treated with DNA methyl transferases inhibitors (procainamide, 5-azacytidine, and PD98059). We provide further evidence that production of high IL-6 levels by SLE B cells abrogate the ability of SLE B cells to methylate HRES-1 and HERV-CD5 promoters. This effect is reversed in SLE B cells in the presence of a blocking Ab to IL-6 receptor, and in HCs B cells in the presence of rIL-6.

Conclusion: The study reveals that engagement of the BCR silence endogenous retroviral elements and that this mechanism is impaired in SLE B cells. This derepression could in turn promote the expression of endogenous retrovirus and then promote B cell autoreactivity.

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1751

Multiple Pro-Atherogenic Pathways Are Activated in Monocytes After Acute Treatment with Pro-Inflammatory HDL. Brian J. Skaggs, Lori J. Sahakian, Bevra H. Hahn and Maureen A. McMahon, Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: Accelerated atherosclerosis is a major co-morbid condition of women with SLE. Data from our group illustrates that the presence of dysfunctional, pro-inflammatory HDL (piHDL) in plasma of SLE patients increases the risk for carotid artery plaque 16-fold. It is unclear if piHDL directly influences monocytes, recognized as the main immune cell involved in both the initiation and progression of atherosclerosis. We hypothesized that piHDL might be directly responsible for altered monocyte gene expression, protein expression, and function.

Methods: HDL and piHDL were isolated from human plasma (a single subject for each, both with SLE) using a magnetic bead reagent. RNA and protein were isolated from the human monocyte cell line THP-1 after short-term (4 hr) and long-term (24 hr) treatment with normal, anti-inflammatory HDL or piHDL at multiple doses and different concentrations of fetal calf serum (FCS). Transcript levels of 84 atherosclerosis-specific genes were examined by real-time PCR-based gene arrays (SA Biosciences). In addition, other transcripts associated with atherosclerosis in SLE (identified by microarray analysis of human subjects) were examined by independent qPCR assays. Altered transcript levels were confirmed by western blot and ELISA. Migration of HDL-treated THP-1 cells was examined with the QCM chemotaxis kit (Millipore).

Results: Short-term piHDL treatment (20 ug/mL) of THP-1 cells in low FCS (1%) led to significant upregulation of multiple pro-inflammatory transcripts when compared to cells treated with normal HDL. The adhesion molecules CD11c (2.03-fold, p=0.001) and tenascin c (2.77-fold, p=0.007), the inflammatory cytokines IL1-alpha (3.31-fold, p=0.001) and IL-5 (4.45-fold, p=0.002), the HDL receptor ABCA1 (2.25-fold, p=0.006), the TNF family member lymphotoxin-beta (2.27-fold, p=0.001), and both PDGFR-beta (2.84-fold, p=0.037) and PDGFA (2.04-fold, p=0.033) were upregulated by sub-endogenous levels of piHDL treatment. Long-term treatment of THP-1 cells required higher FCS levels (3%) and only PDGFR-beta and ABCA1 were upregulated in piHDL-treated cells versus normal HDL. The number of cells migrating towards an exogenous chemoattractant (MCP-1) was 39% higher in THP-1 cells treated with piHDL for 4 hours versus cells treated with normal HDL (p=0.012).

Conclusion: Treatment of a human monocyte cell line with piHDL upregulates multiple pro-inflammatory and pro-atherogenic molecules. In addition, piHDL treatment activates monocytes and stimulates their migration towards an atherogenic chemoattractant. These results suggest that the presence of piHDL in the plasma of SLE patients initiates atherosclerosis in part by directly activating pro-inflammatory and pro-atherogenic pathways in monocytes.

Disclosure: B. J. Skaggs, None; **L. J. Sahakian**, None; **B. H. Hahn**, None; **M. A. McMahon**, None.

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The Presence of Carotid Plaque in SLE Patients Correlates with Upregulated Monocyte TNF Family Genes. Brian J. Skaggs[1], Lori J. Sahakian[1], David Elashoff[2], Jennifer M. Grossman[1], Bevra H. Hahn[1] and Maureen A. McMahon[1], [1]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose: Premature atherosclerosis is widely recognized as a significant co-morbid condition of SLE. Although the role of the immune system in the initiation and progression of atherosclerosis is now well appreciated, little is known about the cell types and molecular pathways that contribute to plaque in SLE. Monocytes are the main immune mediator of atherosclerosis, and we hypothesized that alterations in monocyte gene expression could provide clues to the mechanism of premature atherosclerosis in SLE and yield novel therapeutic targets and/or biomarkers.

Methods: Monocytes were isolated from 60 subjects from our UCLA cohort by Ficoll and magnetic bead separation of CD14+ cells. B-mode and Doppler ultrasound scanning of carotid arteries assessed plaque. The 60 subjects were stratified into three groups: 1) healthy controls (n=15), 2) SLE no plaque (n=30), and 3) SLE plaque (n=15). We examined monocyte whole genome transcript levels after RNA isolation using Illumina Ref6 chips. Data was analyzed by Illumina BeadStudio software. We confirmed expression levels by real-time PCR (mRNA) and western blot (protein).

Results: Multiple TNF family ligands and receptors, including lymphotoxin-beta(2.21-fold, p=0.0045), lymphotoxin-alpha (2.34-fold, p=0.0044), TNFRSF4/Ox40 (4.75-fold, p=0.0037), TNFSF4/Ox40 ligand (4.72-fold, p=.0294), and TNFRSF25/DR3 (2.93-fold, p=0.0248) were significantly increased in monocytes from SLE plaque subjects versus SLE no plaque (fold and p-values shown above) as well as healthy control subjects (not shown). Functional annotation analysis (DAVID, NIH) revealed that the immune response gene category was the only significant family increased in the comparison between SLE no plaque and SLE plaque subjects (Benjamini corrected p-value 0.0003). When this category was selected as a subset, it was made up of mostly transmembrane proteins (Benjamini p=2.8e-11), including all of the TNF family members above. There were very few significantly altered monocyte transcripts between healthy controls and SLE no plaque subjects. Real-time PCR experiments validated significantly upregulated transcript levels in all genes mentioned. Protein levels of Ox40 and Ox40L were approximately 1.5-2 fold higher in SLE plaque subjects, suggesting that transcript levels are not fully indicative of translated protein levels.

Conclusion: The TNF family members lymphotoxin-beta, lymphotoxin-alpha, Ox40, Ox40L, and DR3 are all upregulated in SLE patients with plaque versus SLE patients without plaque and healthy controls. All of these genes have been implicated in promoting atherosclerosis in non-SLE patients, although no studies have reported cooperation between these three different TNF family pathways. Our results suggest that upregulation of multiple TNF-related signaling pathways could contribute to premature atherosclerosis in SLE.

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LRRC20 Is a Novel Gene Associated with Serum IFN-α in SLE Patients. Silvia N. Kariuki[1], Beverly S. Franek[1], Rachel A. Mikolaitis[2], Joel A. Block[2], Meenakshi Jolly[2], Tammy O. Utset[1], Andrew D. Skol[1] and Timothy B. Niewold[1], [1]University of Chicago, Chicago, IL, [2]Rush University Medical Center, Chicago, IL

Purpose: Interferon alpha (IFN-α) is a heritable risk factor for systemic lupus erythematosus (SLE), although the genetic regulation of this risk factor is complex and not well understood currently. We performed a small scale multi-ancestral background case-case genome-wide study of SLE patients stratified by extremes of phenotype in autoantibodies and serum interferon alpha (IFN-α) to detect novel genes associated with IFN-α in SLE. A SNP in the leucine-rich repeat containing 20 (LRRC20) gene demonstrated an association signal, which is followed up in this study.

Methods: We used a Bayesian algorithm to select candidate genes from the top hits in our GWAS for validation. We chose to follow up a SNP in the 3' UTR region of the LRRC20 gene (rs10762360) in 511 independent cases and 739 matched controls from our multi-ancestral local cohort (cases include 255 African-American, 162 European-American, and 94 Hispanic-American subjects). Genotyping was performed using Taqman genotyping probes, and IFN-α was measured using a sensitive reporter cell assay.

Results: The minor allele of rs10762360 was associated with higher serum IFN-α in our cohort in a dose-response fashion (p=0.0002). This pattern was shared across all of the different ancestral backgrounds included in our study. Additionally, we used logistic regression modeling to detect associations between autoantibodies and this allele in each ancestral background separately. We discovered a strong association between the minor allele of rs10762360 and anti-La antibodies in African-American SLE patients (OR=2.28, p=0.0007), which was not observed in the other ancestral backgrounds. While autoantibodies have been associated with higher serum IFN-α in SLE, this antibody association did not account for the differences we observed in serum IFN-α by genotype. There were no significant differences in allele frequencies between cases and controls in our cohort.

Conclusion: We used a case-case subphenotype strategy to discover a novel gene associated with increased serum IFN-α and autoantibody profile in a multi-ancestral SLE cohort. These data suggest that LRRC20 plays a role in IFN-α signaling in SLE, and will thus mediate disease phenotype and severity.

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Serum Interferon Alpha Correlates with Disease Activity, Specific Clinical Manifestations and Circulating Plasma Cells Levels in Systemic Lupus Erythematosus. Alexis Mathian[1], Christophe Parizot[2], Karim Dorgham[3], Makoto Miyara[1], Julien Haroche[1], Patrice Debré[3], Jean -Charles Piette[1], Pierre Lebon[4], Guy Gorochov[3] and Zahir Amoura[1], [1]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [2]Department of Immunology, Pitié-Salpêtrière Hospital, Paris, France, [3]Inserm Umrs-945, Pitié-Salpêtrière Hospital, Paris, France, [4]Department of Virology, Saint-Vincent de Paul Hospital, Paris, France

Purpose: Previous clinical studies in humans and murine models suggest that Interferon alpha (IFNα) is a key-cytokine in Systemic Lupus Erythematosus (SLE). However, little is known about the association between IFNα and clinical manifestations of SLE. Antibody-Secreting Cells (ASC), comprising plasma cells and plasma blasts, are found in excess in active SLE and are strongly implicated in the pathogenesis of SLE. IFNα have been described to exert a variety of effects on the function and development of B cells, enhancing plasma cells and plasma blasts differentiation. The question arises as to whether IFNα might be responsible for the increased frequency of ASC seen in SLE. We measured serum IFNα levels in SLE and studied their relationship with disease activity, clinical manifestations and circulating levels of ASC.

Method: IFNα levels in sera were calculated using an antiviral cytopathic bioassay. The levels of circulating ASC were determined as $CD27^{high}CD19^{dim}$ cells by fluorescence-activated cell sorting (FACS) analysis. SLE activity was measured by the SLE Disease Activity Index (SLEDAI).

Results: Serum IFNα levels were measured in 136 SLE patients. Levels were increased in 65 SLE patients (47.8%) whereas none of the healthy donors had detectable levels of the cytokine in their sera. Patients with active SLE (SLEDAI $\geq$ 4, n = 66) had higher levels of IFNα than patients with inactive SLE (SLEDAI < 4, n = 70) (4 UI/ml (0-300) versus 0 UI/ml (0-30), $p < 0.0001$). IFNα positively correlates with SLEDAI ($p < 0.0001$; $r = 0.56$). IFNα levels were significantly higher in patients with neurologic involvement compared with patients without neurologic involvement [25 UI/ml (extremes: 2-300) versus 2 UI/ml (extremes: 0-100), p corrected = 0.03], in patients with fever compared with patients without fever [35 UI/ml (extremes: 2-300) versus 2 UI/ml (extremes: 0-100), p corrected = 0.006] and in patients with cytopenia (leucopenia or thrombocytopenia) compared with patients without cytopenia [35 UI/ml (extremes: 3-300) versus 2 UI/ml (extremes: 0-200), p corrected = 0.006]. IFNα positively correlates with circulating ASC levels ($p < 0.0001$; $r = 0.48$).

Conclusion: We demonstrate the association between IFNα, disease activity and specific clinical manifestations of SLE: fever, leucopenia, thrombocytopenia and neurologic involvement. These manifestations are frequently encountered after IFNα injections, for example, in hepatitis C viral infection treatment. Thus IFNα may be a direct mediator of these clinical manifestations in SLE. Furthermore the strong correlation between serum IFNα concentrations and circulating ASC levels suggests a pathogenic role of IFNα on B cell differentiation toward ASC in SLE.

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Mannose-Binding Lectin Polymorphisms in Brazilian Patients with Systemic Lupus Erythematosus. O.A. Monticielo[1], J.A.B Chies[2], T. Mucenic[1], G.G. Rucatti Sr.[1], J.M. Zimmermann Júnior[1], G.K. Silva Sr.[2], N. Glesse Sr.[2], B. Keiserman[1], Y.M. Badad[1], J.C.T Brenol[1] and Ricardo M. Xavier[3], [1]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [2]Universidade Federal de Porto Alegre, Porto Alegre, Brazil, [3]Porto Alegre, Brazil

Purpose: The mannose-binding lectin (MBL) gene has emerged as a candidate for systemic lupus erythematosus (SLE) susceptibility, but studies in Brazilian population has not been achieved. We conducted a case-control study to examine potential associations of the MBL alleles G57E, G54D, IVSnt5, R52C and R52H with susceptibility to and clinical expression of SLE in southern Brazilian patients.

Method: Three hundred and twenty seven consecutive patients with diagnosis of SLE, satisfying the American College of Rheumatology criteria, who were recruited from the outpatient clinic of the Division of Rheumatology of the Hospital de Clínicas de Porto Alegre, and 244 healthy controls from the same geographic area, were genotyped by Restriction Fragment Length Polymorphism-Polimerase Chain Reaction (RFLP-PCR) analysis. Clinical, demographic and laboratory data were collected.

Results: A statistically significant difference in the frequencies of allele R52C was observed in European-derived SLE patients as compared to controls (9.6% vs. 3.3%, P<0.001, odds ratio 3.15, 95% confidence interval 1.761-5.622, P<0.05). The frequencies of alleles G54D and G57E were not different between European-derived SLE patients and controls (allele G54D 15.9% vs. 15.8%, P=0.971 and allele G57E 3.6% vs. 2.9%, P=0.509). There were no differences between clinical and laboratory features in SLE patients according to the presence or absence of MBL allelic variants.

Conclusion: These results support an increased risk of SLE in European-derived individuals carrying the R52C allele. Patients carrying this allele have an approximately 3-fold higher odds ratio of developing SLE when compared with controls. Our data do not support associations between the MBL allelic variants studied and clinical expression of SLE in southern Brazilian population.

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Phenotype Characterization of Regulatory T Cells (CD25highCD127low FoxP3+) in Systemic Lupus Erythematosus. Danilo Mesquita[1], Wilson M. Cruvinel[2], Julio A. P. Araujo[1], Esper G. Kallas[3] and Luis Eduardo C. Andrade[1], [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Catolica de Goias, Goiania, Brazil, [3]Universidade de Sao Paulo, Sao Paulo, Brazil

Purpose: $CD4^+CD25^+CD127^{LOW}$ $FoxP3^+$ regulatory T cells (TREG) are specialized in immune response suppression and are apparently involved in the pathogenesis of autoimmune diseases. A variety of TREG surface markers has been described in healthy subjects but not in systemic lupus erythematosus (SLE). This study aimed to characterize the expression of GITR, HLA-DR, PD-1, OX40, CD40L, CD28, CTLA-4 and CD45RO on $CD25^+CD127^{LOW}FoxP3^+$ TREG cells from patients with active SLE (A-SLE), inactive SLE (I-SLE), and healthy controls (HC).

Method: Thirty-one patients with A-SLE and 32 patients with I-SLE were sequentially retrieved from the outpatient clinic at the University Hospital. Twenty-six HC were recruited among staff personnel. SLE patients fulfilled the ACR classification criteria. Disease activity was established as SLEDAI equal or above six and disease quiescence was defined as SLEDAI equal to zero. Peripheral blood mononuclear cells (PBMC) were analyzed by multicolor flow cytometry and obtained data were analyzed using the FlowJo software.

Results: We detected lower frequency of $CTLA\text{-}4^+$ TREG cells in A-SLE as compared to I-SLE and HC (2.4±4.2, 4.4±6.7, 7.8±10.8, respectively; $p<0.05$). The same was true for $CD28^+$ TREG cells (85.8±12.25, 91±9.7, 92.7±7.9, respectively; $p<0.05$). In contrast, the frequency of $CD40L^+$ TREG cells was higher in A-SLE as compared to I-SLE and HC (5.3±5.4, 2.5±3.1, 0.9±1.2, respectively; $p<0.0001$). In addition the frequency of $CD40L^+$ TREG cells correlated with SLEDAI ($r=0.1080$, $p=0.0163$, $n=53$). The ratio between TREG and effector T cells (Teff) was analyzed for T cell subsets presenting each one of the surface markers. TREG/Teff ratio was decreased in A-SLE and I-SLE as compared to HC for $GITR^+$ cells (1.6±1.3, 1.5±0.9, 2.4±1.5, respectively; $p<0.05$), $HLA\text{-}DR^+$ cells (1.1±0.6, 1.2±0.5, 1.5±0.6, respectively; $p<0.05$), $OX40^+$ cells (1±0.7, 1±0.6, 1.5±0.9, respectively; $p<0.05$) and $CD45RO^+$ cells (1.1±0.3, 1.2±0.3, 1.4±0.4, respectively; $p<0.001$). In contrast the TREG/Teff ratio for CD40L+ cells was increased in A-SLE when compared with I-SLE and HC (5±6.3, 2.1±2.1, 1.7±1.8, respectively; $p<0.05$).

Conclusion: TREG phenotype evaluation indicated derangements in the cellular and molecular balance of CTLA-4, CD40L, GITR and OX40 on TREG and effector T cells in SLE and highlights potential therapeutic target for this disease.

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Weak Association of Systemic Lupus Erythematosus Clinical Features with Susceptibility Alleles. Antonio Gonzalez[1], Marian Suarez-Gestal[1], Manuel Calaza[1], Myriam Liz[1], J. Ordi-Ros[2], E. Balada[2], Marc Bijl[3], C.G.M. Kallenberg[3], Chryssa Papasteriades[4], Iris Kappou-Rigatou[4], PE. Carreira[5], Fotini N. Skopouli[6], Maria Mavromati[6], Reinhold E. Schmidt[7], Torsten Witte[7], Emöke Endreffy[8], Attila Kovacs[8], Maurizio Marchini[9], Raffaella Scorza[9], Sergio Migliaresi[10], Gian Domenico Sebastiani[11], Maria J. Santos[12], Filipe Vinagre[12], Ana Suarez[13], Carmen Gutierrez[13], Ignacio Rego[14], F.J. Blanco[14], Nadia Barizzone[15], Sandra D'Alfonso[15], Rudolf Pullmann Jr[16], Rudolf Pullmann[16], Sarka Ruzickova[17], Ctibor Dostal[17] and J. J. Gomez-Reino[1], [1]H. Clinico Universtiario de Santiago, Santiago de Compostela, Spain, [2]Vall d'Hebron H., Barcelona, Spain, [3]University Medical Center Groningen, Groningen, Netherlands, [4]Evangelismos Hospital, Athens, Greece, [5]Hospital 12 de Octubre, Madrid, Spain, [6]Athens University Medical School, Athens, Greece, [7]Hannover Medical School, Hannover, Germany, [8]University of Szeged, Szeged, Hungary, [9]University of Milan, Milan, Italy, [10]Second University of Naples, Naples, Italy, [11]U.O. Complessa di Reumatologia, Rome, Italy, [12]Hospital Garcia Orta, Almada, Portugal, [13]Hospital Universitario Central de Asturias, Oviedo, Spain, [14]INIBIC-H. U. A Coruña, Coruña, Spain, [15]University of Eastern Piedmont, Novara, Italy, [16]Jessenius Medical Faculty, Martin, Slovak Republic, [17]Institute of Rheumatology, Prague, Czech Republic

Purpose: To analyze the relationship between SLE susceptibility alleles and some clinical features

Method: Genotypes of SLE-associated SNPs in ITGAM, STAT4, C8orf13-BLK, MECP2, BANK1, TYK2, KIAA1542, PXK and 1q25.1 were available for 1579 patients with SLE obtained in 16 European centres. They were correlated with age of disease onset and with ACR classification criteria. Regression analyses were performed according to a genetic additive model. Allelic analyses combined data with the Mantel-Haenszel approach. Consistency of results across recruiting centres and the number of test done were considered for interpretation

Results: A single association was consistent and significant: the rare allele of the SNP in the C8orf13-BLK locus determined increased risk of nephritis (O.R. = 1.35, 95 % C.I. = 1.15-1.60, P = 0.00026). Some other clinical features showed association with genotypes but they were not consistent or not enough significant. Suggestive findings in this category were association of the BANK1 SNP with absence of oral ulcers and of the MECP2 SNP with increased risk of lupus nephritis. We did not replicate the described associations of STAT4 with nephritis or oral ulcers, and only weakly the associations of STAT4 with early age of onset and of BANK1 with immunological criteria and nephritis

Conclusion: Our results together with previous studies indicate that clinical variability of SLE correlate only weakly with the SLE susceptibility alleles. However, it is possible that more complex interactions, between genetic factors or with environmental exposures, play a more significant role in defining the SLE phenotype

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Association of MIF with Disease Activity, Damage, and Serum IL17 and IL6 in Systemic Lupus Erythematosus. Eric F. Morand, Melissa Northcott, A. Richard Kitching, Fiona Brown and Alberta Hoi, Monash University, Melbourne, Australia

Purpose: MIF is a broad-spectrum pro-inflammatory protein with actions in T cells, B cells, macrophages and endothelial cells. MIF-deficiency is protective in MRL/lpr mice, and a single nucleotide polymorphism (SNP) at position -173 in the MIF promoter (rs755622) is associated with increased SLE susceptibility. Associations between MIF and disease manifestations in SLE have not been reported. We examined these associations prospectively.

Method: Patients of the Monash Lupus clinic in Melbourne Australia have routine collection of disease activity (SELENA-SLEDAI) and serum at each visit. Damage (SLICC-ACR) is recorded annually. Serum MIF, IL6, and IL17 concentrations were measured by ELISA and genomic DNA was analysed for MIF -173 polymorphisms.

Results: 350 sera were analyzed from 97 subjects satisfying ACR criteria for SLE (mean (±SD) age 42 ± 14, disease duration 10 years ± 7.3, 78 female:17 male), followed over 17 ± 6 months. MIF was detected in all samples (median 3.1 ng/ml, mean (± SEM) 4.3 ± 0.2 ng/mL). SLEDAI varied during study (median (range) 5 (0 – 26)). Correlation between MIF and SLEDAI was not observed in the overall population,

but in SLE patients without active renal disease, (renal SLEDAI = 0), a significant correlation between serum MIF and SLEDAI was observed (r = 0.16, p = 0.024). MIF genotype was analyzed in 81 patients, with the -173*C MIF allele being present in 21 patients (20 heterozygous, 1 homozygous). In patients with a disease duration > 10 years, the MIF -173*C allele was associated with significantly increased SLICC (3.0±0.68 vs 1.4±0.19, p =0.0274). No association between MIF genotype and SLEDAI or steroid exposure was detected. In samples in which IL17 was above assay detection limit (16ng/mL, n = 131), a significant correlation between MIF and IL17 was present (r = 0.36, p <0.0001). Serum MIF and IL-6 were also significantly correlated (r = 0.18, p = 0.0007). Consistent with this, samples in which MIF concentration was >1SD above the mean were characterized by higher mean IL17 (338±135 pg/mL vs 144±21, p=0.0166) and IL6 (180±73 pg/mL vs 62±12, p=0.0088).

Conclusion: Serum MIF correlates with disease activity, and with serum IL17 and IL6, in SLE, and a MIF overexpression polymorphism is associated with increased disease-related damage in longstanding SLE. These results further support the potential role of MIF in the pathogenesis of SLE, and as a biomarker and outcome predictor. Moreover, these findings suggest the ability of MIF to regulate IL-17 and IL6 expression in SLE.

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Serum IL17 in Systemic Lupus Erythematosus: Association with Serum IL6, MIF, and CNS Disease. Eric F. Morand, Melissa Northcott, A. Richard Kitching, Fiona Brown and Alberta Hoi, Monash University, Melbourne, Australia

Purpose: IL17 is the prototypic Th17 cytokine, believed to be important in autoimmune disease. Preliminary studies in SLE suggest elevated IL17 levels in patients compared to controls, and a pathogenic role of IL17 in mouse models. A recent report suggests IL17 stimulates B cell activation in SLE. Prospective studies of IL17 associations with disease manifestations in SLE have not been reported.

Method: Patients of the Monash Lupus clinic in Melbourne Australia have routine collection of disease activity (SELENA-SLEDAI) and serum at each visit. Damage (SLICC-ACR) is recorded annually. Serum IL17, IL6, and MIF concentrations were measured by ELISA.

Results: 97 subjects satisfying ACR criteria for SLE (mean (±SD) age 42 ± 14, disease duration 10 years ± 7, 78 female:17 male) were recruited. 350 paired sera and SLEDAI samples were obtained during a mean follow up of 17 ± 6 months.

Serum IL17 was undetectable in a majority of samples and varied widely (median 0, range 0 – 3423, mean ± SEM 146 ± 22 pg/mL). Serum IL17 was above assay detection limit (>16 ng/mL) in 131 samples (mean ± SEM 370 ± 50 pg/mL).

Th17 differentiation is in part dependent on IL6, and T cell IL17 release is regulated by macrophage migration inhibitory factor (MIF). In samples in which serum IL17 was detectable, serum IL17 was very highly correlated with serum IL6 (r = 0.62, p <0.0001), and this relationship persisted when all samples were analysed, as undetectable IL17 and IL6 were strongly associated. A significant correlation between serum IL17 and serum MIF was also observed (r = 0.36, p <0.0001) and samples in which serum IL17 levels were >1 SD above the mean were associated with significantly higher MIF (8.3 ±1.1 vs 3.9±0.2 ng/mL, p<0.0001).

Correlations between IL17 and SLEDAI, the presence or activity of renal disease, or SLICC were not observed. Unexpectedly, there was no correlation of either serum IL17 or IL6 with serum CRP. However, patients with elevated IL17 levels (> 1 SD above the mean) had an increased incidence of CNS involvement (defined as positive CNS ACR criteria, a positive CNS SLEDAI during follow up, positive CNS SLICC score or documented CNS disease on blinded chart review (p=0.0459). Similarly, those patients with a history of CNS involvement had a significantly higher IL17 area under the curve during follow up than those without CNS disease (p<0.05).

Conclusion: These prospective data indicate that IL17 is undetectable in a majority of SLE patients and does not correlate with overall measures of disease activity or damage. IL17 is highly correlated with IL6 and MIF in lupus patients, supporting the regulation of IL17 by these cytokines in SLE. Moreover, the observation of increased CNS disease in a subset of patients with elevated IL17 suggests the existence of a subset of patients with distinct clinical features related to IL17 expression. Anti-IL17 therapy, or strategies directed at IL6 or MIF, may be protective in CNS lupus, and selection of patients for the study of anti-IL17 therapy in SLE may be facilitated by these observations.

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The HRES-1/RAB4 Lupus Susceptibility Gene Promotes Nitric Oxide Production in Human T Cells through Direct Interaction with Endothelial Nitric Oxide Synthase Interacting Protein. Tiffany Telarico, Edward Doherty, David Fernandez and Andras Perl, Upstate Medical Univ, Syracuse, NY

Purpose: Polymophic haplotypes of the HRES-1 endogenous retrovirus influence lupus susceptibility. The HRES-1/Rab4 gene product of HRES-1 is overexpressed in lupus T cells which contributes to altered T cell activation via regulating endosomal recycling of surface receptors and adaptor protein involved in signal transduction. Increased production of nitric oxide (NO) has been linked to abnormal activation of lupus T cells and NO production has been localized to the T-cell synapse, we investigated the role of HRES-1/Rab4 in NO production.

Method: Expression of proteins involved in NO production was investigated by microrray analysis of gene expression and follow-up western blot analysis of negatively isolated T cells from 44 Caucasian female lupus patients and 23 age-matched Caucasian female controls. NO production was measured by flow cytometry. The effect of HRES-1/Rab4 on NO production and expression of proteins involved in NO synthesis was investigated by overexpression of a wild-type HRES-1/Rab4 and its dominant-negative form HRES-1/Rab4^{S27N}. Direct interaction of HRES-1/Rab4 with potential binding partners was assessed by pull-down assays.

Results: No production was increased in lupus T cells by 32% (p=0.009) Expression of endothelial NO synthase (eNOS) interacting protein (NOSIP) was reduced by 61% in lupus T cells (p=0.010). Over-expression of HRES-1/Rab4 suppressed NOSIP expression and enhanced eNOS expression, and NO production while dominant-negative HRES-1/Rab4^{S27N} had the opposite effects in human T cells. NOSIP was efficiently pulled down by HRES-1/Rab4-GST but not by GST alone in Jurkat cells and human peripheral blood lymphocytes.

Conclusion: The results indicate that over-expression of HRES-1/Rab4 promotes NO production through a direct interaction with NOSIP, possibly through regulating the intracellular traffic, expression, and activity of eNOS.

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TLR8 and STAT4 Expression Is up-Regulated Differentially by Estrogen Stimulation of Peripheral Blood Mononuclear Cells From Patients with Systemic Lupus Erythematosus. Nicholas Young[1], Hayley James[2], Margaret Shupnik[2] and Wael N. Jarjour[1], [1]The Ohio State University Medical Center, Columbus, OH, [2]University of Virginia Health System, Charlottesville, VA

Purpose: Systemic Lupus Erythematosus (SLE) is a multi-organ autoimmune disorder predominately affecting females in the reproductive age range. This gender-bias of female to male is highest in premenopausal women (12:1) and decreases to 4:3 post menopause. Although the precise pathogenesis of SLE remains to be elucidated, the influence of hormonal factors is evident both experimentally and in humans, and it was further investigated in this study.

Method: Here, gene array analysis of peripheral blood mononuclear cells (PBMC) of premenopausal SLE women was compared to that of healthy individuals. All patients and healthy subjects were not receiving birth control or any hormonal medication. The PBMC were also examined after stimulation with a physiologic dose of estrogen in-vitro in order to determine the contribution of this hormone to SLE pathobiology. Each experimental subject served as her own control by subtracting gene expression at baseline from gene expression after stimulation with estrogen. The gene expression was then compared among the healthy subjects and the lupus patients. The resulting expression profile of statistically significant genes represented the estrogen effect observed in SLE samples.

Results: Our findings reveal significantly elevated expression of both signal transducer and activator of transcription 4 (STAT4) and toll-like receptor 8 (TLR8) in premenopausal SLE women when compared to healthy subjects.

Conclusion: These observations establish a possible mechanism by which estrogen may differentially induce the up-regulation of genes that contribute to the pathogenesis of SLE, as both of these genes have been strongly linked to SLE previously. Ongoing work will investigate the impact of co-stimulation on cytokine signaling, particularly interferon-α, and will examine the effects of various estrogen agonists and antagonists on the expression of STAT4 and TLR8.

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The Number of C4 Gene Copies Is Associated with Autoantibody Profile in SLE. Elisabet Svenungsson[1], Emeli Lundstrom[1], Iva Gunnarsson[1], Johanna Gustafsson[1], Yee Ling Wu[2], Kerstin Elvin[3], Lars-Olof Hansson[4], Anders Larsson[5], Chack-Yung Yu[2] and Leonid Padyukov[1], [1]Dept. of Medicine, Rheumatology Unit, Karolinska Insitutet, Stockholm, Sweden, [2]Dept. of Molecular Virology, Immunology and Medical Genetics, the Ohio State University, [3]Dept. of Clin. Immunology and Transfusion Medicine, Unit of Clin. Immunology, Karolinska Institutet, Sweden, [4]Dept. of Laboratory Medicine, Karolinska Hospital, Stockholm, Sweden, [5]Dept. of Laboratory Medicine, Akademiska Hospital, Uppsala, Sweden

Purpose: Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease characterized by the presence of autoantibodies and complex inheritance. C4A and C4B genes are located on human chromosome 6p21.3, the region with strongest linkage to SLE according to recent whole genome scans. Copy number polymorphism (CNP) is one of many possible sources of phenotypic heterogeneity. We analyzed the associations between C4 CNP and SLE. Among SLE patients we also investigated the association of C4 CNP with plasma levels of complement and autoantibodies.

Method: 283 SLE patients and 180 controls matched for age, sex and region of living participated. C4 CNP was determined with RT-PCR. Plasma levels of C4, C3, and C3d were measured in patients by rate nephelometry and autoantibodies with enzyme linked immuosorbent assay. The Lupus anticoagulant (LAC) test was performed with a Dilute Russel Viper Venom method. Associations were determined with Chi-square and Mann-Whitney tests.

Results: SLE patients more often had < 2 copies of C4A (OR: 2.3, 95% CI: 1.4-3.7) or < 4 copies of 'C4 total' (C4A+C4B) (OR: 2.3, 95% CI: 1.4-3.6) than controls. No association between C4B CNP and SLE was observed. Analyses among SLE patients revealed an association between low copy numbers (<4 copies) and low serum levels of C4 (p = 0.02). No association between C4 CNP and plasma levels of C3 and C3d was observed. A strong association between SLE patients carrying < 2 copies of C4A or < 4 copies of C4tot and presence of SSA/SSB antibodies (OR C4A: 1.8, 95% CI: 1.1-3.1) (OR C4tot: 4.1, 95% CI: 2.4-7.00) was observed. SLE patients carrying < 2 copies of C4A or < 4 copies of C4tot, were less likely to have β2GP1 IgG (OR C4tot: 0.4 95% CI: 0.2-0.7), anticardiolipin (aCL) IgM (OR C4A: 0.5, 95% CI 0.2-0.9) or a positive LAC test (OR C4tot: 0.3, 95% CI: 0.1-0.5). No significant association with aCL IgG, aDNA or aSm antibodies was present.

Conclusion: This study demonstrates a strong association between C4 CNP and autoantibody profile in SLE. Low numbers of C4 gene copies were strongly associated with the presence of SSA and SSB antibodies while SLE patients with high numbers of C4 gene copies were more likely to have antiphospholipid antibodies. Our data corroborate previous findings that a genetic deficiency of C4 is associated with SLE and with low levels of C4 protein in plasma. Further studies related to the complement system are warranted to understand how genetics is related to subgroups of SLE patients with different autoantibody profiles.

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1763

The Association of the Defects in ER Stress-Induced Autophagic Reaction and Apoptotic Cell Death of T Lymphocytes in Systemic Lupus Erythematosus. Eun Gyeong Lee[1], Hee Jin Yun[1], Yun Kyung Hong[1], Myung Soo Lee[2], Hyun-Ok Kim[3], Sang-IL Lee[4], Sung Il Kim[5] and Wan-Hee Yoo[1], [1]Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Iksan, South Korea, [3]Gyongsang University, Jinju, South Korea, [4]College of Medicine, Gyeongsang National University, Jinju, South Korea, [5]Pusan National University Mediacal School, Busan, South Korea

Purpose: Autophagic reaction is involved in the control of CD4+ T lymphocytes homeostasis and also is essential for T lymphocyte survival and proliferation. Systemic lupus erythematosus (SLE) is a prototype of autoimmune diseases of unknown etiology and characterized by high-titer autoantibodies against ubiquitous nuclear self-antigens and aberrant T lymphocyte functions. This study was to define the roles of endoplasmic reticulum (ER) stress-induced autophagic reaction of T lymphocytes in patients with SLE.

Methods and Materials: The survival of T lymphocytes was evaluated with CCK-8 reagent and the percentage of apoptotic cells was examined with flow cytometry with propidium iodide and annexin V in the presence or absence of ER stress with thapsigarnin. The expression of beclin 1 and LC3 as markers of autophagic reaction, and Bcl-2 and Bcl-Xl was examined by immunoblotting. To detect

autophagic reaction, T lymphocytes were transfected with plasmid GFP-LC3 and stained with 0.1% Triton X-100 and counterstained with 4',6'-diamidino-2-phenylindole (DAPI) nuclear dyes and observed under fluorscence microscopy.

Results: ER stress-induced autophagic reaction was decreased in T lymphocytes of patients with SLE compared to healthy controls. Decreased ER stress-induced autophagic reaction was associated with reduced expression of antiapoptotic proteins, Bcl-2 and Bcl-Xl after stimulation with thapsigarnin. It also associated with decreased survival and increased apoptosis of lupus T lymphocytes compared with T lymphocytes of healthy controls.

Conclusion: ER stress-induced autophagic reaction was decreased and associated with survival of T lymphocytes in SLE. Thus, we suggest that defects in autophagic reaction of T lymphocytes are involved in the pathogenesis of SLE.

Disclosure: E. G. Lee, None; **H. J. Yun**, None; **Y. K. Hong**, None; **M. S. Lee**, None; **H. O. Kim**, None; **S. I. Lee**, None; **S. I. Kim**, None; **W. H. Yoo**, None.

1764

B Cell Signatures as Biomarkers in SLE. Chungwen Wei[1], Arumugam Palanichamy[1], Scott A. Jenks[1], Jennifer Barnard Hossler[1], Alex Rosenberg[1], James Kobie[1], Bo Zheng[1], Eun-Hyung Lee[1], Yu Qian[2], Richard Scheuermann[2], Jennifer H. Anolik[3] and Iñaki Sanz[1], [1]University of Rochester Medical Center, Rochester, NY, [2]UT Southwestern, Dallas, TX, [3]University of Rochester, Rochester, NY

Purpose: B cells play central protective roles against infection and key pathogenic roles in autoimmunity. Whether diverse and opposing functions are played by distinct subsets or result from plasticity of the same subsets remains to be understood. This gap in knowledge is a major impediment to understand the pathogenesis of autoimmunity and to develop safe and effective B cell targeted therapies. Thus, a comprehensive and consistent definition of the phenotypic heterogeneity of human B cells is of the essence. Here, we utilize state-of-the-art 11-color flow cytometry and new analytical algorithms to explore B cell diversity in SLE and define B cell profiles as biomarkers of disease activity and prognosis.

Methods: 11-color flow cytometry (on a LSRII cytometer) was used to simultaneously analyze multiple markers: CD19, IgD, CD27, CD24, CD38 and CD21, mitotracker extrusion (specific for naïve B cells), systemic homing (CXCR3), activation (CD69), and proliferation (Ki67) in the peripheral blood of normal controls (n=10) and SLE patients (n=23). Selected experiments also included staining for markers of lymphoid homing (CD62L). Basic subsets were defined using core markers. In order to objectively identify cell populations, we applied a novel methodology, Flow Cytometry Clustering without K (FLOCK), which uses the fluorescence intensity data from all staining parameters simultaneously to automatically define all unique populations. B cell profiles were initially compared in an unsupervised fashion by cluster analysis. SLE disease activity was assessed by SLEDAI.

Results: Human B cell populations, as revealed by FLOCK methodology, display considerable heterogeneity in normal controls and increased heterogeneity in SLE samples with 12-16 distinct populations identified in peripheral blood. In an analysis of 23 SLE patients several distinct B cell profiles were identified. As a whole, the SLE group had higher transitional B cells (14%+/-11 SLE vs. 7.7%+/-2.8 controls, p=0.04) and CD69+ plasmablasts (10.6%+/-7.5 SLE vs. 4.3%+/-2.9 controls, p=0.01). CD27+ memory predominant SLE patients (defined as 2 SD above the control mean) (observed in 36%) had a relative paucity of transitional and naïve B cells. This phenotype is also associated with an expansion of isotype switched CD27- B cells with an effector phenotype (CXCR3+CD62L-; observed in 46%). Disease flare was associated with a memory predominant B cell profile. In contrast, the normal controls clustered with the SLE patients with low SLEDAI scores requiring minimal immunosuppression. Expanded numbers of patients, detailed clinical correlations, longitudinal analysis, and additional mining tool application are underway.

Conclusion: Human B cell diversity has previously been underappreciated given the limitation of pauci-color flow cytometry strategies. Our results suggest that B cell profiles can be utilized as biomarkers of disease activity in SLE. We hypothesize that autoimmunity reflects a dysregulation in the balance between functionally distinct lymphocyte populations that is reflected in distinct B cell profiles.

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1765

Single Anti P-Ribosomal Antibodies Are Not Associated to Lupus Nephritis in Patient with Active Systemic Lupus Erythematosus. Theory of the Nephritogenicity by Clusters. Gerardo Quintana[1], Paola Coral-Alvarado[1], Gustavo Aroca[2], Paul Mendez[1], Philippe Chalem[1], Antonio Iglesias[3] and Ariel Ruiz[3], [1]Unidad de Reumatología, Universidad Nacional de Colombia, Bogota, Colombia, [2]Clinica de la Costa, Colombia, [3]Universidad Nacional de Colombia, Bogota, Colombia

Purpose: In the clinical practice sometimes it is difficult to diagnose a relapse in patients with Systemic Lupus Erythematosus (SLE) and lupus nephritis (LN) with potential complications including renal insufficiency and death. Some immunological markers can help to determine their association with LN and diagnose early this complication. The aim of this study was to evaluate the association between systemic and kidney activity and the anti-P ribosomal antibodies and to determine its coexistence with anti-dsDNA on nephritogenicity's theory in patients with active SLE.

Method: Three-hundred and eighty nine patients were analyzed but only 140 were included (inclusion criteria), 70 in each group in a case-control study in Colombian population with SLE - ACR 1997 -. All of the subjects had some score of activity. The activity was determined by SLEDAI. Those patients with active LN (proteinuria ≥ 0.5 grams/24 hours; urinalysis with cellular cylinders, proteinuria and/or hematuria; and/or an increase ≥ 30% of the basal serum creatinine levels) were considered to be "cases". We use ELISA'S kit and the indirect immunofluorescence method with *Crithidia luciliae* for determining the presence of antibodies anti-P ribosomal and anti-dsDNA, respectively.

Results: No association between anti-P ribosomal and the LN (p=0.2971) was found, but if it was between anti-P ribosomal and SLEDAI > 5 (OR=4.87, IC 95% 1.32-17.98, p=0.008). The coexistence of anti-P ribosomal and anti-dsDNA was associated to LN (OR = 3.52; IC 95% 1.07-13.42, p=0.019). Finally, anti-dsDNA was associated to LN (p=0.001). None histopathologic type of LN was associated to anti-P ribosomal.

Conclusion: There was not association among anti-P ribosomal and LN, but the coexistence of anti-P ribosomal and anti-dsDNA was associated with it, what suggests that the coexistence of two antibodies is more nephritogenic. Anti-P ribosomal is associated with activity score with/without LN. Additional studies are needed to evaluate coexistences of antibodies specific to kidney on SLE to determine the biological nature of the LN.

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ACR/ARHP Poster Session C

Scleroderma and Fibrosing Diseases II

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1704

Sensorineural Hearing Loss in Diffuse Systemic Sclerosis. Tatiana A. Monteiro[1], Romy B. C. Souza[2], Eloisa Bonfa[1], Ricardo F. Bento[1], Elaine S. Novalo[1] and Laura G. E. Vasconcelos[1], [1]Faculdade de Medicina da USP, Sao Paulo, Brazil, [2]University of Sao Paulo, Sao Paulo, Brazil

Purpose: Hearing loss has been reported in 77% patients with limited SSc but there are no systematic evaluation regarding diffuse SSc subtype. Since this later form has distinct clinical manifestation with a more extensive organ involvements we have evaluated auditory dysfunction in 26 consecutive SSc patients with diffuse subtype.

Methods: 26 diffuse SSc patients (ACR criteria) were included in this study. All patients were interviewed with a standard questionnaire regarding otological symptoms. A completed ear/nose/throat physical examination was performed followed by speech/pure tone audiometry and impedance measurements. In those with unilateral or asymmetrical hearing loss a magnetic resonance imaging was performed to exclude retrocochlear etiology. Hearing loss was defined when audiometric tests disclosed pure-tone thresholds equal to or greater than 25 dB HL in 2 frequencies of the audiogram. Individuals with a history of cranial trauma, meningitis, ototoxic drugs use, noise exposure, acoustic trauma, ear malformation, otologic surgery and other connective tissue disease were excluded.

Results: Two patients with other autoimmune diseases were excluded. Among the 24 analyzed, the mean age was 47.0 ± 11.9 years with mean disease duration of 9.4 ± 9.1 years and a clear female predominance (83%). The questionnaire revealed auditory complaining in 50% (25% hearing loss, 20% aural fullness, 20% tinnitus and 20% dizziness). Patients had a uniform normal otoscopy, except for two patients (central neotympani and tympanosclerosis). Audiometric diagnosis of hearing loss occurred in almost half of the patients (45.8%), all of them had a sensorineural component, 8 (72,8%) a descending configuration in the audiogram and recruitment phenomenon occurred in 6 (54,5%), suggesting cochlear involvement. Stapedial reflex was present in 23 (96%) and abnormal tympanogram in 5 (21%). Asymmetrical or unilateral hearing loss occurred in 2 patients and both had a normal MRI.

Conclusion: The finding of predominant sensorineural hearing loss in diffuse SSc suggests that inner ear damage is probably due to the vascular involvement of the disease.

Disclosure: T. A. Monteiro, None; **R. B. C. Souza**, None; **E. Bonfa**, None; **R. F. Bento**, None; **E. S. Novalo**, None; **L. G. E. Vasconcelos**, None.

1705

Clinical and Histopathologic Comparison of Generalized Subcutaneous Morphea (GSM) with Eosinophilic Fasciitis (EF). Fazleomar Mahmood[1], Ann J. Impens[1], Elena Schiopu[1], Kristine Phillips[1], Lori Lowe[2], Stephen Olsen[2] and James R. Seibold[1], [1]Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]Division of Dermatopathology, University of Michigan, Ann Arbor, MI

Purpose: GSM (morphea profunda) and EF are both characterized by inflammation and fibrosis involving the lower dermis, subcutaneum, fascia and even superficial muscle. Clinical and laboratory findings overlap as well but these entities have been classified as distinct syndromes. We identified 25 patients investigating clinical and histopathologic distinctions as well as response to therapy and outcomes.

Methods: Retrospective chart review (1998-2008) by ICD9 codes. Cases were selected from the database of outpatient clinical services at the University of Michigan Health Center. Reference area: 3200 patients. Patients with systemic sclerosis and other forms of indurative skin disorders were excluded. Collected data included demographic, clinical and diagnostic variables. Two dermatopathologists have reviewed 8 out of 24 blinded biopsy specimens to date.

Results: 19 patients [10 male, mean age 50.7 y (range 18-83)] diagnosed as GSM and 6 [3 male, mean age 46.3 y (range 27-62] with EF were identified. Important clinical descriptors are represented in the following table.

	GSM n=19		**EF n=6**	
Intense physical activity	3 (n=5)	60 %	1 (n=2)	50%
Skin Induration	19 (n=19)	100 %	6 (n=6)	100%
Peau d' orange	11 (n=11)	100%	4 (n=4)	100%
Venous furrowing	11 (n=13)	84.6%	5 (n=5)	100%
ANA positivity	4 (n=15)	26.7%	2 (n=6)	33.3%
Hypergammaglobulinemia	4 (n=5)	80%	3 (n=4)	50%
Hypereosinophilia	6 (n=17)	35.3%	2 (n=5)	40%
Corticosteroids	18 (n=19)	94.7%	6 (n=6)	100%
Methotrexate	11 (n=19)	57.8%	5 (n=6)	83.3%
Mycophenolate Mofetil	8 (n=19)	88.8%	1 (n=6)	16.6%

Pathology diagnoses of GSM were made in 6/8 cases by one and 5/8 cases by the other blinded reader. The remaining cases were assigned EF.

Important histopathologic descriptors were:

	GSM		EF	
	Pathologist 1	Pathologist 2	Pathologist 1	Pathologist 2
Dermal Inflammation	50% (3/6)	40% (2/5)	0 (0/2)	0 (0/3)
Dermal Sclerosis	100% (6/6)	100%(5/5)	0 (0/2)	33.3%(1/3)
Subcutaneous Inflammation	66.7%(4/6)	60%(3/5)	0 (0/2)	33.3%(1/3)
Fascial Inflammation	66.7%(4/6)	60%(3/5)	100%(2/2)	100%(3/3)

No differences were identified in treatment response and time to remission.

Conclusion: Clinical and laboratory features are indistinguishable between GSM and EF. Based on the 8 out 24 biopsy reviews so far, there are some histopathologic differences between GSM and EF, although these data do not support separate terminology, prognosis or approach to therapy.

Disclosure: F. Mahmood, None; **A. J. Impens**, None; **E. Schiopu**, Actelion Inc, 8 ; **K. Phillips**, None; **L. Lowe**, None; **S. Olsen**, None; **J. R. Seibold**, None.

1706

Correlation Between Submaximal Exercise Testing and Right Heart Catheterization in Patients with Systemic Sclerosis (SSc).

Suparaporn Wangkaew[1], Ann J. Impens[1], Melvyn Rubenfire[2], Vallerie V. McLaughlin[2], Daniel G. Montgomery[2] and James R. Seibold[1], [1]Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]Cardiology, University of Michigan, Ann Arbor, MI

Background: The six-minute walk test (6MWT) has been used as a primary outcome measure in studies of pulmonary arterial hypertension (PAH). Correlations of 6MWT and right heart catheterization (RHC), a gold standard of PAH diagnosis, have not been examined in SSc patients.

Purpose: To determine the correlations between the 6MWT and RHC variables in SSc patients.

Method: 41 SSc patients with 1 test set of RHC, 6MWT and PFT within 12 weeks of the corresponding RHC were retrospectively identified. Data included clinical characteristics; RHC variables: right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), mixed venous O2 saturation (SvO2), cardiac output (CO); 6MWT variables: 6MW distance, SaO2 (baseline, nadir), Δ SaO2 (SaO2base-nadir), heart rate (HR baseline, peak), HR change (Δ HR: HR peak-base), Borg Dyspnea Index (BDI rest, peak), Borg Fatigue Index (BFI rest, peak); and PFT variables: FVC and DLCO (% predicted). Forehead probe pulse oximeter was used to measure SaO2. PAH was defined as mPAP >25 mmHg at rest and PCWP ≤ 15 mmHg. Interstitial lung disease (ILD) was defined as % FVC < 85. Pearson correlation coefficients were used to determine the correlations between 6MWT and RHC variables.

Results: Mean (SD) age was 55.8 (10.1) yrs and mean disease duration 6.5 (4.9) yrs. 85.4% were female; 82.9% were classified as limited SSc, 58.5% SSc-PAH-ILD, 19.5% SSc-ILD, 17.1% SSc-PAH, 2.4% SSc-PH-LVdys, and 2.4% SSC-none. Mean (SD) values were: RAP 9.3 (6.3) mmHg; mPAP 40.2 (15.7) mmHg; PCWP 10.5 (4.0) mmHg; PVR 7.1 (4.4); SvO2 64.8 (8.2) %; CO 4.6 (1.3) L/min; 6MWD 312.6 (94.6) m; HR baseline 83.7 (15.3) beat/min; HR peak 118.4 (17.9); Δ HR 34.2 (14.8); SaO2 baseline 98.0(1.5); SaO2 nadir 91.8 (4.4); Δ SaO2 6.2 (4.4); BDI rest 0.8 (1.2); BDI peak 4.2 (3.0); BFI rest 0.9 (1.3); BFI peak 3.5 (2.8); % FVC 67.9 (20.5), and % DLco 34.7 (15.8). 6 (14.6%) patients were on current use of beta blockers and 18 (43.9%) who used oxygen supplementation during the 6MWT. Correlations between 6MWT and RHC variables were:

Variable	6MWD	HR base	HR peak	Δ HR	SaO2 base	SaO2 base	ΔSaO2	BDI rest	BDI peak	BFI rest	BFI peak

Total grp. (N=41)											
RAP	-.47** 40	.15 40	-.24 38	-.44** 38	-.42** 40	.12 38	-.25 38	.37* 32	.27 34	.16 30	.40* 30
mPAP	-.48** 41	.06 41	-.30 39	-.42** 39	-.24 41	-.11 39	.03 39	.29 33	.37* 35	.03 31	.33 31
PVR	-.40* 37	.00 37	-.32 35	-.38* 35	-.27 37	-.08 35	-.00 35	.25 29	.21 31	-.00 27	.17 27
SvO2	.39* 35	.05 35	.37* 33	.39* 33	.16 35	-.14 33	.18 33	.01 28	.08 30	.24 26	-.01 26
CO	.36* 41	.13 41	.39* 39	.36* 39	.19 41	-.19 39	.25 39	-.27 33	-.11 35	-.01 31	-.19 31

*p< 0.05, ** p< 0.01

Conclusion: 6MWD and heart rate change show statistically significant low to moderate correlation with the RHC variables. Correlations between RHC variables and HR peak, SaO2 baseline, BDI, and BFI peak, if significant, are low to moderate. HR baseline, SaO2 (nadir, □ SaO2), and BFI rest reveal no significant correlations with RHC variables. Further study is needed to validate HR response as an outcome measure of SSc-PAH.

Disclosure: S. Wangkaew, None; **A. J. Impens**, None; **M. Rubenfire**, None; **V. V. McLaughlin**, None; **D. G. Montgomery**, None; **J. R. Seibold**, None.

1707

Relevance of the Heart Rate Recovery After Six-Minute Walk Test (6MWT) in Patients with Systemic Sclerosis (SSc). Suparaporn Wangkaew[1], Ann J. Impens[1], Melvyn Rubenfire[2], Elena Schiopu[1], Vallerie V. McLaughlin[2], Daniel G. Montgomery[2] and James R. Seibold[1], [1]Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]Cardiology, University of Michigan, Ann Arbor, MI

Background: Heart rate recovery (HRR) after 6MWT has been shown to be predictive of mortality in patients with idiopathic pulmonary fibrosis (1), but its role has not been examined in patients with SSc.

Purpose: To examine the correlations of HRR with other non-invasive measures of cardiopulmonary function.

Methods: 147 SSc patients were retrospectively identified as having had at least one test set of 6MWT, PFT, and echocardiogram performed within 12 weeks. Abstracted data included clinical characteristics, 6MW distance (6MWD), Δ oxygen saturation (Δ $SpAO_2$ baseline minus nadir), peak heart rate (HR peak) during 6MWT, HR at 1 min of recovery, FVC and DLco (% predicted), and estimated systolic pulmonary artery pressure (sPA). Heart rate recovery (HRpeak-1min) was recorded as HR peak minus HR-1min. PAH was defined as estimated sPA ≥ 45 mmHg. Interstitial lung disease (ILD) was defined as % predicted of FVC < 85. Student's *t* test was performed to determine mean difference in HRR in subgroups of SSc.

Results: Mean (SD) age was 53.8 (10.9) yrs and mean disease duration 8.0 (8.0) yrs. 86.4% were female and 70.1% were classified as limited SSc. Patients were categorized as 42.9% SSc-ILD, 17.0 % SSc-PAH and ILD, 4.8 % SSc-PAH and 35.4% SSc with neither ILD or PAH. Mean (SD) values were: 6MWD 394.3 (129.0); Δ $SpAO_2$ 3.2 (4.1); HR-1m 20.6 (11.3); % of predicted FVC 77.7 (19.6); % of predicted DLco 54.6 (21.1), and sPA 40.2 mmHg (26.2). 84 (57.1%) patients had 6MWD ≥ 380 m. Echocardiography revealed sPA ≥ 45 mmHg in 32 (21.8%), right ventricular dysfunction (RV dys) in 24 (16.3%) and left ventricular diastolic dysfunction (LVD dys) in 14 (9.5%). 13 (8.8%) of patients were receiving beta-blockers.

Differences in mean HRpeak-1min between subgroups were:

Subgroup			Mean (SD)	Mean (SD)	Mean difference	P
	A	B	A	B	A-B	
Distance (m)	<380	≥380	15.8 (10.5)	24.0 (10.6)	-8.2	<0.01
sPA (mmHg)	<45	≥45	21.8 (10.3)	15.9 (13.6)	5.9	<0.05
RV dys	without	with	22.4 (10.4)	10.5 (10.4)	11.9	<0.01
LVD dys	without	with	21.2 (11.3)	15.2 (7.7)	5.9	NS
Beta-blockers	without	with	21.2 (11.3)	14.5 (8.8)	6.7	<0.05

Conclusion: Mean HRpeak-1min after 6MWT are significantly decreased in SSc patients with poor 6MWD, higher sPA, right ventricular dysfunction, and current use of beta- blockers. Left ventricular dysfunction did not affect HRpeak-1min. HRpeak-1min offers promise as a measure of outcome and response in patients with SSc.

1. Swigris JJ, Swick J, Wamboldt FS, Sprunger D, du Bois R, Fischer A, et al. Heart Rate Recovery After 6-Minute Walk Test Predicts Survival in Patients With Idiopathic Pulmonary Fibrosis. Chest 2009.

Disclosure: S. Wangkaew, None; **A. J. Impens**, None; **M. Rubenfire**, None; **E. Schiopu**, Actelion Inc, 8 ; **V. V. McLaughlin**, None; **D. G. Montgomery**, None; **J. R. Seibold**, None.

1708

Improvement in Long-Term Prognosis of Pulmonary Arterial Hypertension in Patients with Connective Tissue Diseases, Including Systemic Sclerosis, Mixed Connective Tissue Disease and Systemic Lupus Erythematosus. Sumiaki Tanaka, Tatsuhiko Wada, Reiko Matsushita and Shunsei Hirohata, Kitasato University School of Medicine, Sagamihara, Japan

Purpose: Under current circumstances where a variety of potent drugs for treating pulmonary arterial hypertension (PAH) have become available, sophisticated strategy for treatment of PAH has become more important in patients with connective tissue disease (CTD). We aimed to assess whether our strategy for treating PAH improves long-term prognosis of PAH associated with CTD, including systemic sclerosis (SSc), mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE)

Method: We performed a retrospective-cohort study among 96 PAH patients with CTD, including SSc (40 patients), MCTD (20 patients) or SLE (18 patients), who received treatments and were followed up between 1980 and March 2009 in our hospital. Our therapeutic strategy for PAH intended to achieve the following goals: 1) improvement in WHO-functional class after 6 month of treatment and 2) reduction of serum BNP level of less than 73.8 pg/ml, based on our previous study results as well as on the results demonstrated by Hoeper et. al, (Eur Respir J 2005; 26: 858–863). The PAH-specific medications, including bosentan, sildenafil, epoprostenol, and beraprost (an oral prostacyclin analog that is only available in Japan), were switched from drug to drug or adopted in combination so as to achieve these predetermined therapeutic goals. Survival was measured from the date of the diagnosis of PAH, and analyzed using Kaplan-Meier method and Cox's proportional hazard model.

Results: Thirty-seven patients who were treated under this therapeutic strategy were placed in the goal-oriented treatment Group. The PAH-specific medications in this group at the last observation are shown in table 1. Fifty-nine patients including 27 patients who were treated using beraprost without intention for achievement of the therapeutic goals, and 32 patients who had been treated before these PAH-specific medications became available or who had been unavoidably treated with only conventional drugs due to adverse effect, were placed in the control group. Patients in the goal-oriented treatment group showed significant improvement in survival (Figure 1). Multivariate analysis for survival demonstrated that our therapeutic strategy markedly improved long-term prognosis (Table 2). The age and WHO- functional class at the diagnosis of PAH also affected survival, while the type of CTDs did not affect survival.

Conclusion: Our therapeutic strategy for PAH using the PAH-specific medications markedly improved long-term prognosis of CTD patients complicated with PAH. These data clearly indicate that early diagnosis and early intervention to inhibit the progression of WHO-functional class and reduce serum BNP levels are important for CTD patients susceptible to PAH.

Table 1. PAH-specific medications

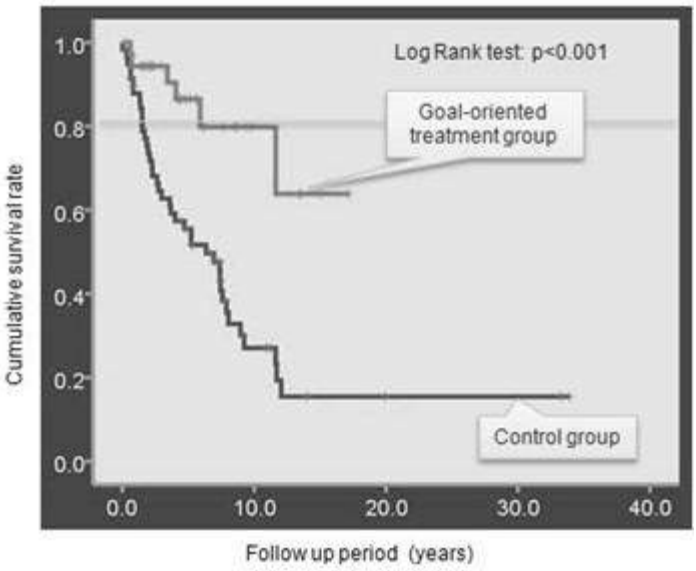
PAH-specific medications	cases
BPS	14
BPS + BOS	1
BPS + SIL	1
BPS + BOS + SIL	5
BOS	12
EPO	2
EPO + SIL	2

BPS: beraprost sodium, BOS: bosentan,
SIL: sildenafil, EPO: epoprostenole

Table 2. Multivariant analysis for mortality hazard using Cox model

covariant	HR	95% CI	p
age at the diagnosis of PAH	1.029	1.001 - 1.059	0.042
sex	0.757	0.249 - 2.298	0.623
SSc	0.989	0.452 - 2.163	0.978
MCTD	1.710	0.597 - 5.157	0.907
SLE	2.137	0.852 - 4.801	0.066
ILD (>1/4)	0.632	0.284 - 1.403	0.259
WHO-FC (III-IV)	3.382	1.666 - 6.905	0.001
Goal-oriented treatment	0.216	0.087 - 0.536	0.001

Figure 1. Survival of CTD-PAH Patients in Our Department



Disclosure: S. Tanaka, None; **T. Wada**, None; **R. Matsushita**, None; **S. Hirohata**, None.

1709

Employment Status and Burden in Systemic Sclerosis: A Cross-Sectional Survey. Christelle Nguyen[1], Serge Poiraudeau[1], Caroline Mestre-Stanislas[2], François Rannou[1], Alice Bérezné[2], Agathe Papelard[1], Michel Revel[1], Loïc Guillevin[2] and Luc Mouthon[2], [1]Rehabilitation Department, Cochin Hospital, Paris-Descartes University, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, [2]Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France

Purpose: To assess employment status and burden in systemic sclerosis (SSc).

Method: Eighty-seven SSc patients (72 females), fulfilling the ACR and/or the Leroy and Medsger criteria, were assessed for employment status and burden. Statistical analysis was performed using nonparametric Mann-Whitney and Fisher's exact tests.

Results: Mean age and disease duration were 48.6±8.5 and 8.1±6.4 years, respectively. Seventy percent of SSc patients were on full-time sick leave and 35.6% were disabled. Twenty percent of patients were professionally reoriented after the diagnosis of SSc was made. Myalgias were the only clinical manifestation more frequently encountered in sick leave patients than in others (73.6% vs. 47.1%, p = 0.012). Karnofsky performance status was reduced in SSc patients on sick leave or disabled as compared to others (78.1±8.7 vs. 83.1±11.2, p = 0.016; and 78.5±10.6 vs. 85.8±9.0, p = 0.004, respectively). In addition, greater hand and mouth disabilities and depression were observed in patients on sick leave (Cochin hand function scale 21.7±18.9 vs. 10.7±12.1, p = 0.003; mouth handicap in SSc scale 20.2±10.8 vs. 14.6±10.0, p = 0.021; and depression dimension of the hospital anxiety and depression scale 7.1±3.9 vs. 4.8±3.4, p = 0.003). Lastly, disabled patients reported more frequent income decrease (71% vs. 23.2%, p < 0.001), absence of advancement (71% vs. 28.6%, p < 0.001), and a feeling of discrimination (22.6% vs. 5.4%, p = 0.030).

Conclusion: In SSc patients, perceived health status and disability are associated with sick leave status and represent major factors of the employment burden.

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1710

Endothelial Dysfunction Is Associated with Decreased Circulating Endothelial Progenitor Cells in Pateints with Systemic Sclerosis.

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Background: The role of circulating bone marrow derived endothelial progenitor cells (EPCs) for vascular repair in scleroderma (SSc) remains unclear.

Purpose: To examine endothelial dysfunction in SSc patients and to correlate findings with biochemical markers of endothelial injury, circulating EPC count, disease activity and organ involvement.

Methods: Endothelial dependent and independent vasodilation responses were assessed by changes in flow mediated dilation (FMD%) and nitroglycerin challenge (NTG%) in the brachial artery respectively in SSc patients compared to age- and sex- matched controls. Serum levels of vascular endothelial growth factor (VEGF) and soluble vascular cell adhesion molecule (sVCAM)-1 were measured by ELISA. Enumeration of circulating CD133/VEGFR2+ EPCs was performed by flow cytometry.

Results: Median FMD% (4.8% vs. 7.8%, P<0.001) and NTG% (17.0% vs. 21.4%, P=0.002) were found to be significantly lower in SSc patients (n=52) than controls (n=52), especially in patients with limited disease (lSSc). Median circulating EPC count was significantly lower in lSSc patients (23.0/µl) compared to controls (73.0/µl) (P<0.001). This was accompanied by higher level of sVCAM-1 in these patients compared to those with diffuse disease (P=0.01). Lower circulating EPC count was found to be associated with high disease activity (P=0.04), abnormal forced vital capacity (P=0.003), longer disease duration (P=0.04), total skin score>20 (P=0.03) and lSSc subset (P<0.001). Multivariate analysis identified disease duration as the only independent predictor for circulating EPC count (P=0.04).

Conclusion: Endothelial dysfunction was demonstrated in SSc and correlated with biochemical markers of endothelial injury. Lower circulating EPCs might contribute to deficient vascular repair in SSc patients.

Disclosure: M. Y. Mok, None; **H. F. Tse**, None; **Y. Lo**, None; **W. Wong**, None; **C. S. Lau**, None.

1711

An On-Line Screening Tool for Cardiopulmonary Complications of Scleroderma - the Australian Scleroderma Screening Program.

Susanna M. Proudman[1], Jill Byron[2], J. Zochling[3], Peter Youssef[4], P. Nash[5], Kathleen Tymms[6], Madelynn Chan[7], Allan D. Sturgess[8], Leslie Schrieber[9], Catherine Hill[10], David Celermajer[4], Joanne Sahhar[11] and Wendy Stevens[2], [1]Royal Adelaide Hospital, Adelaide, Australia, [2]St Vincent's Hospital, Melbourne, Australia, [3]University of Tasmania, Hobart, Australia, [4]Royal Prince Alfred Hospital, Sydney, Australia, [5]University of Queensland, Brisbane, Australia, [6]Canberra Hospital, Canberra, Australia, [7]Royal Perth Hospital, Perth, Australia, [8]St George Hospital, Sydney, Australia, [9]Royal North Shore Hospital, Sydney, Australia, [10]The Queen Elizabeth Hospital, Adelaide, Australia, [11]Monash Medical Centre, Melbourne, Australia

Purpose: It is recommended that patients with scleroderma (SSc) be screened annually for the serious complication of pulmonary arterial hypertension (PAH), as it is often clinically silent early in the disease and is now treatable. Compliance with evidence-based clinical guidelines (CG) in a real-life setting can be poor.

Method: A nation-wide, multicentre on-line database of patients with SSc was established in 2007, with a computer decision support system (CDSS) for implementing screening CG for PAH. Doppler echocardiograms (ECHO) and pulmonary function tests (PFTs) are performed annually and recommendations for diagnostic tests for PAH including right heart catheter (RHC) are made by the CDSS after risk stratification according to systolic pulmonary artery pressure (sPAP), diffusing capacity (DLCOc) and symptoms. Definitions of risk categories are: high risk: ECHO sPAP > 50 mmHg; moderate risk: sPAP 40-50 mmHg; at risk: unexplained dyspnoea and/or DLCOc < 50% with FVC > 85 % despite sPAP < 40 mmHg. Detailed clinical and laboratory data are collected annually and entered on-line.

Results: By April 2009, 714 patients (66% lSSc; 26% dSSc) had been recruited into the database from 12 centers and screened. Of these, 341 (45%) had had a second visit, 75 (10%), a third. Mean±SD age and disease duration at entry were 57.9±12.5 and 12.5±10.4 years respectively. Clinical characteristics included esophagitis (82% lSSc cf 84% dSSc), fecal incontinence (16% cf 12%), digital ulcers (24% cf 38%), joint contractures (21% cf 65%), pulmonary fibrosis (19% cf 39%), modified Rodnan score (9 cf 21) and renal crisis (1% cf 5%). 28 (4%) had had RHC-defined PAH prior to 2007. 47 (6.7%) of the remaining 686 patients had RHC-defined PAH as a result of screening (9 on

exercise RHC). Of 33 patients at high risk, 22 were found to have PAH. Of 62 patients at moderate risk, 23 with symptoms were referred for RHC and 11 had PAH. Of 32 at risk patients, 10 were diagnosed with PAH (one with unrecordable ECHO sPAP). A further 5 patients had PAH due to left ventricular dysfunction. The most common reason for CG violation in the moderate risk group was underestimation of symptoms.

Conclusion: Not all patients with PAH have an abnormal ECHO and risk stratification which includes PFTs and symptoms, aids detection. This is the first time a CDSS has been used to facilitate compliance with CG for screening for PAH in SSc, allowing comprehensive clinical assessment and early institution of potentially beneficial therapy. This web-based database serves as a model for effective multi-centre collection of data for an uncommon rheumatic disease.

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1712

Elevated B-Type Natriuretic Peptide Levels Are Associated with Worse Survival in Systemic Sclerosis Associated Pulmonary Hypertension. Lorinda Chung[1], Miho Bennett[1], Roham T. Zamanian[1], Virginia D. Steen[2] and the PHAROS Investigators, [1]Stanford University, Palo Alto, CA, [2]Georgetown Univ Medical Center, Washington, DC

Purpose: B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are cardiac neurohormones that are released in response to myocardial pressure or volume overload. Elevation of these hormones has been associated with worse outcomes in patients with idiopathic pulmonary arterial hypertension (PAH), and elevated NT-proBNP has been shown to predict mortality in patients with systemic sclerosis (SSc)-associated PAH. We sought to assess the prognostic utility of natriuretic peptide levels in SSc patients at high risk for or with incident pulmonary hypertension (PH).

Methods: PHAROS is a multicenter prospective cohort of patients at high risk for PAH (pre-PAH) or with definite PH diagnosed by right heart catheterization (RHC) within 6 months of enrollment. Criteria for pre-PAH include any one of the following: diffusing capacity (DLCO) <55% predicted, forced vital capacity (FVC)/DLCO ratio >1.6, or pulmonary artery systolic pressure (PASP) on echocardiogram >35 mmHg. Patients with definite PH have a mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest or ≥30 mmHg with exercise on RHC. A pulmonary capillary wedge pressure ≤15 mmHg was used to differentiate Group I (PAH) from Group II (PH related to left heart disease). Those with moderate or severe interstitial lung disease on chest imaging and FVC <60% predicted were included in Group III (PH related to hypoxemia). BNP and NT-proBNP levels were log-transformed when used as continuous variables as their distributions were highly skewed. For Cox regression and survival analyses, elevated natriuretic peptide levels were defined as BNP ≥ 180 or NT-proBNP ≥ 553 pg/mL.

Results: 69 definite PH (51 Group I, 9 each in Groups II and III) and 99 pre-PAH patients had natriuretic peptide levels available. Mean(SD) BNP and NT-proBNP levels were significantly higher in the definite PH compared with the pre-PAH patients (226.6(437.7) vs. 62.7(58.6) pg/mL, p<0.0001 ; 1426.1(2684.7) vs. 201.2(453.6) pg/mL, p=0.005, respectively). Group I tended to have the highest levels (mean BNP 249.6(473.2) pg/mL, mean NT-proBNP 2061.0(3121.9) pg/mL, p=0.09 compared with Groups II and III for both tests). In the definite PH group, NT-proBNP but not BNP correlated with mPAP (r=0.65 vs. 0.36) and pulmonary vascular resistance (r=0.77 vs. 0.17). In the pre-PAH group, NT-proBNP had a moderate correlation with PASP on echocardiogram (r=0.56). In the definite PH group, an elevated BNP or NT-proBNP level was associated with >8-fold increased risk of death, which remained when correcting for creatinine and New York Heart Association functional class, but this did not reach statistical significance (HR 8.6(0.8-92.2), p=0.07). 1- and 2-year survival in those with an elevated BNP or NT-proBNP was 89.4% and 78.2%, respectively, but remained 97.6% through 2 years in those with levels below the designated cut-off values (log-rank p=0.03).

Conclusion: B-type natriuretic peptide levels, and NT-proBNP in particular, may be useful in monitoring and predicting outcomes in patients with SSc-associated PH.

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1713

Renal Dosimetry for Patients Treated with Total Body Irradiation (TBI) for Severe Systemic Sclerosis (SSc) On the SCOT (Scleroderma: Cyclophosphamide or Transplantation) Trial. O. Craciunescu, B. Steffey, C. Kelsey, R. Prosnitz, N. Larrier, C. Paarz-Largay and KM Sullivan, Duke University Medical Center, Durham, NC

Purpose: To describe techniques and dosimetry in delivering TBI to patients with severe SSc enrolled on a multicenter stem cell transplant (SCT) protocol.

Methods: The SCOT protocol employs an immunoablative regimen of high-dose CY, ATG and 800 cGy TBI given in 200 cGy fractions twice a day followed by CD34 selected autologous SCT. Due to possible organ impairment from SSc, shielding is used to limit irradiation to kidney and lung to a total of 200 cGy. Since renal shielding has not been previously used during TBI, block thickness and dosimetry were investigated and guidelines developed for safety and technique. Due to concern for worsening of SSc nephropathy, CT-based planning was performed without IV contrast. Data on kidney shape and the shifts from prone to standing position were assessed using diagnostic ultrasound (US). During treatment, we performed *in vivo* dosimetry for each patient using OneDose® (Sicel Technologies) at eleven locations, including the umbilicus, mid mediastinum, lumbar spine, hip, and under the lung/kidney block and calculated the mean dose at each location. Minimum distances between the kidney blocks (dkB) and the dose to the lumbar spine were also determined.

Results: Phantom measurements revealed that a 10 - 20 % dose inhomogeneity in the lumbar spine region could be achieved with a minimum kidney block separation of 4-5 cm (typical width of a vertebral body). Eleven subjects have been treated on the transplant arm of the trial at Duke since 2006. The average lumbar spine dose was 179.6 ± 18.1 cGy, with an average dkB of 5.0 ± 1.0 cm. Block design and placement were accomplished using a combination of CT and US or CT alone. Kidney-localization based on the combination of CT and US yielded more accurate block positioning and reduced superior-inferior block margins. Kidney shape proved similar among the eleven patients imaged, leading to a potential use of standard kidney blocks. The US information revealed a wide range of kidney displacement, both inferior and superior. The mean inferior displacement of the left kidney was 1.2 ± 1.1 cm, and 1.0 ± 1.3 cm for the right kidney. One subject exhibited a superior displacement of 3.5 cm for the right kidney. The average dose measured for the prescription point was 193.4 ± 5.1 cGy, for the mid mediastinum area 196.6 ± 10.6 cGy, for the hip area 206 ± 11.8 cGy, for under the lung blocks 54.7 ± 7.7 cGy, and under the kidney blocks, 50.8 ± 7.1 cGy. With this technique, no deterioration in renal function was observed and the study continues to enroll patients.

Conclusion: Prescribed TBI can be delivered with acceptable homogeneity over the entire body. Attenuation of TBI dosing to the kidneys by 75% can be achieved while maintaining a 10-20% dose inhomogeneity. Localization of the kidneys is more accurate using both CT and US as compared to CT alone. Supported by NIH award AI-05419.

Disclosure: O. Craciunescu, None; **B. Steffey**, None; **C. Kelsey**, None; **R. Prosnitz**, None; **N. Larrier**, None; **C. Paarz-Largay**, None; **K. Sullivan**, None.

1714

Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Two-Year Outcomes for Patients with Pulmonary Hypertension. Lorinda Chung[1], Vivien M. Hsu[2], Marcy B. Bolster[3], ME. Csuka[4], Laura K. Hummers[5], John Varga[6], Ann J. Impens[7], Virginia D. Steen[8] and the PHAROS Investigators, [1]Stanford University, Palo Alto, CA, [2]UMDNJ, New Brunswick, NJ, [3]Med Univ South Carolina, Charleston, SC, [4]Med Coll of Wisconsin, Milwaukee, WI, [5]Johns Hopkins University, Baltimore, MD, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, [7]University of Michigan, Ann Arbor, MI, [8]Georgetown Univ Medical Center, Washington, DC

Purpose: Pulmonary hypertension (PH) is a frequent complication of patients with systemic sclerosis (SSc) and remains a leading cause of death. Pulmonary arterial hypertension (PAH, World Health Organization Group I) is the most common form of PH in SSc, but PH related to left heart disease (Group II) and interstitial lung disease (ILD, Group III) can also occur. The purpose of this analysis was to characterize patients with incident PH from the PHAROS Registry.

Methods: PHAROS is a multicenter prospective, observational study to determine risk factors and outcomes of patients who are at high risk or have PH. Patients with definite PH, defined as mean pulmonary artery pressure (MPAP) ≥25 mmHg at rest or ≥30 mmHg with exercise on right heart catheterization within 6 months of enrollment or newly developed during follow-up, were included in the analysis. A pulmonary capillary wedge pressure ≤15 mmHg differentiated Group I from Group II patients. Those with moderate or severe ILD on chest imaging and forced vital capacity <60% predicted were included in Group III. ANOVA analyses were used to compare baseline features among the groups.

Results: Of the 103 patients with PH, 79 were included in Group I (10 with exercise-induced PAH), and 12 each in Groups II and III. Overall, 85% of the patients were female with a mean(SD) age of 57.8(10.8) years and disease duration from first non-Raynaud's symptom of 9.1(7.8) years. Group III had more African Americans (42% vs. 13% (Group I) and 17% (Group II), p=0.007) and a higher proportion with the SCL-70 antibody (25% vs. 5% (Group I) and 8% (Group II), p=0.02) and a lower proportion with the centromere antibody (8% vs. 28% (Group I) and 25% (Group II), p=0.03), but the groups did not differ by SSc subtype (overall 63% limited). MPAP was similar among the groups with an overall mean of 33.9(11.3) mmHg. Pulmonary vascular resistance was highest in Group I (404(245) dyn·s·cm-5 vs. 210(182) (Group II) and 305(215) (Group III), p=0.03). The groups did not differ with respect to New York Heart Association functional class or percentage using home oxygen. In Group I, initial treatment was with prostacyclins, endothelin receptor antagonists, sildenafil, and combination PH therapies in 13%, 22%, 30%, and 8%, respectively. At last follow-up, the proportion of patients taking these therapies increased to 15%, 38%, 42%, and 19%, respectively. There were 7 deaths in Group I, none in Group II, and 1 in Group III over a mean follow-up time of 22.8(12.2) months. 1- and 2-year survival rates in Group I were 93% and 91%, respectively.

Conclusion: Patients with SSc-associated PH have improved short-term outcomes compared with historical controls. Early diagnosis and treatment of all forms of SSc-associated PH may result in improved short-term outcomes.

Disclosure: L. Chung, Gilead, 2, Actelion, 8, United Therapeutics, 2 ; **V. M. Hsu**, None; **M. B. Bolster**, None; **M. Csuka**, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5 ; **L. K. Hummers**, None; **J. Varga**, PHAROS, 2 ; **A. J. Impens**, None; **V. D. Steen**, Gilead Pharmaceutical, 8, Gilead, 2, United Therapeutics, 2, Bristol-Myers Squibb, 2, Actelion Pharmaceuticals US, 2 .

1715

Plasma Oxidative Stress in Patients with Diffuse Systemic Sclerosis Versus Control Group. Maria del Pilar Cruz-Dominguez[1], Olga Vera-Lastra[1], Daniel Montes-Cortes[1], Gabriela Medina[2] and Marco Medina[1], [1]MD, Mexico City, Mexico, [2]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico

Purpose: To evaluate plasmatic biomarkers of lipid peroxidation, oxidized proteins and total antioxidant capacity (TAC) in patients with DSS compared with a healthy group

Method: We included 28 patients with DSS according to The American College of Rheumatology. They were grouped according to disease evolution: early DSS (less than five years) and late DSS (longer than to five years). Patients suspended all medications that interfered with plasmatic OS, 72 hours previous to obtaining serum samples. As a control we used thirty-two healthy people with similar age and gender. Patients who had some other conditions that will increase the OS, another systemic illness, pregnancy or acute infection were excluded. Biomarkers of oxidative stress: lipid peroxidation products (malondialdehyde, MDA) and protein oxidation (reduction of nitroblue tetrazolium (NBT) to formazan, protein carbonyl levels and dityrosines) were measured. We also investigated total antioxidant capacity (CAPT). Statistical analysis was performed using the Student's t-test, ANOVA, Tukey's test and Spearman's rank correlation.

Results: We studied 28 patients with DSS (32% early and 68% late) and 32 healthy controls (47.5+/-10 y 48+/-7 years old respectively, p=ns). DSS patients showed higher concentrations of MDA (17.6+/-8.6 versus 6.58+/-3.59 nmol/mg free fatty acids, p<0.01), dityrosines (530.6+/-149.7 versus 132.76+/-48.6 pmol/mg proteína, p<0.01), protein carbonyls (1.75+/-0.39 versus 0.68 +/- 0.47 nmol/mg protein, p<0.01) and formazan (17.2+/-3.46 versus 10.2 +/-2.79 nmol/mg protein, p<0.01) compared to healthy people respectively. Compared with control subjects, DSS patients had lower CAPT (0.64+/- 0.095 U versus -2.7+/-0.96 U, p<0.001). There were no significant differences between early and late DSS or among target organs.

Conclusion: Biomarkers concentrations of oxidative stress to lipids and proteins in plasma were in all cases significantly higher in DSS patients than healthy controls. The treatment with anti-oxidants may be important in these patients

Disclosure: M. D. P. Cruz-Dominguez, None; **O. Vera-Lastra**, None; **D. Montes-Cortes**, None; **G. Medina**, None; **M. Medina**, None.

1716

High-Resolution 18 MHz Ultrasonography(US) of Carpal Tunnel Syndrome (CTS) in Systemic Sclerosis (SSc). Francesca Bandinelli[1], Olga Kaloudi[1], Irene Miniati[1], Maria Letizia Conforti[1], Antonio Candelieri[2], Daniela Melchiorre[1] and Marco Matucci-Cerinic[1], [1]University of Florence, Italy, Florence, Italy, [2]University of Calabria, Italy, Italy

Purpose: To evaluate with ultrasound (US) tunnel carpal syndrome (TCS) in Systemic sclerosis (SSc) patients

Method: 64 SSc patients (55 women and 9 men, mean age 57±14 years) were consecutively studied by two observers with US of the carpal tunnel (My Lab 25 XVG US Esaote 18 MHz linear array transducer) and compared with 19 healthy controls. The median nerve cross-sectional area (MNA) and the transverse (MNT) and anteroposterior (MNAP) diameters were measured in the transverse plane at the proximal boundary of the carpal tunnel at the level of the pisiform bone (1). The Italian version of the Boston Carpal Tunnel Questionnaire (I-BCTQ) was used (2). Friction tendon rubs of flexor tendons and Tinel sign were verified clinically and with US. The following was also collected: duration of disease, subset (limited, diffuse), clinical phase (oedematous, fibrotic, atrophic), and modified Rodnan skin score. EMG was performed in 50 patients (distal motor latency and sensory conduction velocity from the third and fourth fingers to the wrist for median nerve).

Results: MNA (11,1±3,6 mm^2, $p<0,001$) and MNT (6,8±1,6 mm $p<0,005$) were significantly higher in SSc, while no difference in MNAP was found. Intraobserver and interobserver agreement was high (interclass correlation coefficient 0,9). MNT correlated positively with BCTQ ($p<0,05$, Pearson coefficient 0,3). No significant difference of median nerve US area and diameters was observed between Tinel test positive and negative patients. There was no correlation between median nerve and subset, clinical phase, and skin score. Only lower MNAP correlated inversely with longer disease duration ($p<0,05$, Spearman coefficient -0,2). 20/50 patients (40%) had EMG positive for STC and all US values were significantly higher in patients with EMG positive for TCS ($P<0,001$). In two cases only friction rubs of the flexor tendons were detected, and only one was positive at EMG.

Conclusion: US is a sensitive tool that identifies detailed investigation of median nerve in all phases of SSc.

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1717

Predicting Lung Function Decline in Systemic Sclerosis. Shikha Mittoo[1], Keng Wong[1], David B. Robinson[2], Marie Hudson[3], Csrg and Murray Baron[4], [1]University of Manitoba, Winnipeg, MB, [2]University of Manitoba, Winnipeg, [3]McGill University and Jewish General Hospital, Montreal, QC, [4]Jewish General Hospital, Montreal, QC

Purpose: Lung involvement is a common and lead cause of mortality in systemic sclerosis (SSc), but progression to end-stage restrictive lung disease is variable and predictors of rapidly progressive lung function decline are unknown. As treatment for lung disease carries significant toxicity, there is a pressing need for biomarkers to predict which patients are most likely to suffer a rapid decline. Surfactant-D (SP-D), a glycoprotein expressed in lung airways, indicates early lung damage and correlates with lung function in SSc. It is not known if SP-D levels correlate with the rate of change in lung function and predicts a rapid decline in lung function.

Methods: Baseline serum from SSc patients enrolled in a multi-center cohort who had at least 2 pulmonary function tests (PFTs), separated by a year, was analyzed for SP-D levels by ELISA. Levels were correlated with: (1) the annual rate of change in percent (%) predicted forced vital capacity (FVC) and % predicted carbon monoxide diffusing capacity (DLCO) on PFT and (2) a rapid decline in lung function (rapid progressors), defined as an annual rate of decline in % predicted FVC at a rate two fold faster than the general population (>2%/year). Values reported as mean ± SD.

Results: Of 67 SSc patients with an age of 54.5 ± 12.1 years, disease duration of 8.6 ± 7.3 years, 88% were women, 90% Caucasian, and 36% current smokers. Forty diffuse and 27 limited cutaneous SSc subtype had serial PFTs with a duration between PFTs of 32.7 ± 11.7 months; 18 and 17 had positive anti-centromere and anti-Scl 70 antibodies, respectively. No patient was on cyclophosphamide at baseline. The % predicted FVC and DLCO at baseline was 94.2 ± 26.8 % and 71.8 ± 23.0 %, respectively. The annual rate of change in % predicted FVC and DLCO was -2.9 ± 13.4 %/year and -3.3± 7.7 %/year, respectively; 63% were rapid progressors. SP-D levels among rapid progressors were significantly higher than levels in non-rapid progressors (237.9 ± 176.7 ng/mL and 173.5 ± 95.1ng/mL, respectively,p=0.02).
A significant, inverse correlation between SP-D level with annual rate of change in % predicted FVC (r=-0.27, p=0.03), but not with DLCO, was observed. SP-D significantly predicted rapid progressors (p=0.03). Age, gender, disease duration, anti-Scl 70 antibody status, smoking status, SSc subtype, presence of restrictive lung disease, or radiographic findings of pulmonary fibrosis were not associated with rapid progressors. Adjusting for age, smoking status, disease duration, SP-D, and SSc subtype, SP-D [OR=1.5 per 100 ng/mL, 95% CI of 1.09-1.10, p=0.02] and active smoking [OR=3.7, 95% CI of 1.008-13.4, p=0.05] were significantly associated with rapid progressors.

Conclusion: Baseline SP-D levels significantly correlate with the annual rate of decline in % predicted FVC. SP-D levels and current smoking predicts a rapid decline in lung function. SP-D may be useful to identify a high risk group of SSc patients for close monitoring and therapeutic intervention.

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1718

Effectiveness of a Multidisciplinary Treatment Program in Comparison with Usual Care in Patients with Systemic Sclerosis. A.A. Schouffoer[1], M.K. Ninaber[2], F.J. van der Giesen[1], A.J.M. Schuerwegh[3], L.J. Beaart-van de Voorde[1], Z. de Jong[1], J. Stolk[2], A.E Voskuyl[4], J.M. van Laar[5] and T.P.M. Vliet Vlieland[3], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Pulmonology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Newcastle University, Newcastle, United Kingdom

Purpose: In many rheumatic conditions the effectiveness of multidisciplinary team care has been established, however in systemic sclerosis (SSc) the evidence is scanty. The aim of this study was to compare a multidisciplinary treatment program with usual outpatient care in patients with SSc.

Methods: Patients with limited or diffuse SSc, stable medication over the past 2 months and no pulmonary or cardiac contra-indications for aerobic exercises were randomly assigned to a multidisciplinary day treatment program (2 days per week, 12 weeks, with individual treatments and group exercises and education) or usual outpatient care. Assessments were done at baseline, 12 and 24 weeks. Primary outcome measures were the 6-minute walk test and the Physical Component Summary Scale of the SF-36 (PCSS). Secondary outcome measures were maximal oxygen consumption during bicycle exercise test (VO2max), SSc-HAQ (Health Assessment Questionnaire), and the Mental Component Summery Scale of the SF-36 (MCSS).

Results: Fifty-three patients were randomised (28 intervention and 25 control). Thirty patients (57%) had diffuse SSc, the mean age was 53.4 yrs (SD 10.6), the mean disease duration was 8.3 yrs (SD 7.5) and the mean Modified Rodnan Skin Score 5.1 (SD 5.1). Drop-out rates were 4 (14%) in the intervention and 3 (12%) in the control groups after 24 weeks. At 12 weeks, the improvements of the 6 minute walk test and HAQ score were significantly greater in the intervention group than in the control group (6 minute walk test mean 42.9 m (95% confidence interval 22.1, 63.6) versus 3.9 (-20.8, 28.5) meter, p=0.015; HAQ -0.18 (-0.36, -0.01) versus +0.13 (-0.02, 0.27), p=0.003). For all other outcome measures, the 12 and 24 weeks change scores did not differ significantly between the two groups.

Conclusion: A multidisciplinary treatment program in SSc improved physical functioning more than usual outpatient care in patients with SSc. This emphasises the importance of rehabilitation in systemic sclerosis.

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Clinical Significance of Anti-RNA Polymerase III Antibodies in A Cohort of Patients From the Australian Scleroderma Screening Program (ASSP) Database. Maree E. Micallef[1], Pravin Hissaria[2], Susanna M. Proudman[2], Jillian Byron[1], William Paspaliaris[1], Joanne Sahhar[3], P. Nash[4], Allan D. Sturgess[5] and Wendy Stevens[1], [1]St Vincent's Hospital, Melbourne, Australia, [2]Royal Adelaide Hospital, Adelaide, Australia, [3]Monash Medical Centre, Melbourne, Australia, [4]University of Queensland, Brisbane, Australia, [5]St George Hospital, Sydney, Australia

Purpose: Anti-RNA polymerase III antibodies (anti-RNAP Abs), detectable in up to 25% of patients with systemic sclerosis (SSc), may define a novel subset of patients with severe cutaneous disease and an increased risk of renal hypertensive crisis. This is the first time the clinical associations of this Ab have been examined in an Australian population. We examined the prevalence and clinical variables associated with anti-RNAP Abs in a cohort of patients from the Australian Scleroderma Screening Program (ASSP) Database, a national prospective on-line electronic registry of clinical, laboratory and investigational parameters related to SSc and MCTD.

Method: Review of patients from the ASSP Database tested for anti-RNAP Abs, since 2007. Anti-RNAP was measured using a commercially available ELISA kit (Quanta Lite RNA Pol III-Integrated Sciences) and compared with anti-Scl70 Ab.

Results: Of the 714 patients on the ASSP database, 219 were tested for anti-RNAP Abs and 36 (16%) were positive. These patients were more likely than RNAP negative patients to have diffuse (dcSSc) than limited (lcSSc) cutaneous disease (72% cf 28% $p<0.001$), higher mean Rodnan skin scores (20 cf 10, $p<0.001$), more joint contractures (66% cf 22%, $p<0.001$), more hypertension (56% cf 32%, $p<0.01$), and more suspected or proven renal crisis (18% cf 2%, $p<0.001$). In the subset of patients with dcSS, anti-RNAP Abs were associated with higher mean skin scores (23 cf 18, $p <0.05$), joint contractures (81% cf 48%, $p<0.05$) and hypertension (54% cf 26%, $p<0.05$), suggesting additional risk beyond that seen in patients with dcSSc subtype alone. 215 of the 219 patients were also tested for anti-Scl70 Ab. 44(20%) were positive, 53% had dcSSc and 45% lcSSc. Anti-RNAP Ab positive patients compared to anti-Scl70 Ab positive patients had higher mean Rodnan skin scores (20 cf 14), more joint contractures (67% cf 45%), hypertension (56% cf 34%) and suspected or proven renal crisis (18% cf 2%). Only 1 patient was positive for both anti-RNAP and anti-Scl70 Ab.

Conclusion: The ASSP Database results support findings from previous studies showing an association between RNAP Ab positivity and severe skin and renal disease. Our results suggest the risk is above that seen with diffuse disease subtype or anti-Scl-70 Ab alone. ELISA testing for anti-RNAP Abs may therefore be useful to predict those at risk of severe skin and renal disease.

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1720

Lower Extremity Ulcers in Systemic Sclerosis: Features and Response to Therapy. Victoria K. Shanmugam, Christopher E. Attinger and Virginia D. Steen, Georgetown University Medical Center, Washington, DC

Purpose: Lower extremity ulcers are a recognized complication of scleroderma but their prevalence and etiology are unknown. We report the features of a series of 12 scleroderma patients with lower extremity ulcers and estimate the prevalence of this complication.

Methods: The Connective Tissue Disease Leg Ulcer Etiology (CLUE) study is a prospective observational study. Between August 2007 and April 2009, 7 scleroderma patients were evaluated in the CLUE study, and during the same time period, 249 scleroderma patients were seen in the rheumatology clinic, 2 of whom also had leg ulcers. Prior to August 2007, an additional 3 patients with leg ulcers and scleroderma had been evaluated, but have since been lost to follow-up. The clinical and laboratory features of all 12 patients and the outcomes of the 7 patients in the CLUE study are reported.

Results: In a cohort of 249 scleroderma patients evaluated over a 21-month period, 9 had active leg ulcers, giving a prevalence of 3.6%. Of the 12 patients reported, only 3 had diffuse disease; 7 had limited scleroderma, and 2 had scleroderma sine scleroderma. The demographic distribution reflects that seen in our scleroderma population (75% female, 83% Caucasian). Ulcers were bilateral in 91%. The mean age at first ulcer was 59.33 years. The mean disease duration at the time of ulcer development was 16.78 years (range 2-46). However, patients with diffuse scleroderma had shorter disease duration prior to ulcer development (mean 3.33 years +/-0.67) compared to limited scleroderma

(mean 23.50 years +/-4.82, p value 0.02). Anti-centromere antibody was positive in 4 of the 7 patients with clinically limited disease. Biopsy specimens were available in 7 cases, and the most common finding was vasculopathic changes with fibrin plugging.

The prevalence of antiphospholipid antibodies in scleroderma is approximately 19%; however, 5 of the 7 patients reported here had positive antiphospholipid antibodies (71%). Genetic procoagulant work up was completed in 7 patients; 5 had heterozygous MTHFR gene mutation, 3 had heterozygous and 1 homozygous plasminogen activator inhibitor-1 gene mutation. Factor V leiden and prothrombin gene mutations were not seen in any of the patients tested.

Healing was seen within 3 months in 2 patients with high antiphospholipid antibody titers treated with low-dose low-molecular-weight-heparin (enoxaparin 40mg daily); however, 2 other patients with lower antibody titers did not respond. One of these refractory patients was subsequently successfully treated with recombinant erythropoietin. Another patient healed following arterioplasty, and the remaining 2 patients have had continued refractory lesions and have been unable to get insurance approval for either medication.

Conclusion: The prevalence of lower extremity ulcers in scleroderma is 3.6%, and antiphospholipid antibodies may have a role in their pathogenesis. We propose that scleroderma patients who develop leg ulcers should be evaluated for anti-phospholipid antibodies, and if present a trial of low-molecular-weight-heparin is warranted.

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High Frequency Ultrasound Measurement of Digital Dermal Thickness in Systemic Sclerosis (SSc). Olga Kaloudi[1], Francesca Bandinelli[1], Emilio Filippucci[2], Maria Letizia Conforti[1], Irene Miniati[1], Serena Guiducci[1], Antonio Candelieri[3], Domenico Conforti[3], Walter Grassi[4] and Marco Matucci Cerinic[1], [1]University of Florence, Italy, Florence, Italy, [2]Università Politecnica delle Marche, Ancona, Italy, [3]University of Calabria, Italy, [4]Rheumatology Department, Jesi, Ancona, Italy

Purpose: In SSc, measurement of dermal thickness is essential to identify the disease subset and the prognosis of the disease and is currently performed by palpation with the modified Rodnan Skin Score (mRSS). The purpose of this study is to verify if high frequency ultrasound (US) may be a reliable and a reproducible method to measure digital dermal thickness.

Method: In 80 SSc patients, skin thickness and echogenicity were evaluated with US by two observers in two different sites (1.5 cm over the dorsal aspect of the proximal phalanx and 1cm over the dorsal aspect of the distal phalanx) of the second digit of the dominant limb to determine the inter-observer variability. Patients and controls were examined twice by the first observer for intra-observer variability. Patients were divided into three subgroups according to (oedematous, fibrotic and atrophic) skin involvement. US measurements of dermal thickness were compared with local and systemic mRSS.

Results: At both examined areas, US showed a significant dermal thickening ($p<0,001$) in all SSc patients. A low intra- and inter-observer variability of US measurements was found (ICC: 0.960 for site 1 and ICC: 0.917 for site 2) and (ICC: 0.969 for site 1 and ICC: 0.924 for site 2) . A highly significant correlation between the global mRSS and the digital dermal thickness at the two examined sites (p:0.032 and p:0.021, respectively) was detected. No correlation was found between US and local digital mRSS. Skin thickness resulted significantly higher in the oedematous than in the fibrotic group ($p<0.001$) and significantly higher in the fibrotic and the oedematous group ($p<0.001$) than in the atrophic group ($p<0.002$), respectively.

Conclusion: US is a reliable and reproducible tool, able to detect digital dermal thickening in SSc. In the future, US may become a reliable outcome measure in clinical trials.

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1722

Assessment of Skin Involvement in Systemic Sclerosis (SSc) with Ultrasound Elastography. Annamaria Iagnocco[1], Chiara Perella[1], Valeria Riccieri[1], Olga Kaloudi[2], Francesca Bandinelli[2], Francesco Porta[2], Guido Valesini[1] and Marco Matucci Cerinic[2], [1]Cattedra di Reumatologia, Dip Clinica e Terapia Medica, Sapienza Università di Roma, Roma, Italy, [2]University of Florence, Italy, Florence, Italy

Purpose: Excessive dermal deposition of collagen and changes in the architecture of connective tissue components are hallmarks of SSc that is characterised by reduced dermal elasticity due to tissue thickness and fibrosis. A new tool able to correlate tissue US imaging with tissue structure and/or pathology, namely US elastography (UE), has been used to assess skin elasticity in SSc.

Method: 18 consecutive SSc patients (mean age 58.8 years) and 15 healthy controls (mean age 29.8 years) were studied. Each UE exam was performed separately by two blinded sonographers who repeated each single exam twice and each evaluation was then repeated, after an interval of 4 weeks, up to calculate intra- and inter- observer reliability. Modified Rodnan skin score, physical examination and assessment of organ involvement were performed. UE was performed on the middle forearm and on the fingers. The echo signals captured in real-time during free-hand operations of probe compression and relaxation produced images representative of tissue elasticity, consisting in translucent coloured bands superimposed on the B-mode images. The colour scale varied within a large band-spectrum from red, indicative of a soft and highly elastic tissue, to blue, which denoted a hard and scarcely elastic one.

Results: On the forearm of all patients, UE showed a homogeneous blue area corresponding to the dermis visualized in B-mode image; in controls, a blue pattern was never detected and a predominance of green with sporadic areas of pale blue was observed. At sequential evaluations UE of fingers produced inconstant and changeable coloured areas, this might be due to the reduced presence of tissue and the prevalent bony component within the elastographic field. The overall inter-observer sonographers agreement and the intra-observer reliability, for patients and controls, resulted always of 100%

Conclusion: The imaging pattern observed in the forearm of SSc patients may represent the reduction of strain in the dermis due to loss of elasticity. The finger evaluation instead was not reliable for the measurement of skin elasticity. UE may evaluate skin involvement in SSc in areas where the dermis is highly expressed and where the bone hyperreflection is minimal. Further studies and in particular, correlations with histopathologic findings, are needed to confirm our results and determine the criterion validity of this new imaging modality.

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Endothelial-Dependent Flow Mediated Dilation of the Brachial Artery Correlates with Nailfold Microvascular Involvement and Identifies Endothelial Dysfunction in Systemic Sclerosis. Daniela Rollando[1], Alberto Sulli[2], Gian Paolo Bezante[1], Maurizio Cutolo[2], Claudio Brunelli[1], Francesco Indiveri[3] and Massimo Ghio[3], [1]Unit of Cardiology, Genova, Italy, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Genova, Italy, [3]Unit of Clinical Immunology and Internal Medicine, Genova, Italy

Purpose: Vascular impairment is one of the main features in the pathogenesis of systemic sclerosis (SSc), and it is detectable in the early phase of the disease. Recent evidences show that SSc vascular impairment might be considered as a consequence of the endothelial cell dysfunction, involving both macro- and microvascular systems. The aim of the study was to assess possible correlations between endothelial-dependent flow mediated dilation of the brachial artery (FMD) and nailfold microvascular involvement as evaluated by nailfold videocapillaroscopy (NVC) in SSc patients.

Method: Forty-seven consecutive patients (mean age 51.0±10.8SD years) affected by SSc were studied. Twenty-four patients were suffering from limited cutaneous SSc (lcSSc) and 13 were complaining of diffuse cutaneous SSc (dcSSc). Twenty-seven healthy subjects (mean age 48.0±8.4) were recruited as controls. Ultrasound assessment of FMD, was performed in all subjects in order to evaluate macrovascular function (1). Following the NVC analysis the patients were divided into three different patterns of microvascular damage (“Early”, “Active” and “Late”), and the microangiopathy evolution score (MES) was calculated, as previously reported (2,3). Statistical analysis was carried out by non parametric tests.

Results: FMD was significantly reduced in SSc patients compared to the healthy subjects (median 6% vs 16% respectively, $p<0.0001$). Moreover, FMD was significantly reduced in SSc patients with the Late NVC pattern of microangiopathy (median 3.0%) when compared to Active and Early patterns (median 8.6% and 9.4% respectively) ($p=0.03$ and $p=0.05$, respectively). A negative correlation between FMD and MES was found in SSc patient ($p=0.04$). No statistically significant difference concerning the FMD was observed between patients with lcSSc and dcSSc (median 6.0% and 5.4% respectively).

Conclusion: A correlation between macro- and microvascular dysfunction in SSc patients seems evident, and the endothelial function impairment is suggested as the common pathway.

References: 1. Corretti MC, et al. J Am Coll Cardiol. 2002; 16;39(2):257-65. 2. Cutolo M, et al. Rheumatology 2004; 43:719-26. 3. Sulli A, et al. Ann Rheum Dis 2008; 67:885-7.

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1724

The Prevalence of Sicca Symptoms and Sjogren's Syndrome of Patients with Systemic Sclerosis. Gercek Can[1], Sulen Sarioglu[2], Merih Birlik[3], Ozgul Soysal[1], Vedat Gerdan[1], Dilek Solmaz[1], Fatos Onen[4], Nurullah Akkoc[5] and Servet Akar[4], [1]Dokuz Eylül University Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylül University Faculty of Medicine, Pathology Department, Turkey, [3]Dokuz Eylül University Faculty of Medicine, Istanbul, Turkey, [4]Turkish Takayasu's Arteritis Study Group, Istanbul, Turkey, [5]Dokuz Eylül University, Istanbul, Turkey

Purpose: Systemic sclerosis (SSc) is a heterogeneous systemic disorder that is characterized by massive deposition of collagen and other matrix substances in connective tissue.Sicca symptoms are thought to be a frequent complaint associated with SSc although little is known about how often they occur.The aim of this study was to determine the prevalence and contributing factors of sicca symptoms and Sjogren's syndrome (SS) in patients with SSc.

Method: *C*onsecutive *79* SSc patients [71 female(90%), mean age 53,17 ± 10,773)]followed by an outpatient rheumatology clinic at a university hospital in Izmir, a city located in western Turkey were included in the study.All of the patients fulfilled the criteria proposed by the American College of Rheumatology for the classification of SSc.The patients were evaluated for sicca symptoms.The systematic first-line clinical evaluation included a questionnaire specific for the subjective presence of xerophthalmia and xerostomia,based on the revised American–European Consensus Group criteria for SS, together with the Schirmer I test and unstimulated whole salivary flow.If the findings of the first-line clinical evaluation were positive a labial salivary gland biopsy was performed.The presence of focal lymphocytic sialadenitis with a focus score ≥ 1 was necessary for a diagnosis of SS. Glandular fibrosis was also evaluated.Routine blood tests and serologic analysis for antinuclear antibody (ANA) and extractable nuclear antigens (ENA) were performed.

Results: Of 79 patients,64 (83%) had limited SSc(lcSSc),9(%12) diffuse SSc (dcSSc),and 4(5%) had sine scleroderma.The most common type of ANA detected was homogenous pattern (48%).The other antinuclear and ENA types identified included centromeric(38%), nucleolar(3%),scl-70 (42%),SSA alone or combination with another ENA(5.6%).Fifty-seven patients(72,2%) had sicca syndrome(50[63,3%] had xerostomia, and 40[50,6%] had xerophthalmia).Forty-one of the 79 patients (62%) had positive findings on the Schirmer test and 27(34%) patients had positive salivary flow test.A total salivary gland biopsy was indicated in 70 patients according to our study protocol.Three patients refused the procedure therefore biopsy were performed sixty-seven (85%) patients.On histopathologic examination of biopsy samples; fibrotic lesion were observed in 56 out of 67 (84%) and in 30 (45%) focus score was ≥1.Fifteen patients (19%) fulfilled American European Consensus Group criteria for SS.Fourteen patients who diagnosed SS had lcSSc and one of them had sine scleroderma.

Conclusion: Despite fibrosis seems to be main cause of sicca symptoms our study showed one of the highest prevalence of SS in patients with SSc.These results suggest that limited cutaneous subtype of SSc carries a greater risk for SS.

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Lymphatic Vessels Are Decreased in Patients with Systemic Sclerosis and Correlate Inversely with Fingertip Ulcers. Alfiya Akhmetshina[1], Jürgen Beer[1], Matthias Englbrecht[2], Karin Polzer[1], Clara Dees[1], Nicole Busch[1], Oliver Distler[3], Georg Schett[4] and Jörg HW Distler[1], [1]Dept Int Med 3, Univ Erlangen, Erlangen, Germany, [2]Dep Int Med 3, Univ Erlangen, Erlangen, Germany, [3]Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland, [4]University of Erlangen-Nuremberg, Erlangen, Germany

Purpose: Systemic sclerosis (SSc) is a connective tissue disease with progressive vascular manifestations. The irregular architecture and the reduced capillary density are major hallmarks in microvasculature of the blood vascular system. However, the lymphatic vessel (LV) system has not been studied in SSc.

The aim of the present study was to analyze, whether the LV system is affected in SSc patients and whether potential alterations of the LV are associated was dystrophic changes and tissue damage in SSc.

Method: Skin biopsies from SSc patients (n = 27) and from age and sex matched healthy volunteers (n = 20) were analyzed by immunohistochemistry (IHC). Antibodies against podoplanin and prox-1 were used to detect specifically lymphatic endothelial cells and discriminate between LV and blood vessels. CD31 was used as pan-endothelial marker. Statistical analysis was performed using Kruskal-Wallis, Mann-Whitney-U and Spearman's Rank Correlation tests.

Results: The numbers of LV were significantly reduced in SSc. The mean count of podoplanin positive LV in SSc patients was 0.6 ± 0.1 / high power field (HPF) in SSc patients versus 1.9 ± 0.3 / HPF in healthy individuals ($p < 0.001$). Consistent with the findings obtained for podoplanin, the number of prox-1 positive LV was also significantly reduced. Further analysis demonstrated that the reduction of lymphatic precollector vessels was more pronounced than the reduction of lymphatic capillaries (84 ± 17 % and 49 ± 10 %, respectively, compared to healthy individuals). Of note, the number of podoplanin positive precollector LV were significantly lower in SSc patients with fingertip ulcers than in SSc patients without fingertip ulcers ($p = 0.03$). The number of positive LV both podoplanin and prox-1correlated inversely with the number of ulcers at the time of biopsy and the number of ulcers per year ($r = - 0.75/ p < 0.001$ and $r = -0.51/ p = 0.04$, respectively). The inverse correlation between LV counts and the number of fingertip ulcers remained significant after statistical control for blood vessel count, age and mRSS, indicating that lymphangiopathy is an independent risk factor for fingertip ulcers in SSc.

Conclusion: The present study demonstrates for the first time a lymphangiopathy with a severe reduction of lymphatic capillaries and lymphatic precollector vessel in patients with SSc. We show that patients with decreased LV counts are of particular high risk to develop fingertip ulcers. We also present evidence that the lymphangiopathy is an independent risk factor for fingertip ulcers in SSc patients.

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1726

Faecal Incontinence in Systemic Sclerosis Is Related to Neuropathy. Nora M. Thoua[1], Alastair Forbes[1], Christopher P. Denton[2] and Anton V. Emmanuel[1], [1]University College London Hospital, London, United Kingdom, [2]UCL Medical School, London, United Kingdom

Purpose: Systemic sclerosis (SSc) is an autoimmune disorder which can affect multiple organs. The gastrointestinal (GI) tract is affected in up to 90% of patients. The pathogenesis of gastrointestinal abnormalities may be both myogenic and neurogenic. While anorectal involvement occurs in up to 50% of patients, studies have not reliably shown correlation between manometric findings and clinical symptoms.

Method: 44 SSc patients referred to a tertiary referral centre were studied: 24 patients (21 female, mean age 58) with faecal incontinence and other lower GI symptoms (Sx), and 20 (20 female, mean age 61) with no or minimal lower GI symptoms (ASx). Mean disease duration in Sx and ASx groups were 12 and 8 years respectively (p=NS). Patients underwent anorectal manometry, endoanal ultrasound (EAUS), rectal mucosal blood flow (RMBF), rectal compliance (barostat) and rectoanal inhibitory reflex assessment.

Results: (Mean and 95% CI)

Wexner incontinence scores (Sx 11 [9-13] vs ASx 2 [1-4]; $p<0.0001$) and constipation scores (Sx 10 [8-12] vs ASx 4 [2-6]; $p=0.0001$) were significantly different between the 2 groups. Anal pressures, RMBF and rectal compliance did not differ between groups. However anal sensation, not rectal sensation, was significantly attenuated in Sx patients (see table). The RAIR was absent in 11/24 Sx patients but only 2/20 ASx. There was a positive correlation between anal sensory thresholds and incontinence ($r=0.59$; $p<0.001$) and constipation scores ($r=0.46$; $p=0.0015$). IAS atrophy was evident in 75% of Sx patients and 40% of ASx patients.

Conclusion: Anorectal symptoms in SSc are mainly related to neuropathy as suggested by absent RAIR and higher anal sensory threshold and less so to sphincter atrophy and rectal fibrosis. This raises the possibility that sacral neuromodulation may be an option for some minimally symptomatic SSc patients with latent neuropathy.

	Sx – mean (95% CI)	**ASx – mean (95% CI)**	**p value**
Resting pressure (cmH20)	51 (41-61)	64 (54-74)	p=0.07
Squeeze pressure (cmH20)	121 (101-142)	105 (81-128)	p=0.26
Rectal compliance (ml/mmHg)	10.6 (8.8-12.5)	10.9 (9.1-12.7)	p=0.82
RMBF (flux units)	150 (124-177)	158 (134-183)	p=0.64
Anal sensation (mA)	10.4 (8.8-12)	6.7 (5.7-7.7)	**p=0.0003**
Rectal sensation (mA)	24.4 (20.4-28.4)	19.7 (15.5-24)	p=0.1

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Histologic and Molecular Basis of Improved Skin Scores in Scleroderma Patients Treated with Imatinib Mesylate (Gleevec). Jessica Gordon[1], S. Vukelic[1], C.M. Magro[2], Jamie Mersten[1], H. F. Wildman[2], M. K. Crow[1], K. A. Kirou[1] and R.F. Spiera[1], [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical College, New York, NY

Purpose: Imatinib mesylate is a tyrosine kinase inhibitor with activity against the profibrotic effects of TGF-β and PDGF in animal models and in vitro human studies. It is under investigation for the treatment of Diffuse Cutaneous Systemic Sclerosis (dcSSc), and preliminary results show improvement in skin thickness as assessed by the Modified Rodnan Skin Score (MRSS). To investigate the histologic and molecular basis of the improved skin scores, we assessed skin samples from dcSSc patients prior to and after imatinib treatment.

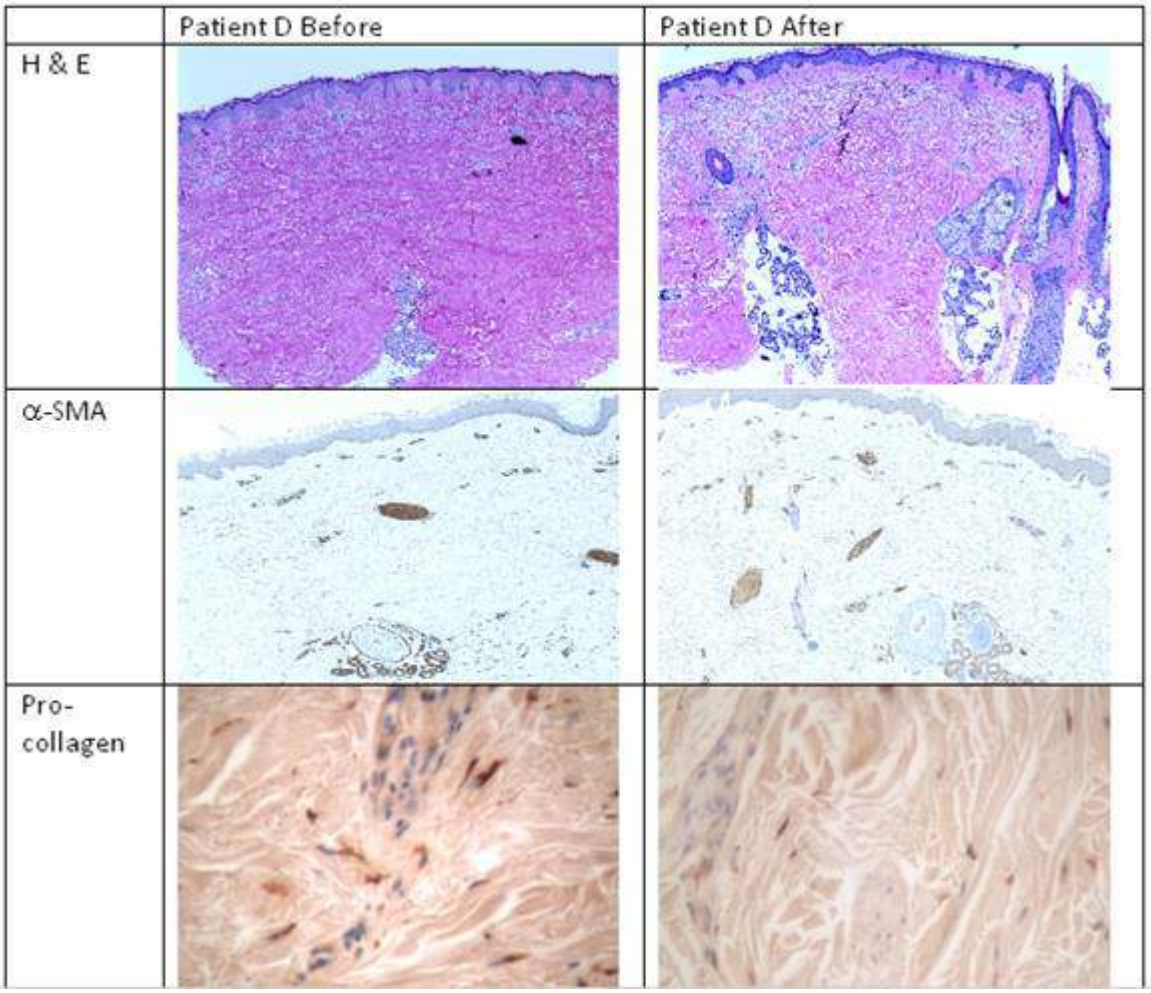
Methods: Four consecutive patients in the Gleevec in Systemic Sclerosis clinical trial at our institution were selected for review of dermatopathology. 4-mm punch biopsies of lesional forearm skin were taken before and after treatment with imatinib 400 mg po daily for 12 months. The post-treatment biopsy was taken 1 cm adjacent to the original biopsy site. Histologic analysis included staining with H & E, Masson's trichrome for collagen, anti-α-smooth muscle actin (SMA) for activated myofibroblasts, and anti-procollagen. To quantify procollagen production, real time polymerase chain reaction (RT-PCR) was performed on cDNA prepared from skin specimens.

Results: The patients are described in the table below. All prebiopsy specimens were similar in appearance showing pandermal sclerosis with a paucity of adnexal structures and increased dermal thickness, as is typical for dcSSc. Collagen bundles showed loss of fibrillar architecture without discernible interstitial space. 3 of 4 post-treatment specimens showed improvement in pandermal sclerosis with narrower caliber collagen bundles and increased space between the collagen bundles. The quantity of adnexal structures in the skin increased in 3 of 4 specimens. Skin thickness decreased in 1 specimen, from 2.45 mm to 1.9 mm, and α-SMA staining decreased in 2 of 4 specimens. Procollagen I staining decreased in intensity in 2/3 patients, an observation supported by RT-PCR analysis of collagen 1α2 expression, which decreased by a mean of 45%.

Conclusion: Treatment of dcSSc patients with imatinib for one year was associated with decreased collagen production and histologic improvement in 3 of 4 patients, corresponding to clinical improvement as assessed by MRSS. These results support further characterization of the effects of imatinib on fibrotic skin in dcSSc and suggest that this agent alters the underlying molecular basis of skin fibrosis in this disease.

Patient	Disease Duration - years	MRSS before	MRSS after 12 Months Imatinib	Change on H&E	% decrease col1a2 expression
A	2	19	10	+	- 70

B	5.5	41	29	+	- 59
C	1.5	23	18	-	- 3
D	0.5	24	15	+	- 48



Disclosure: J. Gordon, None; **S. Vukelic**, None; **C. M. Magro**, None; **J. Mersten**, Rudolph Rupert Scleroderma Research Program, 2 ; **H. F. Wildman**, None; **M. K. Crow**, Rudolph Rupert Scleroderma Research Program, 2 ; **K. A. Kirou**, None; **R. F. Spiera**, Novartis Pharmaceutical Corporation, 2, Rudolph Rupert Scleroderma Research Program, 2 .

1728

Gastrointestinal Involvement in Systemic Sclerosis Leads to a Wide Range of Symptoms and a Significant Effect On Quality of Life.

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Purpose: The gastrointestinal tract (GIT) is affected in up to 90% of patients with systemic sclerosis (SSc). Although the most commonly affected site is the oesophagus, the extent as well as the severity of GIT involvement may vary. GIT involvement may be associated with significant morbidity and in severe cases mortality. With improved survival from cardiopulmonary and renal involvement, gastrointestinal symptoms are becoming more prominent. The im of this study was to establish the frequency and range of GI symptoms in SSc patients at the Royal Free Hospital, a tertiary referral centre.

Method: We used a 52-item, previously validated (Khanna *et al*), questionnaire to capture SSc-related gut dysfunction. The questionnaire assesses the *frequency* of 5 categories of symptoms (reflux, distension, diarrhoea, constipation, abdominal pain) and their *impact* on social functioning and emotional well-being during the previous week. The questionnaire was given to consecutive patients with SSc attending the rheumatology outpatient department. Incomplete questionnaires were excluded from analysis. Patients' notes were reviewed to establish disease subtype, autoantibody profile and other internal organ involvement.

Results: We collected 402 completed questionnaires (357 females; mean age 55, range 18-82). 69% of patients had lcSSc and 30% dcSSc with mean disease duration of 11 years. Mean questionnaire scores showed that patients have a wide range of GI symptoms. 83% of patients were taking medication for GI symptoms despite which 94% reported upper and 79% lower GI symptoms. Only 3% of patients reported no symptoms, and 10% reported daily symptoms. 28% reported significant adverse effect on emotional well being. There was no association between disease subtype or autoantibody profile and GI symptoms. There was a positive correlation between diarrhoea scores (high scores = best health) and pulmonary fibrosis ($r=0.134$, $p=0.0068$), suggesting that patients with lung fibrosis were less likely to have diarrhoea. No other association between GI symptoms and other internal organ involvement was found.

Conclusion: GI symptoms, both upper and lower, are common in patients with SSc and have a significant effect on quality of life. Patients should be asked specifically about GI symptoms as they may be under-reported and therefore under-treated. GI focused questionnaire is an effective way to assess gut symptoms and adjust treatment.

Reference:
1. D. Khanna *et al*, Arthr & Rheum 2007; 57: 1280–1286

Disclosure: N. M. Thoua, None; **C. Bunce**, None; **G. Brough**, None; **A. Forbes**, None; **A. V. Emmanuel**, None; **C. P. Denton**, None.

1729

Joint Involvement and Relationships with Systemic Inflammation in the EULAR Scleroderma Trial and Research Group (EUSTAR) Database of Systemic Sclerosis Patients. Jérôme Avouac[1], Ulrich A. Walker[2], Alan Tyndall[3], A. Kahan[4], Marco Matucci-Cerinic[5] and Yannick Allanore[6], [1]Université Paris Descartes; Hôpital Cochin, Service de Rhumatologie A, Paris, France, [2]Felix Platter Spital, Basel, Switzerland, [3]Department of Rheumatology, Basel, Switzerland, [4]Rheumatology A, Cochin Hospital, Paris Cedex 14, France, [5]University of Florence, Firenze, Italy, [6]Paris Descartes Univ, Paris, France

Background: Articular structures may be involved in systemic sclerosis (SSc), causing functional disability. The precise prevalence of clinical articular manifestations has not been accurately defined in a large population of SSc patients.

Purpose: To determine the prevalence of, and independent factors associated with joint involvement in a large population of patients with SSc.

Methods: We queried the EUSTAR database to extract data regarding global evaluation of SSc patients and presence or not of any clinical articular involvement: synovitis (defined by inflammation of the synovial membrane leading to pain and swelling), joint contractures (resulting from joint destruction turning into ankylosis and fibrotic changes in the skin) and tendon friction rubs (defined by tendonitis characterised by fibrosis of the tendon sheaths). Overall joint involvement was defined by the occurrence of synovitis and/or joint contracture and/or tendon friction rubs. We recruited 7286 SSc patients (86% of whom were women); the mean ± SD age was 56±14 years old, the mean ±SD disease duration was 10±29 years and 4210 (58%) had a limited cutaneous subtype.

Results: The point prevalence of joint involvement was 58%: the frequencies of synovitis, joint contractures and tendon friction rubs were 16%, 31% and 11%, respectively. In multivariate stepwise regression, overall joint involvement was associated with the following items, provided in table 1.

Table 1

	Multivariate analysis (stepwise regression) Odds ratio (95% Confidence Interval, CI)
Diffuse Cutaneous subtype	1.84 (1.62-2.10)
Digital ulcers	1.80 (1.60-2.03)
Elevated acute phase reactants	1.66 (1.46-1.88)
Muscle weakness	1.65 (1.45-1.87)
Elevated systolic pulmonary artery pressure (>40 mmHg)	1.62 (1.42-1.84)
European disease activity score	1.40 (1.23-1.64)
Pulmonary fibrosis	1.14 (1.01-1.28)

Focusing on systemic inflammation, when elevated acute phase reactants were considered as the dependent variable, they were found highly associated with joint symptoms (OR: 2.21, 95% CI 1.77-2.77).

Conclusion: Our results highlight the striking level of articular involvement in SSc, as evaluated by systematic examination in the largest worldwide available cohort of patients. In addition, our data also show that synovitis, joint contracture and tendon friction rubs are associated with a more active and severe disease phenotype. Joint involvement also appeared to strikingly contributes to systemic inflammation. The prospective follow-up of this cohort is ongoing; it will allow to confirm the above associations and to assess articular involvement as a marker and a predictor of disease severity.

Disclosure: J. Avouac, None; **U. A. Walker**, None; **A. Tyndall**, None; **A. Kahan**, None; **M. Matucci-Cerinic**, None; **Y. Allanore**, None.

1730

An Analysis of Outcomes in Patients with Systemic Sclerosis- and Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension. Lorinda Chung[1], Juliana Liu[1], Lori Parsons[2], Paul M. Hassoun[3], Michael McGoon[4], David Badesch[5], Dave P. Miller[2], Mark R. Nicolls[1] and Roham T. Zamanian[1], [1]Stanford University, Palo Alto, CA, [2]ICON Clinical Research, San Francisco, CA, [3]Johns Hopkins University, Baltimore, MD, [4]Mayo Clinic, Rochester, MN, [5]University of Colorado, Denver, CO

Purpose: Patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-APAH) have extremely poor outcomes with high mortality rates. A previous study indicated that SSc-APAH is associated with poorer survival than systemic lupus erythematosus (SLE)-APAH. To gain insight regarding pathophysiologic mechanisms responsible for differences between these two groups, their presentation and outcomes were compared.

Methods: The Registry to Evaluate Early and Long Term PAH Management (REVEAL) is a prospective registry of >3,000 patients with World Health Organization Class I pulmonary hypertension from 54 US centers. Kaplan-Meier curves were estimated for survival, freedom from hospitalization, and freedom from initiation of parenteral PAH therapy in patients with SSc-APAH vs. SLE-APAH from the time of enrollment. Differences in outcomes between the groups were assessed by the log-rank test. Multivariable Cox proportional hazards models were developed to assess the risk for poorer outcomes in patients with SSc-APAH, controlling for B-type natriuretic peptide (BNP) levels, diffusing capacity of carbon monoxide (DLCO), pulmonary vascular resistance (PVR), and renal insufficiency (investigator clinical judgment).

Results: Patients with SSc (302: 78 diffuse, 224 limited) had higher BNP levels than patients with SLE (105) with mean(SD) values of 471.2(889.5) vs. 288.0(349.4) pg/mL (p=0.03). DLCO was significantly lower in the SSc patients (43.2(16.6) vs. 52.6(19.1) % predicted, p=0.0003). Baseline mean pulmonary artery pressure and PVR were lower in the SSc group, (44.0(11.9) vs. 46.7(9.2) mmHg, p=0.03; 9.3(5.4) vs. 10.8(5.7) Wood units, p=0.01, respectively). Renal insufficiency was more common in the SSc patients, but this did not reach

statistical significance (8.4% vs. 4.8%, p=0.2). 1- and 2-year outcomes were as follows in the SSc vs. SLE groups: survival 85% and 74% vs. 94% and 84% (p=0.05) (Figure); freedom from hospitalization 69% and 59% vs. 77% and 56% (p=0.7); and freedom from parenteral therapy 91% and 90% vs. 96% and 88% (p=0.6). SLE patients were less likely to die than SSc patients (HR=0.57(0.33-1.0), p=0.05), but this difference was not statistically significant after adjusting for other variables (HR=0.77(0.43-1.4), p=0.38).

Conclusion: Analysis of the REVEAL Registry has demonstrated that poorer survival in patients with SSc compared with SLE-APAH can be explained by differences in clinical parameters, including BNP, DLCO, and renal insufficiency. Further research is necessary to investigate the pathophysiologic role of these markers in SSc-APAH.

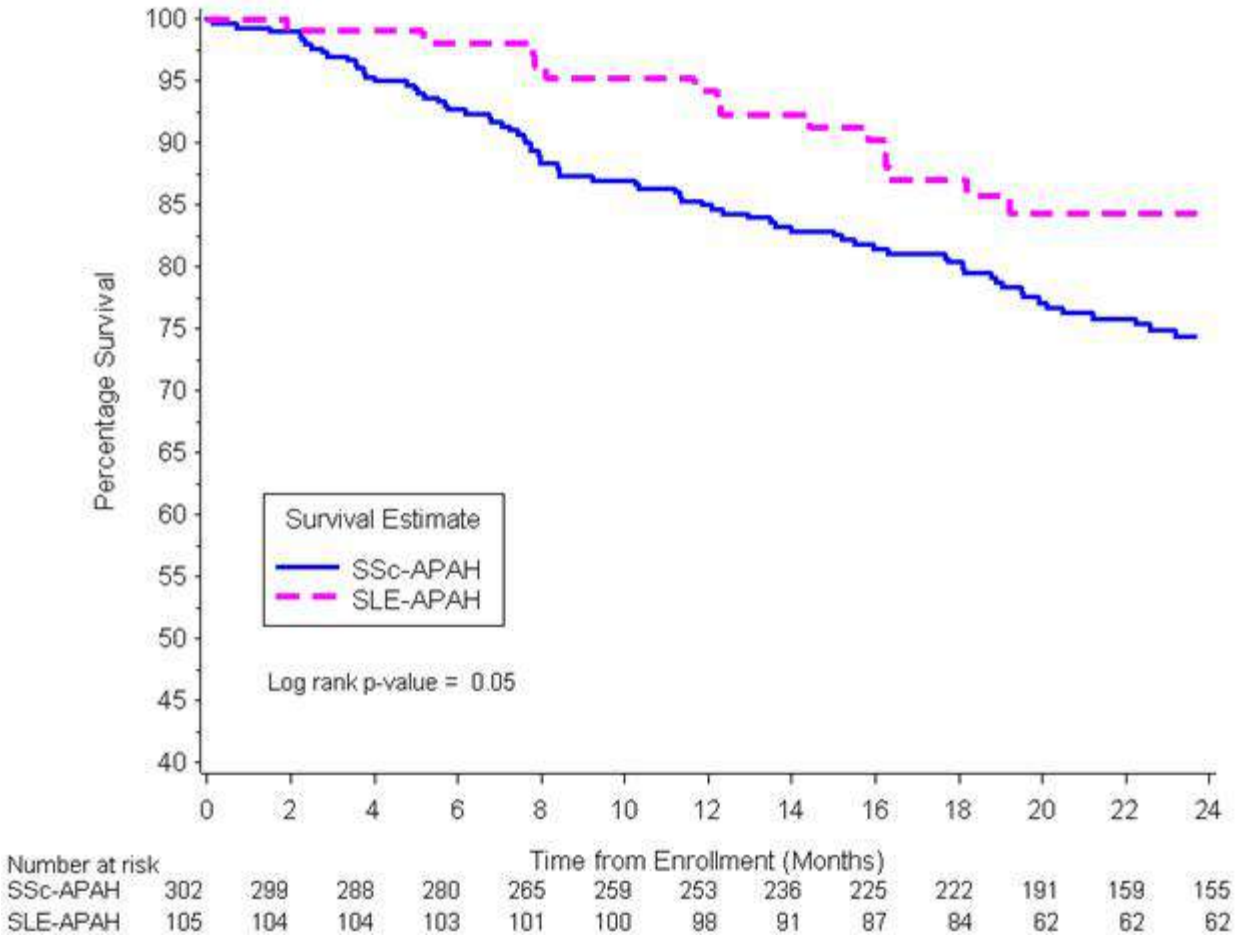

Figure: Survival in Patients with Systemic Sclerosis- and Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension

Disclosure: L. Chung, Actelion, 8, Gilead, 2, United Therapeutics, 2 ; **J. Liu**, Actelion Pharmaceuticals US, 9, Gilead, 5, United Therapeutics, 5 ; **L. Parsons**, Actelion, 2 ; **P. M. Hassoun**, United Therapeutics, 2 ; **M. McGoon**, Actelion Pharmaceuticals US, 9, Gilead, 2, Medtronic, 2, LungRx, 9 ; **D. Badesch**, United Therapeutics, 2, United Therapeutics, 5, Pfizer Inc, 2, Pfizer Inc, 5, Gilead, 2, Gilead, 5, Actelion, 2, Actelion, 9, LungRx, 2, LungRx, 5 ; **D. P. Miller**, Actelion Pharmaceuticals US, 2 ; **M. R. Nicolls**, None; **R. T. Zamanian**, Actelion, 2, Gilead, 5, United Therapeutics, 5 .

1731

A Two Year Prospective Study of Changes in Nailfold Capillary Architecture in Primary and Secondary Raynaud's Phenomenon.

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Purpose: Recent advances in nailfold capillaroscopy, including high magnification videocapillaroscopy and the ability to track change over time, allow non-invasive and detailed analysis of the abnormal capillary morphology which is a characteristic feature of systemic sclerosis [SSc]-spectrum disorders. We have developed software to allow automated measurements of microvessel architecture (width, intercapillary distance, tortuosity and derangement). The time period over which SSc-related microvascular derangement evolves is not currently known. The aim of this prospective study was to assess changes in nailfold capillary architecture over 2 years in different subgroups of patients with Raynaud's phenomenon.

Method: 26 healthy controls, 10 patients with primary Raynaud's phenomenon, 13 patients with undifferentiated connective tissue disease, 15 patients with diffuse cutaneous SSc and 80 patients with limited cutaneous SSc were studied at baseline and at 24 months. Their mean age was 53 years, range 20 to 84 years. 119 (83%) were female. Following acclimatisation for 20 minutes at room temperature (23^{o}C), the ring finger of the non-dominant hand was imaged with video microscopy at 300x magnification. Measurements were made using the automated analysis programme to give measures of capillary width, intercapillary distance, tortuosity (curliness) and derangement (variation in dominant direction of capillaries).

Results: Results for the 5 capillary measurements (4 automated) are summarised in the table. The P-value relates to non-parametric before-and-after testing excluding controls.

Measurement (all arbitrary units)	Baseline Median (IQR)	24 months Median (IQR)	p-value
Automated intercapillary distance*	25312 16851 to 46475	30289 18852 to 56666	0.005
Width	13.8 11.5 to 15.7	12.5 10.4 to 15.1	0.0001
Derangement	11.6 8.6 to 16.4	11.0 8.3 to 15.4	0.05
Tortuosity	3.26 3.15 to 3.34	3.23 3.12 to 3.32	0.04
Manual distance*	113 94 to 150	116 95 to 166	0.06

* analysed on log scale

These results show that for all measurements (except manually measured distance, p= 0.06) there was significant change over two years: intercapillary distance increased, whereas width, derangement and tortuosity all fell over 2 years. Non-parametric group comparison of change scores showed no evidence that the size of the change varied between subject subgroups (although subgroups were small).

Conclusion: 1. Capillary morphology changes over 2 years in patients with Raynaud's phenomenon, lending further support for nailfold capillaroscopy as an outcome measure in long-term clinical trials.

2. The increase in intercapillary distance suggests disease progressed across the different subgroups.

3. The fall in width, derangement and tortuosity were not anticipated and these require further assessment as outcome measures.

Disclosure: A. L. Herrick, None; **T. L. Moore**, None; **A. K. Murray**, None; **A. Vail**, None; **C. J. Taylor**, None.

1732

An Epidemiological Study of the Prevalence of Systemic Sclerosis in South East Norway. Anna-M. Hoffmann-Vold, Oyvind Midtvedt, Torhild Garen and Jan Tore Gran Sr., Oslo University Hospital, Rikshospitalet, Oslo, Norway

Background: SSc is a rare disease and, consequently, it has been difficult to conduct population-based studies revealing its true prevalence. Norway is a relatively small country and its population is homogenous. Potentially noxious environmental factors are rare, with hardly any industry or mines. This could indicate epidemiological differences to other investigated populations.

Purpose: The purpose of the study was to estimate the prevalence of SSc in Norway and to compare this to that of other countries.

Methods: The department of Rheumatology at the Oslo University Hospital (Rikshospitalet) is a highly specialized unit for connective tissue diseases and is a referral unit for South East Norway with a population of 2 672 951 inhabitants. All patients meeting either ACR criteria or the modified Medsger and LeRoy criteria for SSc are recorded in a database which was reviewed. 180 such cases were found.

Results: The median age of SSc patients in Southeast Norway was 57 yr. (19-87 yr.), for women 56 yr., compared to 59 yr. for men. The female: male ratio was 3.6:1, the overall ratio for lSSc: dSSc was 2.8:1 (women 3.5:1, men 1.4:1).

The unadjusted prevalence of SSc was 6.7 per 100.000 (2.9 for male and 10.5 for female). The prevalence by subtype and age group is shown in Table 1 and 2.

Conclusion: The overall prevalence of SSc was estimated to 6.7 per 100.000 which compared to other investigated countries was remarkably low. This can indicate differences due to geographic, climatic and social factors, which strengthens the need for further investigations.

Table 1: Population prevalence per 100.000 for Southeast Norway by SSc subtype

	Male		Female		All	
Type	No.	Prevalence	No.	Prevalence	No.	Prevalence
Limited SSc	23	1.7	110	8.2	133	5.0
Diffuse SSc	16	1.2	31	2.3	47	1.8
Both	39	2.9	141	10.5	180	6.7

Table 2: Prevalence of SSc by age group

Age group	Southeast Norwegian population	Number of SSc per group	Prevalence per 100.000
0-15	529.290	0	0
15-24	328.831	3	0.9
25-34	355.371	12	3.4
35-44	412.033	22	5.3
45-54	361.805	35	9.7
55-64	326.471	59	18.1

65-74	195.538	31	15.9
75-84	137.073	16	11.7
>85	60.150	2	3.3
Total	267.2951	180	6.7

Disclosure: A. M. Hoffmann-Vold, None; **O. Midtvedt**, None; **T. Garen**, None; **J. T. Gran**, None.

1733

Late-Age Onset Scleroderma. Rebecca L. Manno, Fredrick M. Wigley and Laura K. Hummers, Johns Hopkins University, Baltimore, MD

Purpose: Peak age for the onset of scleroderma is mid-life between 40 to 50 years. However, late-onset disease does occur and with the population aging it may become more common. We sought to determine unique characteristics of scleroderma associated with late-age of onset focusing on elderly with age of scleroderma onset greater than 65 years.

Methods: Data were retrospectively reviewed from a comprehensive database at a University based Scleroderma Center where data is prospectively collected every 6 months. Patients from this cohort were dichotomized by age of onset. Late-onset disease was defined as first non-Raynaud's phenomenon (RP) symptom of scleroderma that started after age 65 years. All patients with an established date of scleroderma onset were included in this analysis. Comparisons of covariates by age of scleroderma onset were made by Pearson chi-squared and student's t-test.

Results: 2359 patients from the cohort were analyzed. 1797 (77.5%) satisfied American College of Rheumatology criteria for scleroderma. There were 222 patients with age of disease onset greater than 65 years, 114 of whom had disease onset at age 70 or greater. Table 1 summarizes comparisons made between those with scleroderma onset before and after age 65. Patients with late-onset disease had more co-morbid illnesses and a drastically different temporality of malignancy. Older patients were more disabled as assessed by HAQ score. They had less severe Raynaud's but more significant renal, cardiac, and pulmonary disease. Older patients had more anti-centromere antibodies (41.18% vs 26.7%, p=0.001) and less anti-RNP (3% vs 9.35%, p=0.032) with all other autoantibodies being comparable.

Table 1	Age of onset < 65 years	Age of onset ≥ 65 years	p-value
Total # patients	2137	222	
% female	82.83	85.59	0.297
% limited subtype	62.68	68.78	0.074
SSc duration			
Years from RP onset to 1st non-RP SSc symptom	2.56	6.47	<0.001
Years from 1st non-RP SSc symptom to SSc diagnosis by physician	2.30	0.47	<0.001
Years to death from SSc onset	11.60	4.69	<0.001
Mean number of visits to Scleroderma Center	4.63	3.05	<0.001
Co-morbidities			
% with cancer diagnosis	8.11	16.22	<0.001
Years to cancer diagnosis after SSc onset	-5.61	0.914	0.004
Function			

HAQ score	1.10	1.22	0.055
SSc VAS: disease	1.58	1.50	0.746
intestine	0.95	0.79	0.074
breathing	1.00	1.07	0.445
Raynaud's	1.28	0.94	<0.001
digital ulcers	0.96	0.66	0.006
Organ involvement			
Skin score: diffuse	23.17	25.52	0.130
% with history of digital ischemia	56.32	37.38	<0.001
% renal crisis	2.95	4.95	0.103
% any weakness	23.16	32.00	0.009
Mean max Medsger severity score:			
General	1.04	1.13	0.339
GI	1.43	1.21	<0.001
Renal	0.29	0.57	<0.001
Cardiac	0.72	1.16	<0.001
Mean max RVSP	44.34	49.71	0.004
Mean min ejection fraction	56.62	55.55	0.150
Pulmonary	1.88	2.18	0.005
Mean min % predicted FVC	69.33	75.08	<0.001
FEV1/FVC	97.07	98.13	0.217
TLC	78.90	87.29	<0.001
DLCO	61.23	61.54	0.879

Conclusion: Patients with onset of scleroderma after the age 65 have unique characteristics and clinical outcomes compared to younger onset disease. These data suggest that the temporal relationship of malignancy diagnosis, severe Raynaud's, cardiopulmonary complications and poor functional status are distinct features in this older group.

Disclosure: R. L. Manno, None; **F. M. Wigley**, None; **L. K. Hummers**, None.

1734

Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Utility of Six Minute Walk Test.

Ann J. Impens[1], Monique E. Hinchcliff[2], Laura K. Hummers[3], M. Mayes[4], Chris T. Derk[5], Lee S. Shapiro[6], Robyn T. Domsic[7], Barbara M. Segal[8], Avram Z. Goldberg[9], Firas Alkassab[10], Virginia D. Steen[11] and the PHAROS Investigators, [1]University of Michigan, Ann Arbor, MI, [2]Northwestern University, Chicago, IL, [3]Johns Hopkins University, Baltimore, MD, [4]U.Texas Houston, Houston, TX, [5]Jefferson Medical College, Philadelphia, PA, [6]Albany, NY, [7]University of Pittsburgh, Pittsburgh, PA, [8]Hennepin County Medical Center, Minneapolis, MN, [9]North Shore-LIJ Health System, Lake Success, NY, [10]Univ of Massachusetts Med Schl, Worcester, MA, [11]Georgetown University Medical Center, Washington, DC

Purpose: 6MWT is a standardized measure of submaximal exercise capacity and has served as a major outcome measure in pulmonary arterial hypertension (PAH) clinical trials. This study looks at the effectiveness of serial 6MWTs to evaluate PH in SSc patients.

Methods: PHAROS is a multicenter prospective, observational study to determine risk factors and outcomes of patients who are at high risk for PAH or have PH. We identified patients with multiple 6MWT's in the following PH subgroups: a.Pre-PAH **(PRE)** patients with one of the following entry criteria: DLCO ≤ 55% predicted without significant fibrosis, FVC%/DLCO% ratio > 1.6, or echocardiographic systolic PAP (sPAP) >40 mmHg; b.Definite pulmonary hypertension patients (**PH**) - mean pulmonary artery pressure ≥25 mmHg at rest or ≥30 mmHg with exercise on right heart catheterization , c.New PH patients **(NPH)-** patients in the PRE group who developed PH during follow up. Analyses used included Anova, t-test analyses and Pearson.

Results: 115 patients had multiple 6MWT's. Selected results at different time points are shown in Table. There was a significant difference in 6MWT distance (6MWD) between **PRE** and **PH** groups at all time points. 6MWD was remarkably stable over time, but some trends in change over time were evident. In the **NPH** group the 6MWD decreased by 62m near the time of diagnosis of PH . In the **PH** group, a mean increase of 54m occurred in 30 patients with walks 6 months after starting treatment (p=0.18); and in the **PH** group, patients with 'clinical worsening' decreased their 6MWD by 76m at time of worsening (p=.02) In the **PRE** group, the 6MWD showed significant correlations with FVC%/DLCO%, the sPAP. In **PH** patients significant correlations were found with Echo sPAP, PFTs and patient reported measures at the different points in time.

Conclusion: The 6MWD appropriately differed between the **PRE** and **PH** groups. Although stable over time in **PRE** and **PH** groups, there was data supporting its use to measure change within specific subgroups. In spite of its non specificity to PH, serial 6MWTs may be a valid measure to use in the PH spectrum of SSc patients.

	PRE	NPH	PH
N	53	18	44
Age	54.5 yrs (10.1)	59.8	56.8 yrs (11.9)
% Female/%Caucasian	85/76	83/56	86/70
Disease duration yrs (from first non Raynaud's symptom)	12.9 (20.86)	12.34 (9.98)	9.59(7.66)
% Limited SSc	58.5	66.7	56.8
T1 6MWT	406.2 (130.8)	325.08 (162)	343.3 (121.8)
T2 6MWT	405.6 (139)	351.98 (154.6)	340.7 (146.2)
6MWD Correlations			
FVC%/DLCO	-.344 T1		
Echo sPAP	-.319 T1		-.435 T2
UCSD-dyspnea index			-.520 T1, -393 T2
S-HAQ DI			-.443 T1, -.318 T2

Disclosure: A. J. Impens, None; **M. E. Hinchcliff**, None; **L. K. Hummers**, None; **M. Mayes**, None; **C. T. Derk**, None; **L. S. Shapiro**, Actelion, 2 ; **R. T. Domsic**, None; **B. M. Segal**, None; **A. Z. Goldberg**, Gilead, 5, Actelion Pharmaceuticals US, 8 ; **F. Alkassab**, None; **V. D. Steen**, Gilead, 2, Bristol-Myers Squibb, 2, United Therapeutics, 2, Actelion Pharmaceuticals US, 2, Gilead, 8 .

1735

Effectiveness and Safety of Mycophenolate Mofetil in the Treatment of Interstitial Lung Disease in Patients with Systemic Sclerosis. Giovanna Cuomo[1], Giuseppina Abignano[2], Michele Iudici[1], Ambrogio Petrillo[2] and Gabriele Valentini[2], [1]Second University of Naples, Naples, Italy, [2]Second University of Naples, Napoli, Italy

Purpose: Interstitial lung disease (ILD) is a frequent manifestation of systemic sclerosis (SSc). ILD heralds a poor prognosis and is associated with high mortality. Cyclophosphamide (CYC) is commonly used in SSc-ILD and is presently considered the first line therapy for this condition (1). Some recent report have pointed out the efficacy of mycophenolate mofetile (MMF) in SSc both in patients with early diffuse disease and in those with SSc-IDL whatever the disease duration and the subset (MMF) (2-4). Since, in our experience, CYC treatment fails in about 24% of SSc-ILD patients treated, we underwent a prospective observational study in such patients to investigate the effectiveness and the safety of MMF.

Methods: From October 2006 we identified and subsequently enrolled into the study 18 (16 female, 2 male; median age 46: range 18-68; disease duration 7 years; range 1-25) consecutive patients with SSc and active ILD unresponsive [i.e. decrease of either Forced Vital Capacity (FVC) or diffusing lung capacity for CO (DLCO) >10% of the basal value after 10 grams total CYC dosage] to therapy with low dose of CYC i.v. MMF was administered orally at a dosage of 2000mg daily. Treatment duration ranged from 5-24 months. At basal, after 6 and 12 months were evaluated as outcome measures were evaluated: FVC, DLCO. Every three months side effects were registered.

Results: At 6 months, DLCO (n=16) increased from 47.6 (% of the predicted value)±8.8 to 49.7±9.2 ($p<0.05$) No other significant difference was detected. At 12 months (n=10) no significant difference has been pointed out. The following adverse effects occurred: liver toxicity,1; otitis media, 1; bacterial bronco-pneumonitis infection,1; herpes zoster infection, 1; neutropenia, 1; arthritis, 1.

Conclusion: Previous studies have pointed out the effectiveness of MMF in SSc-ILD. Our data suggest that MMF might freeze the deterioration of lung function, but does not seen to reverse the process in most cases

References:
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Plastiras et al, Rheumatology 2006
Gerbino et al, Chest 2008

Disclosure: G. Cuomo, None; **G. Abignano**, None; **M. Iudici**, None; **A. Petrillo**, None; **G. Valentini**, None.

1736

Prevalence and Clinical Associations of Pulmonary Involvement in Systemic Sclerosis – Data From the German Systemic Sclerosis Network Registry (DNSS). M.O. Becker[1], D. Huscher[2], C. Brückner[1], DNSS Centres, Gerd R. Burmester[3] and Gabriela Riemekasten[1], [1]Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Center (DRFZ), Berlin, Germany, [3]Charite University Hospital, Berlin, Germany

Purpose: Systemic sclerosis (SSc) is characterized by abnormal fibrosis of the skin and other organs. Its main cause of death is pulmonary involvement which may be pulmonary arterial hypertension (PAH) or interstitial lung disease (ILD) or both. We analysed data from the German DNSS network registry to evaluate the prevalence and clinical associations of pulmonary involvement in SSc patients.

Method: Data from 2062 SSc patients were analyzed and grouped according to the type of pulmonary involvement. Baseline demographic, clinical and laboratory variables were analyzed to reveal significant statistical associations. In addition, we calculated the estimated Kaplan-Meier survival curves.

Results: Of 2062 patients in the DNSS register, 965 patients (46.8%) had pulmonary involvement and of these 140 had PAH (6.8%), 591 had ILD (28.7%) and 234 patients had both (11.3%). Clinical and laboratory parameters as well as the survival curves revealed significant differences amongst the three groups: PAH was associated with limited SSc, anti-centromere antibodies, a lower median modified Rodnan skin score (mRSS) and heart involvement, whereas ILD had associations with diffuse SSc, anti-Scl70 antibodies, a higher median mRSS and kidney involvement as well as a higher male/female ratio. The third group (PAH and ILD) was similar to the ILD group in its association with diffuse SSc, a higher male/female ratio and higher mRSS and kidney involvement, but had also the highest percentage of heart involvement and dyspnoea as well as the lowest diffusing capacity for carbon monoxide (DLCO). The mean DLCO was highest in patients with PAH (>ILD>PAH and ILD). Vice versa, restrictive defects were most frequent in the PAH and ILD group (>ILD>PAH). A follow-up

of lung function parameters in selected patients revealed no significant differences after 3 consecutive visits. 41 registered SSc patients died and of these, 11 were PAH patients (7.9%), 18 had ILD (3.1%) and 12 had both PAH and ILD (5.1%). The survival curves revealed three distinct groups: patients without pulmonary involvement had the best survival, followed by patients with ILD and patients with both ILD and PAH. Patients with isolated PAH were least likely to survive. Of those patients who died, the ones with PAH and ILD had a tendency to die more quickly than others and there were significant differences to patients still alive for male gender (PAH, PAH and ILD), mRSS (PAH), DLCO (PAH), age (ILD) and organ involvement (ILD, PAH and ILD).

Conclusion: Pulmonary involvement in SSc can be divided into three groups of patients according to the presence of PAH and ILD. Although patients with PAH and ILD share many features with ILD patients, they also share some features with PAH patients. This study emphasizes the need for further investigations into the natural history and subgroups of patients with pulmonary involvement.

Disclosure: M. O. Becker, None; **D. Huscher**, None; **C. Brückner**, None; **G. R. Burmester**, None; **G. Riemekasten**, None.

1737

Myopathy Independently Predicts Mortality in Scleroderma Patients. Ritu Valiyil, Laura K. Hummers and Fredrick M. Wigley, Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Skeletal muscle dysfunction and weakness, or myopathy, is prevalent in systemic sclerosis (SSc) and can be caused by numerous factors including malnutrition, disuse, medications, inflammatory myositis, or muscle fibrosis. We postulated that presence of myopathy of any cause during the course of disease associates with unique clinical features and outcomes.

Method: We searched our cohort database that documents clinical and laboratory information prospectively collected every 6 months of all SSc patients seen at our specialty scleroderma center. Myopathy was defined if muscle weakness graded less than 5/5 by manual muscle strength testing and any one of the following characteristics was present: elevated muscle enzymes (CK or aldolase), abnormal muscle MRI, abnormal electromyography, or abnormal muscle biopsy. For each subject with myopathy, one SSc control without myopathy was selected by closest last visit and matched by age (± 5 yrs) and disease duration (± 3 mo). Demographic, disease activity, laboratory, pulmonary, and echocardiogram data were obtained from the database. Differences between SSc patients with and without myopathy were analyzed by chi-squared analysis or student's t test. Conditional multivariable logistic regression models were used to assess associations.

Results: 178 of 2,359 SSc patients met our criteria for myopathy and were matched to 178 patients without myopathy. Between the myopathy and non-myopathy groups, there were no statistical differences in mean age (55 yrs), disease duration (8.4 yrs), and sex (78% female vs. 85% respectively). When compared to controls, subjects with myopathy were more likely to be the diffuse skin subtype (66 vs. 37%, p<.001) and African-American (34 vs. 17%, p=0.001). Arthralgias were more frequent with myopathy (83 vs. 69%, p=0.003), as were tendon friction rubs (34 vs. 17%, p<.001) and synovitis (24 vs. 11%, p=0.001). SSc patients with myopathy were more likely to have lung disease with a lower mean % predicted FVC (59.3) than SSc patients without myopathy (73), p<.001, as well as cardiac dysfunction with a mean lower ejection fraction (54%) compared to controls (58%), p=0.004. Anti-RNP antibodies were strongly associated with myopathy (OR 5.5, CI 1.22-24.8), while antibodies against centromere and topoisomerase I were negatively associated (OR 0.09, CI 0.02-0.39 and OR 0.29, CI 0.11-0.80 respectively). In adjusted multivariable analysis, a significant association was observed between myopathy and diffuse skin subtype (OR 2.7, CI 1.1-6.5) and % predicted FVC ≤ 60 (OR 3.27, CI 1.8-6.0). There was no association with smoking, cancer, FEV_1/FVC ratio, and maximum RVSP. Increased mortality was associated with myopathy (OR 3.4, CI 1.3-8.9) and % FVC ≤ 60 (OR 14.5, CI 2.5-82). In subjects with % FVC >60, death was more frequent in subjects with myopathy (27 vs. 9%, p<.001).

Conclusion: Myopathy in scleroderma is significantly associated with diffuse skin subtype and lung disease and independently predicts mortality. Early recognition of muscle disease may identify scleroderma patients at high risk for poor outcomes and provide an opportunity for therapeutic intervention.

Disclosure: R. Valiyil, None; **L. K. Hummers**, None; **F. M. Wigley**, None.

1738

Aminaftone Enhances Iloprost Beneficial Effects in Patients with Systemic Sclerosis and Recurrent Ulcers. Raffaella Scorza, Monica Caronni, Alessandro Santaniello, Karen Toussoun and Lorenzo Beretta, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena and University of Milan, Italy, Milan, Italy

Purpose: Endothelin-1 (ET-1) and adhesion molecules overexpression plays a pivotal role in the pathogenesis of vascular remodelling that characterizes systemic sclerosis (SSc). Indirect observations indicate that ET-1 is relevant in the pathogenesis of digital ulcers (DU) in scleroderma subjects. Treatment of digital ulcers in SSc patients is challenging as in many patients they tend to be chronic and relapse and largely affect the quality of life, in spite of efficacious pharmacological treatment like prostanoids and the dual ET-1 receptor blocker. In this study we investigated whether aminaftone that downregulates in vitro ET-1 (1) production and ex vivo expression of endothelial adhesion molecules (2) should favour ulcers' healing in SSc patients with recurrent and/or refractory ulcers resistant to cyclic iloprost treatment.

Method: Thirteen patients referring to our outpatient clinic (11 females and 2 males) with diagnosis of SSc according to ACR criteria where included in this study. Five patients had a diagnosis of dcSSc, 8 a diagnosis of lcSSc. Mean age ± s.d. was 54 ± 10 years (range 35-69); disease duration (mean ± s.d.) was 9 ± 5 years. All the patients had chronic and/or recurrent digital ulcers (number of active ulcers/patients 2,43 ± 1,02) in spite of the chronic treatment with cyclic iloprost (2ng/kg/min for 8 hrs every 4 weeks). Iloprost treatment duration (mean ± s.d.) was 6 ± 1 years (range 5-9). All the patients had careful information about aminaftone, its usual therapeutical use in capillary disorders and gave informed consent to the treatment with oral aminaftone (75 mg t.i.d.), in addition to cyclic iloprost treatment. The duration of the aminaftone treatment was 12 months. The effect of aminaftone in enhancing Iloprost effect was analyzed by Students' T-test for paired samples.

Results: The addition of aminaftone to cyclic Iloprost treatment in patients with refractory/relapsing digital ulcers favoured the healing (number of ulcers pre- and post-treatment: 2,43 ± 1,02 Vs 1,29 ± 0,61, $p<0.005$).

Conclusion: These results show that aminaftone is able to increase the beneficial effects of iloprost in the management of digital ulcers secondary to SSc, supposedly by its capability to reduce ET-1 production and adhesion molecule expression. Further randomized study are needed to confirm whether this cheap and well tolerated drug is effective in association with conventional therapy to favour the healing of digital ulcers.

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2. Scorza R, *et al*. Effects of aminaftone 75 mg TID on soluble adhesion molecules: a 12-week, randomized, open-label pilot study in patients with systemic sclerosis. Clin Ther. 2008;30:924-9.

Disclosure: R. Scorza, None; **M. Caronni**, None; **A. Santaniello**, None; **K. Toussoun**, None; **L. Beretta**, None.

1739

The Development of Updated Criteria for Systemic Sclerosis (SSc) Using Delphi Technique and Cluster and Frequency Analyses From a Large SSc Patient Database. Corrine Coulter[1], Canadian Scleroderma Research Group, Scleroderma Clinical Trials Consortium, Marie Hudson[2], Russell Steele[3], Murray Baron[4] and Janet Pope[5], [1]University of Western Ontario/St. Joseph's Health Care, London, ON, [2]McGill University and Jewish General Hospital, Montreal, QC, [3]McGill University, Montreal, QC, [4]Jewish General Hospital, Montreal, QC, [5]St Joseph Health Care, London, ON

Purpose: The ACR classification criteria for Systemic Sclerosis (scleroderma, SSc) fail to identify at least 12% of individuals in the Canadian Scleroderma Research (CSRG) database all of whom have been diagnosed with SSc by a rheumatologist and this finding is concordant in other databases, thus modification of criteria is welcome.

Method: Literature was searched for a list of possible suggested SSc criteria, and a list thorough list of signs, symptoms and tests was composed and sent in random order to 96 SSc experts {from the Scleroderma Clinical Trials Consortium (STCC), CSRG and others} who were also asked to add other criteria that may be missing from the list. A Delphi Consensus exercise of three rounds was conducted. Cluster analysis (using Tetrachoric correlations and Proc VARCLUS) reduced the final consensus list to criteria with a best fit. The CSRG database was used to determine the proportion of patients the criteria classified and the 1000 Faces of Lupus database was used to determine the frequency of some of the criteria that were suggested within that database.

Results: 71 of 96 (71%) completed all 3 rounds (response rate round 1, and 2 were 80% and 74%); where 47 items on the original list of possible criteria were expanded to 76 in the second round (some were combinations of previous criteria or different definitions of criteria such as ILD) and 30 items on round 3 that had at least 50% consensus were included. In round 3, 18 items had >75% agreement to include (a priori cut point), ranging from 75 to 100% agreement. Cluster analysis identified subset criteria into 4 categories: skin involvement, capillary characteristics, auto-antibodies and tissue damage. Frequency analysis of skin involvement that was on fingers and proximal to MCPs (identified 80% of patients) or 1 or more items from at least 2 of 3 categories were able to identify 94% of the CSRG patients including Vascular: dilated capillaries, telangiectasia, Raynaud's phenomenon (RP), auto-antibodies {anti-centromere or anti-topoisomerase (Scl70)}, sclerodactyly, damage (esophogeal dysmotility / dysphagia, fibrosis, digital ulcers). The best fit was skin involvement of the fingers and proximal to the MCPs; or sclerodactyly plus one of: RP, anti-centromere (ACA) or Scl70 which described 98% of the CSRG patients. We studied the frequency of potential SSc criteria in SLE patients (n>600) where 1.1% had a digital ulcer ever, 2% were Scl70+, 0.5% were ACA+ and 0.5% had telangiectasia and sclerodactyly proximal to the MCPs did not occur in lupus without a SSc overlap. Thus, these criteria may also have good specificity.

Conclusion: Updated classification criteria should improve disease identification and case definitions for research purposes, and patient care. This is a first step toward developing new criteria as the sensitivity and specificity have not been determined.

Disclosure: C. Coulter, None; **S. Clinical Trials Consortium**, None; **M. Hudson**, None; **R. Steele**, None; **M. Baron**, None; **J. Pope**, Ontario Scleroderma Society, 2 .

1740

Genetic and Biological Models of Epistasis to Predict Digital Ulcer Occurrence in Italian Systemic Sclerosis Patients. Lorenzo Beretta[1], Alessandro Santaniello[1], Michael Mayo[2], Francesca Cappiello[1], Maurizio Marchini[1] and Raffaella Scorza[1], [1]Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena and University of Milan, Italy, Milan, Italy, [2]University of Waikato, Hamilton, New Zealand, Hamilton, New Zealand

Purpose: Digital ulcers (DUs) are a frequent complication of systemic sclerosis (SSc) that may occur in up to 50% of patients during their disease history and that constitute a significant cause of discomfort and morbidity. DUs are thought to be the consequence of endothelial injury and small-vessel vasculopathy, which may be sustained by immune system activation and cytokine release.

Method: Twenty-two functional cytokine single nucleotide polymorphisms (SNPs) and 3 HLA-class I and II antigens, -including HLA-B*3501 which may contribute to regulate the endothelin-1 (ET-1) production (1), HLA-DR*11 and HLA-DR*07, previously associated with SSc in Italian subjects (2), were typed at the genomic level by polymerase chain-reaction in 200 Italian SSc patients. Associations with DUs were sought by parametric models and with the Multifactor Dimensionality Reduction (MDR) algorithm to depict the presence of gene-gene or gene-environment interactions. Biological models consistent with MDR results were built by means of Petri nets to better describe the metabolic significance of our findings.

Results: On the exploratory analysis, the dcSSc subset was the only factor associated with DUs (p=0.045, ns after Bonferroni correction). Gene-gene and gene-environmental analysis showed that a 3-factor model comprising the IL-6 C-174G, the IL-2 G-330T SNPs and the HLA-B*3501 allele was associated with DUs (testing accuracy=66.9%, p<0.005 after permutation testing). Petri nets allowed us to build a biological model to explain the non-linear interactions among the abovementioned variables. The main findings that emerge from this model are the following: 1) IL-6 and HLA-B*3501 synergize to eventually determine DUs occurrence; 2) IL-6 may sustain/amplify HLAs responses; 3) IL-6 production is amplified by an autocrine loop where IL-2 acts as a co-enhancing factor.

Conclusion: We provide evidence for a complex genetic susceptibility to DUs in Italian SSc patients. In the model we found, IL-6 appears to be a key-factor in determining DUs occurrence. This model is biologically plausible and may constitute the basis for further translational research.

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2.Scorza R *et al*: HLA-DR antigens, clinical manifestations and autoantibodies in Systemic Sclerosis (Scleroderma). EOS. 1992; 12: 157-162

Disclosure: L. Beretta, None; **A. Santaniello**, None; **M. Mayo**, None; **F. Cappiello**, None; **M. Marchini**, None; **R. Scorza**, None.

1741

Associations with Digital Ulcers (DU) in a Large Cohort of Systemic Sclerosis (SSc). Sarit Khimdas[1], Sarah Harding[2], Ash Bonner[3], Brittany Zummer[2], Canadian Scleroderma Research Group, Murray Baron[4] and Janet Pope[5], [1]Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, [2]University of Western Ontario, London, ON, [3]McMaster University, Hamilton, ON, [4]Jewish General Hospital, Montreal, QC, [5]St Joseph Health Care, London, ON

Purpose: Digital ulcers (DU) are a common disabling complication of systemic sclerosis/scleroderma (SSc) and can be associated with devastating complications such as osteomyelitis and amputation. There is debate as to whether DUs are increased in SSc with pulmonary arterial hypertension (PAH) as the literature is controversial in this area[1, 2]. Although occurring in 30 to 50% of patients, information is lacking on whether DUs are associated with other organ complications and SSc subsets.

Method: Data from the CSRG (Canadian Scleroderma Research Group) are collected annually on an incident and prevalent SSc cohort. Presence, location and number of digital ulcers are collected annually as well as complications and other internal organ involvement, skin score and labs results. Correlation coefficients, Chi squared and logistic regression modeling were done to determine the associations of DUs (and subset of complicated DU) with other factors such as internal organ complications

Results: 938 patients were included. 86% were women, mean age was 56 and disease duration was 14 years. 53% had limited SSc. 15% had a DU currently, 46% had a DU ever and 53% had digital pits. DUs were not associated with PAH (P=0.35). Complicated DUs including gangrenous (P=0.72) and amputated (P=0.93) digits were not associated with PAH. In patients with a disease duration longer than three years, DUs were associated with higher skin scores (P=0.00). Gender (P=0.95) and smoking (0.91) were not associated with DUs. Organ involvement including renal crisis (P= 0.66) and interstitial lung disease (P=0.20) were not associated with DUs. DUs were associated with: a decreased DLCO in diffuse SSc (P=0.01) and both earlier age of Raynaud's (P=0.00) and first non-Raynaud's symptom (P=0.00). DUs were further associated with GERD in diffuse SSc (P=0.00) and esophageal hypomotility as measured by esophageal dilatation (P=0.00). DUs were associated with the presence of topoisomerase 1 (Scl-70) antibodies (P=0.00). Patients with diffuse SSc were almost twice as likely to have had a DU than patients with limited SSc. However, neither patients with gangrenous (P=0.61) nor amputated digits (P=0.46) were associated with a subtype of SSc.

Conclusion: It appears that DUs are not associated with PAH. DUs increase with diffuse SSc, early onset of disease, low DLCO, esophageal involvement and presence of topoisomerase 1 (Scl-70) antibodies. Complicated DUs are not associated with an SSc subtype or specific organ involvement. Some of the associations are confounded as diffuse SSc onsets earlier than limited and thus earlier age of onset increases DU risk. Understanding the associations with digital ulcers in scleroderma may help to risk stratify patients and better treat or prevent this disabling complications. 1. Sunderkotter C. British J Dermatology, 2009

2. Tiev KP. J Rheumatol, 2009

Disclosure: S. Khimdas, None; **S. Harding**, None; **A. Bonner**, None; **B. Zummer**, None; **M. Baron**, None; **J. Pope**, None.

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Pilot Study of Intense Pulsed Light (IPL) for the Treatment of Systemic Sclerosis-Related Telangiectases. Andrea K. Murray[1], Tonia L. Moore[1], Helen L. Richards[2], Holly Ennis[3], Christopher Griffiths[1] and Ariane L. Herrick[1], [1]University of Manchester, Salford, United Kingdom, [2]Mercy University Hospital, Cork, Ireland, [3]University of Manchester, Manchester, United Kingdom

Purpose: Cutaneous telangiectases, caused by dilation of microvessels, are a major source of concern and disfigurement in patients with systemic sclerosis (SSc) especially when they occur on the face. Current treatments include camouflage techniques and laser therapy, although the latter is time-consuming, can result in considerable bruising, and not all lesions respond. Our aim was to examine the safety and tolerability of intense pulsed light (IPL) treatment in an open pilot study.

Method: 20 patients (mean [range] age 55[37-70] yrs; 4 male 16 female; 18 limited cutaneous SSc, 2 diffuse cutaneous SSc) with telangiectases of face and/or upper limb were recruited. If the patch test at the screening visit was uneventful, all patients received 3 IPL treatments to a selected area at monthly intervals, unless lesions completely resolved after the first or second treatment, in which case no further treatments were given. Patients were followed for up to 12 months. Outcome measures included the appearance of the telangiectases from clinical photographs [2 observers compared each post treatment image to baseline and judged lesions as – worse, no change, improved,

much improved or resolved], the Hospital Anxiety and Depression Scale (HADS), and the Derriford Appearance Scale (DAS-59) (an assessment of distress and dysfunction in relation to appearance). Telangiectases were imaged at each visit by laser Doppler, but these results are not included in this analysis.

Results: One patient failed the patch test, one patient was subsequently excluded for not fulfilling the study criteria and 1 patient's images were ungradable. Of the remaining 17, all but one had all 3 IPL treatments. Two weeks after the final treatment, patients were categorised as follows: 4 ‘no change', 5 ‘improved' and 8 as ‘much improved'. At the follow-up visits (6 to 12 months) patients were categorised as 5 ‘no change', 8 ‘improved' and 4 ‘much improved'. The median HADS anxiety score pre-treatment was 5 (range 0 to 11) and post-treatment 7 (range 1 to 14) (p=0.4) and the median HADS depression score pre-treatment was 4 (range 1 to 11) and post-treatment 6 (range 1 to 12) (p=0.7). Median DAS-59 pre-treatment was 81 (range 25 to 173) and post-treatment 78 (range 29 to 218) (p=0.9). The treatment was well tolerated in most patients but one patient withdrew after the first treatment following facial swelling, and one had blistering of the dorsum of the hand following the third treatment.

Conclusion: 1. Most patients improved after IPL treatment and the treatment was well tolerated.

2. The degree of improvement was not maintained in all patients at 6-12 months, suggesting that further treatments might be necessary.
3. Improvement was not matched by an improvement in the HADS or DAS-59.
4. This was a small pilot study and longer term studies are now required, comparing IPL to laser treatment.

Disclosure: A. K. Murray, None; **T. L. Moore**, None; **H. L. Richards**, None; **H. Ennis**, None; **C. Griffiths**, None; **A. L. Herrick**, None.

ACR/ARHP Poster Session C

Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment II
Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Cartilage Biomarkers Profile and Correlations with Measures of Disease Activity in Ankylosing Spondylitis Patients. J.L Fernandez-Sueiro[1], J. Pinto[2], Sonia Pertega[3], A. Atanes[1], J.C. Fernandez-Lopez[4], Natividad Oreiro[3], E. Gonzalez-Diaz de Rabago[1], F. Galdo[1] and Francisco J. Blanco[5], [1]Hospital Universitario Juan Canalejo, La Coruña, Spain, [2]Hospital, La Coruña, Spain, [3]INIBIC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [4]MD, La Coruña, Spain, [5]Hospital Juan Canalejo, A Coruna

Purpose: To evaluate the biomarkers profile and their correlations with measurements of disease activity in a longitudinal observational cohort of anti-TNF naïve AS patients.

Method: 79 AS patients and 86 healthy controls (HC) were studied. Current ASAS recommendations as well as radiological examination with BASRI were performed in AS anti-TNF naïve patients. Serum determinations of YKL-40, C2C and CPII were performed in AS patients at the entry in the cohort, time 0 (t0), and at 12 months (t1). Determinations in healthy controls were performed at t0. YKL-40, C2C and CPII were determined by ELISA with commercial kits following manufacturer’s instructions results are shown in ng/ml. Comparisons between AS patients and HC were performed using the Mann-Whitney test. Changes in biomarkers between t0 and t1 were assessed by the Wilcoxon’s signed rank test. Correlations were assessed using the Spearman’s rho correlation coefficient.

Results: At t0 there were statistical significant differences between AS patients and HC in the levels of CPII (390.5 vs 271.8) ($p<0.001$) and CPII/C2C (18.5 vs 12.7) ($p<0.001$), but not in the levels of YKL-40 (126.4 vs 128.4) (p=0.989) and C2C (23.6 vs 22.8) (p=0.610). Among AS patients, there were statistical significant differences between t0 and t1 in the three markers: YKL-40 (mean increase: 38.3, $p<0.001$), C2C (mean increase: 3.7, p=0.002), CPII (mean decrease: 84.2, p=0.001) and CPII/C2C (Mean increase: -6.9, $p<0.001$). There was a significant correlation between basal levels of CPII/C2C and changes in disease activity; BASDAI t1-t0 (Rho=0.358, p=0.001), physician global assessment t1-t0 (Rho=0.225, p=0.047). On the other hand there was a correlation between biomarkers variation and changes in disease activity; BASDAI t1-t0 (Rho=-0.227, p=0.047), Physician global assessment (Rho=-0.237, p=0.037).

Conclusion: As the disease progress there seems to be a worsening of cartilage break down products. The increase of YKL-40 and the decrease of CPII/C2C at T1 suggest the persistence of an ongoing inflammation. There was a direct correlation of the basal CPII/C2C ratio with an increase in measurements of activity such as BASDAI and physician global assessment. On the other hand a decreased in the CPII/C2C ratio correlated with a worsening of the disease measured by BASDAI and physician global assessment.

Disclosure: J. L. Fernandez-Sueiro, Instituto de Salud Carlos III, FIS PI051945 , 2 ; **J. Pinto**, None; **S. Pertega**, None; **A. Atanes**, None; **J. C. Fernandez-Lopez**, None; **N. Oreiro**, None; **E. Gonzalez-Diaz de Rabago**, None; **F. Galdo**, None; **F. J. Blanco**, None.

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Axial Metrology Measurement and Functional Status in Ankylosing Spondylitis. J. Sieper[1], Amitabh Singh[2], Bruce Freundlich[2], Andrew S. Koenig[2] and Wenzhi Li[3], [1]Rheum/Charite Hosp, Berlin, Germany, [2]Wyeth Research, Collegeville, PA, [3]Wyeth Research, Philadelphia, PA

Purpose: It has been suggested that evaluation of spinal mobility using axial metrology could be used to assess disease modification in ankylosing spondylitis (AS). Although axial metrology has been shown to have a good correlation with radiography, its relationship with functional status has not been systematically evaluated. To assess the relationship between spinal mobility measured using axial metrology and functional status.

Method: In a randomized, 16-week, double-blind, randomized, multicenter, active comparator [sulfasalazine (n=187)] study to assess the efficacy and safety of etanercept (50 mg once weekly (n=379)] in patients with AS, spinal mobility was measured by Bath Ankylosing Spondylitis Metrology Index (BASMI: range 0-10). Functional status was measured with Bath Ankylosing Spondylitis Functional Index (BASFI: range 0-100). We estimated how the end of study (Week 16) changes (δ) in functional status would be related to δ in disease activity, δ in spinal mobility, age, gender and disease duration. The relationships were estimated with a linear regression model with change in BASFI as the dependent variable. Three alternative scoring algorithms have been proposed for BASMI: BASMI 2, BASMI 10 and BASMI Linear. Although the range of score is unaffected, BASMI Linear has been found to be most sensitive to change, followed by BASMI 10 and BASMI 2. Accordingly, three separate regression models were estimated using these different scoring algorithms for BASMI.

Results: The study population was predominantly male (75%) with an average age of 40.7y and disease duration of 7.6y. The baseline BASMI 2, BASMI 10, and BASMI Linear scores were 3.66, 4.08, and 4.10 respectively. The table below presents the standardized beta coefficients for the 3 regression models (I: BASMI 2, II: BASMI 10, III: BASMI Linear)

	Regression Models		
	I (N=519)	**II (N=519)**	**III (N=519)**
δ BASDAI	0.777^{+}	0.761^{+}	0.757^{+}
δ BASMI 2, δ BASMI 10, δ BASMI Linear	-0.089^{+}	-0.115^{+}	-0.128‡
Disease Duration	-0.034	-0.033	-0.033
Age	0.059	0.058	0.058
Gender (Male=1)	0.020	0.021	0.020
Adj R^2	0.64	0.65	0.65
‡P<0.001			

Each of the 3 models was able to explain about 64% of the variation in BASFI. Only δ in disease activity and δ in spinal mobility were significantly associated with BASFI. δ in BASFI was independent of disease duration, gender and age. Apart from disease activity, changes in spinal mobility had the largest impact on functional status.

Conclusion: This study demonstrated that changes in spinal mobility are significantly associated with changes in functional status in patients with AS. Because BASMI has shown good correlations with radiography, the potential for using BASMI as a surrogate for disease modification should be further examined.

Disclosure: J. Sieper, Abbott, Schering-Plough, Wyeth, Research grants, Abbott, BMS, Roche, Schering-Plough, Wyeth, Consulting fees, Abbott, Roche, Pfizer, Scheering-Plough, Wyeth, Speakers' bureau, 5 ; **A. Singh**, Wyeth Research, 3 ; **B. Freundlich**, Wyeth Pharmaceuticals, 3, Wyeth Pharmaceuticals, 1 ; **A. S. Koenig**, Wyeth Pharmaceuticals, 3, Wyeth Pharmaceuticals, 1 ; **W. Li**, Wyeth Research, 3 .

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The Electronic Version of the Psoriatic Arthritis Screening Questionnaire (EPASQ) Is An Effective Tool in Detecting Patients with Psoriatic Arthritis. Majed M. Khraishi and Jonathan Mong, Nexus Clinical Research, St Johns, NF

Purpose: Psoriatic arthritis (PsA) is a serious inflammatory disease that can cause significant joint damage, disability and co-morbidities. Early PsA detection and effective treatment may prevent these serious problems. We developed the Psoriatic Arthritis Screening Questionnaire (PASQ) as a tool for reliable diagnosis of PsA in patients with skin psoriasis. In a previous communication (Poster presentation EULAR 2008) we reported that the PASQ was highly sensitive and specific in detecting patients with psoriatic arthritis (PsA) fulfiling the CASPAR criteria A natural next step was to provide an easy to perform electronic version that can be widely distributed and eliminate possible inaccuracies of the diagram scoring.

Objectives: To examine the sensitivity and specificity of an electronic version of the PASQ and validate it against the original paper version.

Method: The electronic version of the PASQ (EPASQ) was developed using Adobe Creative Suite 4 software, and was based on the previous paper version of the PASQ. The EPASQ was programmed to provide a maximum of 15 points. The PASQ contained 10 differently weighted questions as well as a diagram where patients marked where they had or have had pain and or swelling. The same questions were included in the EPASQ in addition to a diagram with 68 joints plus the spine. The diagram and the questionnaire can be electronically marked and automatically scored. Validation was conducted using the questionnaires from 42 patients with confirmed PsA (mean disease duration 12 months). Questionnaires from 12 psoriasis patients without PsA were used as a control. Comparison of scores obtained from the manual and the electronic versions were conducted. A receiver operating curve (ROC) was determined for both the paper version as well as the electronic version using MedCalc® software. Descriptive statistics for both were obtained using SPSS.

Results: The original PASQ, data was collected from 87 patients (58 with established PsA meeting the CASPAR criteria and 29 with psoriasis and no evidence of arthritis). Analysis of the PASQ score [AUC = 0.913, 95% C.I.: (0.833, 0.963), p = 0.0001] yielded an optimal cut-off score of 9, with 86.27% sensitivity and 88.89% specificity. A score of 8 would yield a sensitivity of 91.16% and a specificity of 77.78%.

The electronic (EPASQ) Data was collected from a prospective cohort of 42 patients with early PsA (meeting the CASPAR criteria), and from 12 psoriasis patients without PsA. All but two of the PsA patients scored 8 or more in the paper PASQ. Concordance of the paper and electronic scores was very high with only one patient who scored 7 in the paper PASQ and 11 in the EPASQ. The ROC Curve of the entire group yielded an optimal 97.62% sensitivity and 75.00% specificity for a cut-off score of 7. A cut-off point of 8 yielded a sensitivity of 88.10% while still maintaining a specificity of 75.00%.

Conclusion: The electronic version of the PASQ is a simple self-administered and scored program with a high sensitivity and specificity. It can be an effective tool to screen for early and established PsA patients.

Disclosure: M. M. Khraishi, Abbott Laboratories, 2, Amgen, 2, Wyeth Pharmaceuticals, 2 ; **J. Mong**, None.

1769

Major Clinical Response of Rituximab in Active TNF-Blocker-Naive Patients with Ankylosing Spondylitis but Not in TNF-Blocker-Failure Patients- An Open Label Clinical Trial. In-Ho Song[1], Frank Heldmann[2], Martin Rudwaleit[3], Joachim Listing[4], Heiner Appel[1], J. Braun[5] and J. Sieper[6], [1]Charite, Campus Benjamin-Franklin, Berlin, Germany, [2]Centre of Rheumatology, Herne, Germany, [3]Charité - Campus Benjamin Franklin, Berlin, Germany, [4]DRFZ, Berlin, Germany, [5]Rheumazentrum Ruhrgebiet, Herne, Germany, [6]Rheum/Charite Hosp, Berlin, Germany

Background: Histological studies have shown B-cell clusters in the facette joints of patients with ankylosing spondylitis (AS) [1]. On this background an immunotherapy targeting B cells in AS is of interest.

Purpose: To examine the efficacy and safety of rituximab in NSAID-refractory AS patients with or without previous treatment with TNFalpha-blockers.

Methods: In this open label phase-II-clinical trial rituximab 1000mg was administered intravenously at baseline and week 2 in 20 patients with active AS, 10 TNF-naïve and 10 TNF-refractory patients. Clinical outcome assessments included disease activity (BASDAI, patient global assessment), function (BASFI), assessments of pain, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Results: Baseline characteristics: out of 20 patients 75% were male; 90% HLA-B27 positive, mean age 39.7 (SD 10.6); mean disease duration 16.8 years (SD 9.5). Patients had active disease and all suffered from axial pain. 85% of the patients reached week 24.

In the TNF-naïve group (n= 10) at week 24 ASAS20 was reached by 50%, ASAS40 by 40% and ASAS remission by 30%; BASDAI20 by 60% and BASDAI50 by 50%. Significantly more patients reached a BASDAI50 response in the TNF-naïve group (50%) compared to the TNF-failure group (0%), p= 0.033. There was nearly no change in the BASDAI values in the TNF-failure AS patients. In the TNF-naive patient there was a significant improvement between screening and week 24 regarding BASDAI (5.7 to 3.7, p= 0.047), patient pain assessment (7.3 to 4.4, p= 0.021) and CRP-values (24.6 mg/L to 19.1 mg/L, p= 0.017).

Overall, rituximab was well-tolerated, 5 serious events (SAEs) occurred during the study. 1 SAE (surgical treatment of hemorrhoids) occured before baseline, so this was definitely not drug-related. The other SAEs were an ulnar fracture, a nephrolithiasis, a skin abscess after colonscopy and a GI-bleeding which was considered to be not related to study drug.

Conclusion: While rituximab does not seem to be effective in TNF-failure AS patients it shows a significant efficacy in TNF-naive patients. Therefore a further application in TNF-naïve AS patients should be explored.

References:
Appel H et al. Correlation of histopathological findings and magnetic resonance imaging in the spine of patients with ankylosing spondylitis. Arthritis Res Ther 2006;8(5):R143.

Disclosure: I. H. Song, None; **F. Heldmann**, None; **M. Rudwaleit**, Abbott, MSD, Schering-Plough, Pfizer, and Wyeth, Consultancies, speaking fees, honoraria, 5 ; **J. Listing**, None; **H. Appel**, None; **J. Braun**, Abbott, Schering-Plough, Wyeth, Centocor, Amgen, Reiumbursements, fees, grants, 5 ; **J. Sieper**, Abbott, Schering-Plough, Wyeth, Research grants, Abbott, BMS, Roche, Schering-Plough, Wyeth, Consulting fees, Abbott, Roche, Pfizer, Scheering-Plough, Wyeth, Speakers' bureau, 5 .

1770

Treatment of DMARD Resistant Knee Monoarthritis with Repeated Intra-Articular Infliximab: Clinical and Ultrasound Outcome. Sarah J. Levy, Oliver Wignall, Christine Heron, James Pilcher and Patrick D. Kiely, St Georges Hospital, London, United Kingdom

Purpose: Intra-articular (IA) injection of steroid and systemic DMARD therapy are often used to treat inflammatory monoarthritis. Therapeutic options are limited in those who fail this regimen. Recent reports suggest that IA Infliximab (IF) may give benefit in refractory knee monoarthritis but little is known about the optimum use of this therapy.

Method: We studied 14 (8 M, 6 F) patients (diagnosis: seronegative monoarthritis (7), psoriatic (3), rheumatoid (3), enteropathic (1)). 8 were on DMARD monotherapy and 6 on combination therapy. Each patient was treated with a maximum of 3 IA injections of 100mg Infliximab. Clinical (Composite Knee Score (CKS), Pain Visual Analogue Score, Function Score), Ultrasound (synovial thickness, appearance and power doppler) and haematological parameters were recorded at baseline and weeks 2, 4, 8, 12, 20, 24, 28, 36, 46 and 52. Primary response criteria was reduction in the CKS by at least 2 points and relapse was defined as return to baseline CKS. Patients were eligible to be retreated

if they had at least 8 weeks benefit from the previous injection. During the latter half of the study patients were pre-treated with IA long acting steroid 1 week prior to the IF injection in an attempt to prolong duration of response to IF.

Results: 14/14 patients responded to the 1st injection with a mean time to response of 3.4 weeks and a mean response of 2.86 CKS points. 3/14 (21%) remained in remission at 1 year and 11/14 (79%) relapsed at a mean 10.54 weeks and were retreated. Of these, 1/11 remained in remission at 1 year, 2 were withdrawn due to short duration of response to the 2nd injection (< 8 weeks) and one moved away. 7 patients were treated with a 3rd injection. Mean duration of response for 2nd and 3rd injections was 8.77 and 10.16 weeks respectively and pre-treatment with IA steroid did not improve duration of response (mean duration with IA steroid 8.95 weeks compared with 9 weeks without). Patients who were in remission at 1 year were more likely to be female (M:F 1:3 compared with 7:3) and to have less severely affected knees at baseline (CKS mean 2:4.1, synovial thickness mean 3.6mm: 4.55mm, mean PD 0.66:0.71). Lack of complete response to initial injection (clinical and US) predicted relapse.

Conclusion: IA IF resulted in clinical and US remission at 1 year in 4/14 (29%) patients. In this study female patients with less severely affected knees at baseline were less likely to relapse. The addition of IA steroid 1 week prior to IF injection did not prolong duration of response.

Ultrasound parameters paralleled clinical changes accurately but did not offer advantage over clinical measures in either measuring response or predicting relapse.

IA IF is safe and easy to administer in the clinical setting and may result in prolonged remission in over a quarter of patients with the majority responding after a single injection.

Disclosure: S. J. Levy, None; **O. Wignall**, None; **C. Heron**, None; **J. Pilcher**, None; **P. D. Kiely**, Schering Plough, 5 .

1771

Effects of 14 Weeks of TNF Alpha Blockade Treatment On Lipid Profile in Ankylosing Spondylitis. Sylvain Mathieu, Christelle Gibert, Jean-Jacques Dubost, Jean-Michel Ristori and Martin Soubrier, Rheumatology. Gabriel Montpied Teaching Hospital, Clermont-Ferrand, France

Purpose: Cardiovascular morbidity and mortality seem to be increased in ankylosing spondylitis, perhaps as the result of biological inflammation and consecutive dyslipidemia. This study aims to investigate the impact of TNF alpha-inhibitors, an effective treatment, on lipid profile.

Method: Thirty-four ankylosing spondylitis (AS) patients with active disease undergoing anti-TNF alpha therapy (infliximab n=20; etanercept n=7; adalimumab n=7) were recruited. Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels and, disease activity parameters, Visual Analogical Scale (VAS) pain or VAS disease activity, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Bath Ankylosing Spondylitis Functional Index (BASFI), Erythrocyte Sedimentation Rate and C-Reactive Protein, were assessed at baseline and after 14 weeks of treatment.

Results: After 14 weeks of TNF α blockade treatment, there was a significant increase in levels of total cholesterol (5.08 ± 1.20 vs. 4.73 ± 1.12 mmol/l; p=0.014) and HDL cholesterol (1.61 ± 0.47 vs. 1.47 ± 0.35 mmol/l; p=0.008), but no resulting change in the atherogenic index (3.43 ± 1.13 vs. 3.35 ± 0.93; p=0.879). There was also no change in concentrations of triglycerides (1.33 ± 1.22 vs. 1.27 ± 0.98 mmol/l; p=0.794) and LDL cholesterol (3.15 ± 0.99 vs. 2.91 ± 0.93 mmol/l; p=0.248). TNF alpha inhibitor treatment was followed by a significant improvement in all disease activity parameters: VAS pain or VAS disease activity, BASDAI or BASFI, and systemic inflammation. Sub-group analysis showed that monoclonal antibodies increased total and LDL cholesterol levels but did not change the atherogenic index. Conversely, 14 weeks of etanercept treatment was followed by no change in lipid profile.

Conclusion: TNF alpha inhibitors may be successful in reducing cardiovascular risk in ankylosing spondylitis, as in RA, but not by affecting lipid profile. However, we lack sufficient documented evidence, and long-term investigations are needed to define the possible protective mechanisms of TNF-alpha inhibitor treatment in spondylarthropathies.

Disclosure: S. Mathieu, None; **C. Gibert**, None; **J. J. Dubost**, None; **J. M. Ristori**, None; **M. Soubrier**, None.

1772

Identifying Cases of Psoriatic Arthritis in Electronic Medical Records Using Random Forests and Natural Language Processing.

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Purpose: The objective of the current study was to apply reproducible strategies to identify psoriatic arthritis (PsA) cases in an electronic database, and to determine the value of using natural language processing in addition to coded clinical data to predict case status.

Method: An outpatient and inpatient electronic database including electronic notes, lab reports, and billing codes for >1,350,000 patients was searched and 2318 individuals with at least one ICD-9 or billing code for PsA identified. From these, 550 were randomly selected and their records reviewed for case status using the documented opinion of a rheumatologist as the gold standard. The resulting data set was used to train random forest algorithms and create a prediction rule to apply to the remaining 1768 cases. Thirty-one predictors were extracted electronically for all 2318 patients, 16 from electronic notes using natural language processing (NLP) and 15 from coded clinical data. Three algorithms were trained in the subset of 550 reviewed patients using coded predictors only, NLP predictors only, and all available predictors. The algorithm with the largest area under the receiver operator curve (ROC) was used to generate a prediction rule. A cut-point was selected with the goal of achieving a 90% positive predictive value (PPV) with the highest possible predicted sensitivity based on the 550 reviewed records. The prediction rule based on that cut-point was applied to the remaining 1768 charts, and validated by reviewing a random sample of 300 patients from among those predicted to have PsA.

Results: The PPV of a single PsA code was 57% (95%CI 55%-58%). The area under the ROC curve of the algorithm using combined coded and NLP predictors was the largest of the three algorithms generated (figure 1), and was larger than for coded predictors alone (p=0.0007). The prediction rule based on all coded and NLP predictors had a predicted PPV of 90% (95%CI 86%-93%) and predicted sensitivity of 87% (95%CI 83%-91%) based on the training dataset. Among the remaining 1768 cases, the prediction rule classified 851 as having PsA. A review of 300 cases randomly selected from the predicted PsA group showed a validated PPV of 93% (95%CI 90%-96%) for the final prediction rule.

Conclusion: Random forests can be applied to electronic medical record data to reliably identify cases of psoriatic arthritis. Adding NLP predictor variables to readily available coded information increased the area under the curve for the prediction rule.

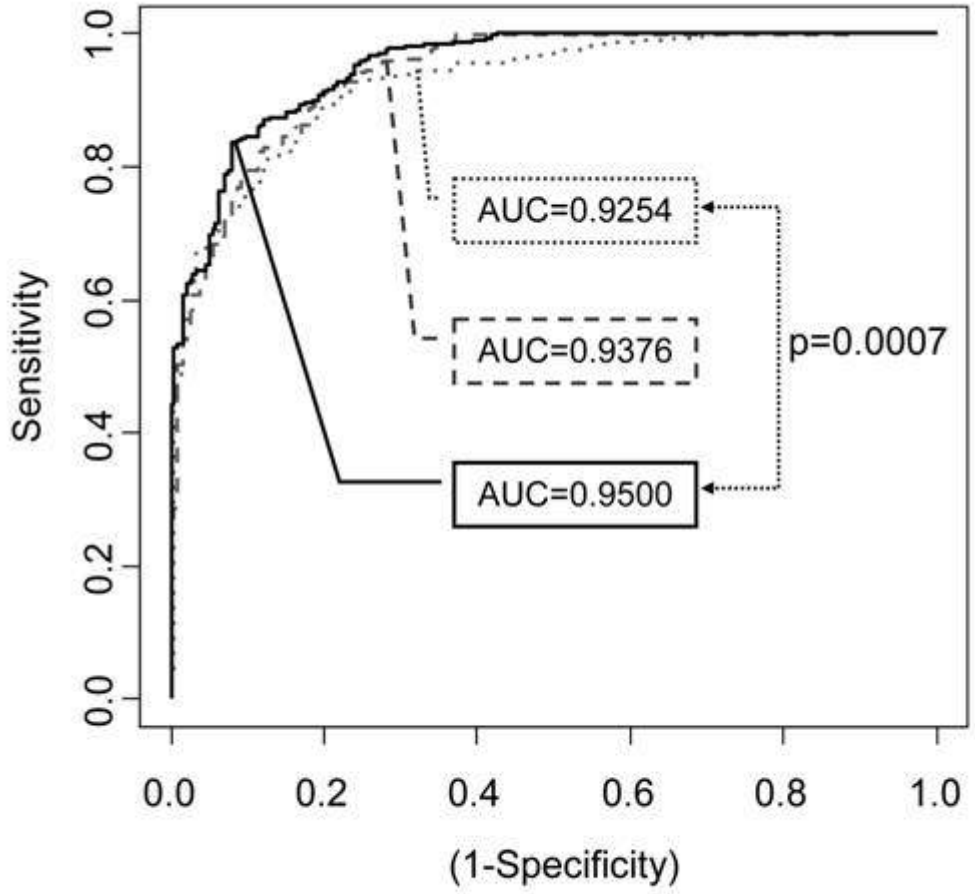

Figure 1 – ROC curves for random forest algorithms based on coded data only (dotted line), NLP data only (dashed) and combined (solid).

Disclosure: T. J. Love, None; **T. Cai**, None; **E. W. Karlson**, None.

1773

Development and Preliminary Validation of A Method for Scoring Bone Proliferation in Ankylosing Spondylitis Using Magnetic Resonance Imaging by the Canada-Denmark MRI Working Group: The Can-Den SAS (Spur and Ankylosis Score). Praveena Chiowchanwisawakit[1], Mikkel Ostergaard[2], Susanne J. Pedersen[2], Robert GW Lambert[3] and Walter P. Maksymowych[3], [1]Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Copenhagen University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB

Purpose: Bone formation in patients with ankylosing spondylitis (AS) is currently assessed on lateral radiographs of the lumbar and cervical spine using the mSASSS scoring method because the thoracic spine is not clearly visualized on radiographs. Further, detection of bone formation by the mSASSS is limited to the anterior margins of the vertebral endplates. MRI may provide superior detection of new bone in the thoracic spine and within intervertebral discs. We aimed to conduct preliminary validation of a new method for scoring bone formation throughout the spine of patients with AS using MRI.

Method: The scoring method is based on assessment of two principal bone lesions observed on sagittal slices using T1-weighted sequences, bone spurs and ankylosis. A bone spur is defined as bright (marrow) signal on T1W extending from the vertebral endplate towards the adjacent vertebra. Ankylosis is defined as bright (marrow) signal on T1W extending from a vertebra and being continuous with the adjacent vertebra. Lesions are scored dichotomously (present/absent). Each lesion is assessed at anterior and posterior vertebral corners on central (i.e. including the spinal canal) sagittal slices. Bone formation at non-vertebral corner locations is assessed on both central and lateral slices (i.e. do not include the spinal canal and the pedicle is continuous between vertebral body and posterior elements). By analogy with the mSASSS a bone spur is assigned a score of 2 while intervertebral ankylosis is assigned a score of 6. The maximal score per discovertebral unit is set at 12. Bone lesions were independently recorded from lower C2 to the upper sacrum of 20 AS patients by 4 readers after a feasibility exercise. Reliability was assessed by intra-class correlation coefficient (ICC).

Results: The mean (SD) (range) score for bone formation per patient was 40.3 (31.5) (6.5-126.5). Overall reliability for the total spine score amongst all 4 readers was excellent (ICC (95%CI) = 0.93 (0.79-0.98)) and was very good (cervical spine ICC = 0.85) to excellent (thoracic and lumbar spine ICC = 0.91 and 0.96, respectively) for spinal segment scores. ICC values for inter-reader pairs was also very good to excellent for thoracic and lumbar segments while good for the cervical spine.

Inter-reader pairs	**C-spine**	**T-spine**	**L-spine**	**Total**
Readers 1 & 2	0.63 (0.03, 0.85)	0.90 (0.76, 0.96)	0.80 (0.48, 0.92)	0.87 (0.68, 0.95)
Readers 1 & 3	0.88 (0.70, 0.95)	0.77 (-0.21, 0.94)	0.97 (0.92, 0.99)	0.88 (0.05, 0.97)
Readers 1 & 4	0.79 (0.43, 0.92)	0.93 (0.83, 0.97)	0.94 (0.85, 0.98)	0.92 (0.76, 0.97)
Readers 2 & 3	0.72(0.30, 0.89)	0.78 (-0.23, 0.94)	0.88 (0.50, 0.96)	0.81 (-0.21, 0.95)
Readers 2 & 4	0.72 (0.31, 0.89)	0.95(0.86, 0.98)	0.92 (0.79, 0.97)	0.95 (0.87, 0.98)
Readers 3 & 4	0.70 (0.04, 0.89)	0.74 (-0.25, 0.93)	0.97 (0.89, 0.99)	0.81 (-0.20, 0.95)
Mean ICC (range)	**0.74 (0.63, 0.88)**	**0.85 (0.74, 0.95)**	**0.91 (0.80, 0.97)**	**0.87 (0.81, 0.95)**

ICC (95% CI) values

Conclusion: The CanDen SAS reliably scores bone proliferation in all regions of the spine in patients with AS.

Disclosure: P. Chiowchanwisawakit, None; **M. Ostergaard**, None; **S. J. Pedersen**, None; **R. G. Lambert**, None; **W. P. Maksymowych**, None.

1774

How Is the New Ankylosing Spondylitis Disease Activity Score (ASDAS) Related to Different Aspects of Health-Related Quality of Life? – A Comparison with SF-36 in a Longitudinal Study of Spondyloarthritis Patients Treated with TNF-α Inhibitors.

Susanne J. Pedersen[1], Inge J. Sørensen[2], Ole R. Madsen[3], Niels Tvede[4], Michael S. Hansen[3], Gorm Thamsborg[5], Lis S. Andersen[6], Ole Majgaard[2], Anne Gitte Loft[7], Jon Erlendsson[8], Karsten Asmussen[9], Annette Hansen[10] and Mikkel Østergaard[11], [1]University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark, [2]Hvidovre, [3]Gentofte, [4]Rigshospitalet, [5]Glostrup, [6]Graasten, [7]Vejle, [8]Horsens, [9]Bispebjerg, [10]Gentofte, Gentofte, [11]Hvidovre and Gentofte, Denmark

Purpose: Recently, ASAS has proposed ASDAS as a new disease activity score for patients with ankylosing spondylitis. We investigated ASDAS in relation to the generic quality of life questionnaire Short-Form Health Survey (SF-36) in patients with spondyloarthritis (SpA) treated with tumor-necrosis-factor-alpha (TNF-α) inhibitors.

Method: ASDAS (0.121 x back pain + 0.058 x duration of morning stiffness + 0.110 x patient´s global assessment + 0.073 x peripheral pain/swelling + 0.579 x Ln(CRP+1) (1)), conventional clinical measures of disease activity and SF-36 were compared in a longitudinal multi-center study of 60 SpA patients (48 men, 12 women, median age 40 years (range 21-62)) treated with TNF-α inhibitors (infliximab (n=41), etanercept (n=13), adalimumab (n=6)).

Results: Patients with high ASDAS disease activity (ASDAS>4.5) (1) at baseline (n=15) had significantly lower scores for Physical Functioning (median 22.5 (range: 13.8-35) v. 65 (40-78)), Bodily Pain (12.0 (0-22) v. 41.0 (22-51)) and Physical Component Scale (22.6 (15.7-26.1) v. 34.4 (26.8-39.2)) (all p<0.001) compared with patients with moderate disease activity (ASDAS≥1.9 but ≤4.5) (n=41). No patients had low ASDAS (<1.90).

Table 1 shows the correlations between SF-36 subscales and summery scales, ASDAS, BASDAI and BASFI. ASDAS, BASDAI and BASFI correlated significantly and to a comparable extent with physical aspects of SF-36, whereas ASDAS was less correlated with mental aspects of SF-36 than BASDAI and BASFI.

	Baseline ASDAS (n=56)	Baseline BASDAI (n=60)	Baseline BASFI (n=60)	Δweek 0-22	ΔASDAS week 0-22 (n=47)	ΔBASDAI week 0-22 (n=53)	ΔBASFI week 0-22 (n=53)
Physical Functioning	-0.58***	-0.67***	-0.75***	ΔPF	-0.58***	-0.60***	-0.70***
Role Physical	-0.20	-0.33*	-0.39**	ΔRF	-0.50**	-0.50***	-0.52***
Bodily Pain	-0.67***	-0.68***	-0.62***	ΔBP	-0.69***	-0.70***	-0.61***
General Health Perception	-0.37**	-0.30*	-0.38*	ΔGHP	-0.41**	-0.34*	-0.51***
Vitality	-0.35**	-0.51***	-0.42**	ΔVI	-0.59***	-0.76***	-0.62***
Social Functioning	-0.26	-0.50***	-0.46***	ΔSF	-0.35*	-0.56***	-0.54***
Role Emotional	-0.13	-0.34*	-0.29*	ΔRE	-0.29	-0.35*	-0.37**
Mental Health	-0.23	-0.34*	-0.29*	ΔMH	-0.52***	-0.47**	-0.60***
Physical Component Scale	**-0.55*** **	**-0.52*** **	**-0.58*** **	**ΔPCS**	**-0.69*** **	**-0.67*** **	**-0.66*** **
Mental Component Scale	**-0.14**	**-0.32***	**-0.23**	**ΔMCS**	**-0.29**	**-0.47*** **	**-0.50*** **

Spearman rank correlation coefficients: p<0.05*; p<0.01**; p<0.001***

Conclusion: ASDAS appears more exclusively related to patient´s perception of physical health compared with BASDAI and BASFI. ASDAS may therefore be a better measure of disease activity, whereas BASDAI and BASFI also reflect aspects of mental health and social functioning.

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1775

European Ankylosing Spondylitis Infliximab Cohort (EASIC): Safety of Longterm Therapy with Infliximab in Patients with Ankylosing Spondylitis (AS). Frank Heldmann[1], Jan Brandt[2], Jürgen Braun[1] and EASIC, [1]Centre of Rheumatology, Herne, Germany, [2]Berlin, Germany

Purpose: The knowledge on longterm safety of anti-TNF therapy is rather limited so far. This trial studies the longterm safety of treatment with infliximab in patients who took part in EASIC, a 2-year open label extension trial.

Method: All 149 European AS patients who took part in ASSERT were asked to continue with EASIC 1.3 ± 0.9 years after ASSERT. 103 patients (69%) from 6 European countries were included in the trial, 89 had been treated with infliximab between the two trials (EASIC group 2) and 14 had not (group 1). Patients of group 2 and 9 patients of group 1 continued infliximab during EASIC, 5 patients of group 1b were only followed up. Patients were examined and treated every 4-12 weeks. All adverse events (AE), all serious adverse events (SAE) and all drop-outs were analyzed.

Results: 88 of 103 patients (85.4%) showed AEs during EASIC, 77 patients (87.5%) had more than one AE. There was a total of 545 AEs of whom 47.2% were infections. 76 patients (73.8%) had infections and 55 (53.4%) showed more than one infection. Of the total of 257 infections, 178 (69.3%) were respiratory and ear infections. The other were gastrointestinal, urogenital, skin infections and other infections.

Ten patients (9.7%) had 20 infusion reactions (3.7% of all AEs) during 15 infusions. 16 of these infusion reactions occurred in 7 patients of group 1. Six of 10 patients with infusion reactions dropped out (4 due to these infusion reactions, all after reintroduction, the latest after visit 3).

There were 8 cases of uveitis in 4 patients, of whom 7 were flares and one was a new onset of uveitis. 1 patient of group 1 showed 3 flares, the other 3 patients belonged to group 2. Fourty-one dermatologic AEs occured during EASIC, 2 of these were established cases of psoriasis and 3 cases of herpes zoster. One worsening of Crohn's disease was reported.

We observed 12 SAEs during EASIC, 9 of those were considered to be unrelated to infliximab. The 3 remaining cases were labelled as possibly related to the drug. One of these 3 SAEs was a pneumonia, one a chronic sinusitis that required surgical intervention. The third SAE was a diverticulitis with colon perforation which required partial colon resection and enterostomy, complicated by impaired wound healing. Two patients dropped out due to SAEs, one was this last case of diverticulitis, one an unrelated intraspinal calcification.

A total of 81 patients (78.6%) completed the trial, 22 (21.4%) dropped out. Of these 22 drop-outs 6 were attributable to AEs (4 to infusion reactions) and 4 due to lack of efficacy. The table summarizes the distribution of AEs of interest between the patient groups.

	Total	Group 1	Group 2
Number of AEs	545	70	475
Patients with AEs	88	13	75
Infections	257	27	230
Serious infections	3	0	3
Tuberculosis	0	0	0
Malignancies	0	0	0
Uveitis	8	3	5
Infusion reactions	20	16	4

Conclusion: Infliximab was well tolerated by the patients taking part in EASIC. Infections were the most common adverse events. Less than 10% of the patients (3.4% of patients in group 2) developed infusion reactions. Overall, infliximab was well tolerated and safe for AS patients over about 5 years.

Disclosure: F. Heldmann, None; **J. Brandt**, None; **J. Braun**, Abbott Laboratories, 2, Centocor, Inc., 2, Wyeth Pharmaceuticals, 2 .

1776

Thalidomide Delays the Rate of Relapse in Ankylosing Spondylitis After Discontinuing Etanercept Treatment. Xiaohu Deng, Feng Huang and Jianglin Zhang, Chinese PLA General Hospital, Beijing, China

Purpose: To determine whether thalidomide can delay relapse after discontinuing the treatment of etanercept in ankylosing spondylitis (AS) and to investigate the predictors of the relapse.

Method: One hundred and twenty male patients with active AS were enrolled to a randomized, double-blind, and placebo-controlled clinical study and treated with etanercept 50mg/wk for 12 weeks. BASDAI, BASFI, BASMI, patient's global assessment (PGA) VAS, nocturnal spinal pain VAS, global spinal pain VAS, morning stiffness, enthesitis indices, total swollen and tender joint counts as well as biochemistry and safety profiles were taken at baseline and at week 12. One hundred and five of them attained an ASAS20 response at week 12. Etanercept was discontinued. These 105 patients were then randomly assigned to an open study to receive either thalidomide 150mg/night, or sulfasalazine (SSZ) 2.0g/day, or non-steroidal anti-inflammatory drugs (NSAIDs) only. All patients were followed monthly for BASDAI, BASFI, PGA and spinal pain VAS. A Kaplan-Meier survival analysis was used to calculate the probability of relapse which is defined by either increase of BASDAI of 2 or more compared to the lowest point, or alternately BASDAI returning to at least of 80% of baseline value before etanercept therapy. Cox proportional hazards regression analysis was used to identify possible predictors of relapse.

Results: One hundred patients completed the follow-up for up to 12 months, with a mean follow-up time 5.1 months. Thirty patients were treated with thalidomide, 33 patients with SSZ and 37 patients with NSAIDs only. At the end of follow-up, 79 patients (79.0%) relapsed. The mean relapse time was 3.2±2.0 months, with the shortest time of relapse 2 weeks. The percentage of patients who relapsed in the thalidomide group was 60.0%, much lower than SSZ group (84.8%) and NSAIDs group 89.2% (P=0.0265 and 0.0053 respectively). No difference was found between the relapse rates of SSZ and NSAIDs only group (P=0.58). In this study, thalidomide was safe and well tolerated. The most frequently reported adverse effects were drowsiness, increased dandruff, constipation and dry mouth. These adverse effects were mild in severity. Multivariate regression analysis revealed that at the point of discontinuing etanercept, the predictors of a early relapse were PGA ≥8 (P=0.0138), higher spine inflammation score (defined as the average of the last 2 VAS scores in the BASDAI concerning morning stiffness intensity and duration) ≥6.4 (P=0.0026) and CRP > 0.8mg/dl (P=0.0425).

Conclusion: Though relapse was common after discontinuing etancercept, thalidomide was more efficacious than SSZ or NSAIDs alone in preventing relapse. High PGA, spine inflammation score and CRP level at baseline predict early disease relapse.

Disclosure: X. Deng, None; **F. Huang**, None; **J. Zhang**, None.

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Assessment of Ankylosing Spondylitis Criteria in Chronic Low Back Pain Patients with Vertebral Endplate Modic 1 Signal Changes. Christelle Nguyen[1], Imad Bendeddouche[1], Katherine Sanchez[1], Marylène Jousse[1], Agathe Papelard[1], Antoine Feydy[2], Michel Revel[1], Serge Poiraudeau[1] and François Rannou[1], [1]Rehabilitation Department, Cochin Hospital, Paris-Descartes University, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, [2]Department of Radiology B, Cochin Hospital, Paris-Descartes University, AP-HP

Purpose: Chronic low back pain (CLBP) patients with vertebral endplate Modic 1 signal changes on lumbar magnetic resonance imaging (MRI) have been reported to display clinical features that could mimic back pain of inflammatory origin, especially back pain related to ankylosing spondylitis (AS). We aimed to assess whether CLBP patients with vertebral endplate Modic 1 signal changes on MRI fulfilled criteria for AS.

Method: Between April and September 2008, all patients (n = 314) referred to a tertiary care physical medicine and rehabilitation department in France were consecutively screened. 185 hospitalized for common CLBP were prospectively assessed. Forty patients (13 males) fulfilling inclusion criteria were consecutively enrolled, and included in 2 groups according to the MRI findings (Modic 1, n = 15 and non-Modic 1, n = 25). MRI were assessed independently by a panel of 2 spine specialists and a radiologist. Human leukocyte antigen (HLA)-B27 antigen status was evaluated in one laboratory. Recording of clinical parameters, fulfilment of Amor (AC) and clinical and radiological modified New York criteria (mNYC) were performed. All assessors were blinded to HLA-B27 antigen status.

Results: Whatever the Modic group, no patient fulfilled the AC and mNYC, and mean total scores were comparable (3 ± 2 [range 0-22; p = 0.977], 1 ± 1 [range 0-3; p = 1.000], and 0 ± 0 [range 0-1; p = 1.000] for AC and clinical and radiological mNYC, respectively). HLA-B27 status was similar in both groups (n = 2 [13%] vs. n = 0 [0%], p = 0.135).

Conclusion: CLBP patients with Modic 1 vertebral endplate signal changes on lumbar MRI do not fulfil widely used and validated criteria sets for AS. CLBP associated with Modic 1 signal changes on lumbar MRI is a clinical entity distinct from AS.

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1778

Soluble Biomarkers Predict Response to Anti-Tumour Necrosis Factor (TNF) Therapy in Psoriatic Arthritis (PsA). Vinod Chandran[1], Hua Shen[2], Remy Pollock[1], Fawnda Pellett[1], Catherine T. Schentag[1], Richard J. Cook[2] and Dafna D. Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON

Purpose: Soluble biomarkers for PsA have been identified. Our purpose was to identify biomarkers associated with response to therapy with anti-TNF agents in patients with active PsA.

Method: The study was conducted at a large observational PsA clinic where patients are assessed according to a standard protocol every 6 months and serum samples are collected and stored once a year at the time of clinical assessment. 40 patients with active PsA who had serum samples collected prior to treatment with anti-TNF agent and after at least 3 months of therapy were identified. Patients were classified as anti-TNF responders if actively inflamed joint count (AJC) was <3, swollen joint count (SJC) was 0 and PASI score was <4 at the time when the second sample was collected. Those not achieving this state were classified as partial responders. The following biomarkers were tested using commercially available ELISA kits: Tumour Necrosis Factor Super Family member 14 (TNFSF14 pg/mL), Matrix Metalloproteinase-3 (MMP-3 ng/mL) , Receptor Activator for Nuclear Factor κB Ligand (RANKL pmol/L), Osteoprotegrin (OPG pg/mL), Cartilage oligomeric protein (COMP ng/mL), C-propeptide of type II collagen (CPII ng/mL), collagen fragment neoepitopes Col2-3/4(long mono) (C2C ng/mL) and Col2-3/4(short) (C1-2C ug/mL), Aggrecan 846 epitope (CS-846 ng/mL) and highly sensitive C - reactive protein (hsCRP mg/L). Paired t-test and logistic regression was used to detect changes in biomarker levels with treatment and association with anti-TNF responder status.

Results: The 40 patients (28 males, mean age 44 years, psoriasis duration 17 years, PsA duration 12 years) had mean Actively inflamed Joint Count of 12, Swollen Joint Count of 6, and PASI score of 6.4 pre-treatment. After a mean treatment period of 11 months with anti-TNF agents (Etanercept 28, Adalimumab 6, Golimumab 4, Infliximab 2), 29 were classified as anti-TNF responders and 11 as partial responders. There was a significant decline in the serum levels of hsCRP ($p<0.001$), MMP-3 ($p<0.001$) and the ratio CPII/C2C ($p=0.039$), whereas there was an increase in RANKL ($p=0.002$) and C2C ($p=0.021$). Only reduction in MMP-3 correlated with reduction in hsCRP (correlation coefficient 0.43, $p=0.005$). Multivariate logistic regression showed that baseline level of MMP-3 was associated with attaining responder status [Odds ratio (OR) 1.067 for each one unit increase, 95% CI (1.002,1.138), $p=0.045$]. A reduction in MMP-3 levels increased the odds of achieving response (OR 1.213 for each one unit increase, 95% CI (1.019,1.445), $p=0.030$), whereas a reduction in COMP decreased it (OR 0.587, for each 100 units increase, 95% CI (0.354, 0.973), $p=0.039$).

Conclusion: Baseline as well as reduction in serum MMP-3 levels is associated with response to anti-TNF therapy in patients with PsA. Decline in MMP-3 levels correlate with decline in hsCRP.

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1779

Soluble Biomarkers in Psoriatic Disease: Differences Between Psoriasis and Psoriatic Arthritis. Vinod Chandran[1], Jonathan Edwin[1], Hua Shen[2], Fawnda Pellett[1], Sutha Shanmugarajah[1], Catherine T. Schentag[1], Cheryl Rosen[1], Richard J. Cook[2] and Dafna D. Gladman[1], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON

Purpose: There is high prevalence of PsA in patients with psoriasis seen in dermatology clinic. Biomarkers may be helpful in screening psoriasis patients for PsA. Our purpose was to identify serum biomarkers for psoriasis and PsA.

Methods: Fifty-two patients with psoriasis and 26 healthy controls were recruited. Psoriasis was diagnosed by a dermatologist. 26 of these patients had PsA satisfying CASPAR classification criteria, and in the remaining 26 PsA was excluded by a rheumatologist. Patients with psoriasis and PsA were group matched for age, sex and psoriasis duration, while controls were matched for age and sex. Blood samples were drawn at the time of assessment and serum was analyzed for the following: Interleukin (IL)-12, IL-12 p40, IL-17 (all pg/mL), Tumour Necrosis Factor Super Family member 14 (TNFSF14 pg/mL), Matrix Metalloproteinase (MMP)-3 (ng/mL), Receptor Activator for Nuclear Factor κB Ligand (RANKL-pg/L), Osteoprotegrin (OPG-pg/mL), Cartilage oligomeric protein (COMP-ng/mL), C-propeptide of type II collagen (CPII-ng/mL), collagen fragment neoepitopes Col2-3/4(long mono) (C2C-ng/mL) and Col2-3/4(short) (C1-2C ug/mL), and highly sensitive C - reactive protein (hsCRP mg/L). Data were analyzed using logistic regression and Receiver Operating Characteristic curves.

Results: The 52 patients with psoriatic disease had a mean age of 46 years and psoriasis duration of 16.8 years. Compared to controls, increased serum levels of RANKL [Odds ratio per unit increase (OR) 1.004, 95% CI 1.000,1.008], TNFSF14 (OR 1.007, 95% CI 1.000,1.013), MMP-3 (OR 1.156, 95% CI 1.023,1.306) and COMP (OR 1.001 95% CI 1.000,1.002) independently associated with psoriatic disease ($p<0.05$) in a multivariate reduced full. The 26 PsA patients (mean PsA duration 13 years, actively inflamed joint count 16, swollen joint count 5) were then compared to 26 patients who had psoriasis alone, and to controls. hsCRP, OPG, TNFSF14, MMP-3, CPII/C2C were different between the 3 groups. Increased levels of hsCRP (OR 2.057 95% CI 1.127, 3.754), OPG (OR 1.011 95% CI 1.002,1.021), MMP-3 (OR 1.275 95% CI 1.018,1.597) and the ratio CPII/C2C (OR 4.762, 95% CI 1.352,16.767) were independently associated with PsA ($p<0.03$). ROC analysis using this reduced model showed an area under the curve (AUC) of 0.904. The full model had an AUC of 0.941

Conclusion: This pilot study indicates that hsCRP, OPG, MMP-3 and the ratio CPII/C2C are biomarkers for PsA in patients with psoriasis.

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Infliximab Plus Methotrexate Significantly Improves Synovitis and Psoriatic Lesions in Methotrexate Naïve Psoriatic Arthritis (PsA) Patients: Results of the RESPOND† Trial. H. Raffayova[1], N. Kungurov[2], A. Kubanova[3], A. Baranauskaite[4], A. Venalis[5], L. Helmle[6], S. Srinivasan[7] and E. Nasonov[8], [1]National Inst. for Rheumatology Diseases, Piestany, Slovak Republic, [2]Urals Dermato-venerology Inst., Yekaterinburg, Russia, [3]Central DermatoVenerology Inst., Moscow, Russia, [4]Kaunas Medical Univ. Hospital, Kaunas, Lithuania, [5]Vilnius Univ. Hospital, Vilnius, Lithuania, [6]Schering-Plough Corp., Budapest, Hungary, [7]Schering-Plough Corp., Kenilworth, NJ, [8]Institute of Rheumatology, Moscow, Russia

Purpose: To assess the efficacy of infliximab (IFX) + methotrexate (MTX) vs MTX alone in MTX naïve patients with active, polyarticular PsA. This study is the first to assess anti-TNF + MTX vs MTX alone in early, MTX-naïve active polyarticular PsA.

Method: Patients ≥18 years of age with active PsA (≥5 swollen and tender joints, + one of the following; ESR≥28 mm/hr, CRP≥15 mg/L, morning stiffness≥45 min.) were included in this randomized, prospective, open-label, multi-center, multi-national study. Patients were naïve to MTX, anti-TNF agents, and could not be on DMARDS. Patients were randomized (1:1) to IFX (5 mg/kg) intravenous at week 0, 2, 6, and 14 + MTX (15 mg/week) or MTX (15 mg/week) alone. Study visits were at week 0, 2, 6, 14, and 16. The primary assessment was the proportion of ACR20 improvement at week 16. The study complied with Good Clinical Practices.

Results: 57 patients were randomized in the IFX + MTX group (48.2% male, mean age 40.1 years, mean disease duration 2.8 years)‡ and 58 in the MTX group (61.1% male, mean age 42.3 years, mean disease duration 3.7 years) ‡. Robust differences in clinical response of the articular and skin component favored the IFX + MTX group (table).

Baseline Characteristics‡ and Response‡	IFX + MTX	MTX
Tender joint count, mean (SD)	21.1 (13.32)	20.1 (11.24)
Swollen joint count, mean (SD)	15.1 (10.07)	14.3 (9.47)

CRP, mean (SD)	29.0 (38.83)	25.3 (26.11)
DAS28, mean (SD)	5.16 (1.074)	5.07 (1.178)
PASI, mean (SD)	8.27 (10.197)	11.62 (12.535)
ACR 20/50/70 (%)	86.3/72.5/49.0	66.7º/39.6¹/18.8¹
Good/Moderate DAS28 Response (%)	82.4/15.7	33.3/39.6²
DAS28 remission (%)	68.6	29.2²
PASI 50%/75%/90% (%)	100.0/97.1/70.6	80.0¹/54.3²/28.6¹

The most commonly reported adverse event was increased levels of alanine aminotransferase (~10% in both groups). There were 2 serious adverse events in the IFX+MTX group, 1 infusion reaction with dyspnoea and erythema and 1 latent tuberculosis reactivation. [Sign. levels for table ºp<0.05, ¹p<0.01, ²p<0.0001]

Conclusion: Early MTX naïve PsA patients with active disease achieved significantly greater ACR20 response rates and ≥75% improvement in PASI scores when treated with IFX + MTX compared to MTX alone. †(**RE**micade **S**tudy in **P**sA patients **O**f methotrexate-**N**aive **D**isease) ‡ITT analysis set.

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Sustained Clinical Response in Psoriatic Arthritis Patients Treated with Anti-TNF Agents: A 5-Year Long-Term Study. Ioanna Saougou[1], Theodora E. Markatseli[1], Paraskevi V. Voulgari[2], Charalampos Papagoras[3] and Alexandros A. Drosos[4], [1]Trainee in Rheumatology, Ioannina, Greece, [2]Assistant Professor of Rheumatology, Ioannina, Greece, [3]Fellow in Rheumatology, Ioannina, Greece, [4]Ioannina Medical School, Ioannina, Greece

Purpose: To investigate the efficacy, safety and drug discontinuation in patients with psoriatic arthritis (PsA) treated with anti-tumor necrosis factor (TNF) agents.

Method: Fifty-five patients with PsA were included in this prospective open label study. All patients had active disease which was included: tender or swollen joint count ≥6, Psoriasis Activity Severity Index (PASI) score ≥10 and erythrocyte sedimentation rate ≥28 mmHg/H or C-reactive protein ≥10 mg/l. They were all refractory to at least 2 disease modifying anti-rheumatic drugs. Thirty were treated with infliximab, while 25 with etanercept. Infliximab (5 mg/kg/body weight) was given intravenously at weeks 0, 2, 6 and every 8 weeks thereafter for a period of 5 years, while etanercept was given subcutaneously (25 mg) twice a week for the same period of time. Data concerning anti-TNF therapy efficacy, tolerability, concomitant therapy, adverse events and drug discontinuation were recorded. The percentage of patients who achieved the Psoriatic Arthritis Response Criteria (PsARC) and the improvement of PASI were also recorded as well as the clinical improvement according to the American College of Rheumatology (ACR) criteria and the Disease Activity for 28 joint indices score (DAS-28).

Results: After 5 years of treatment with infliximab, PsARC was achieved by 60% (18/30), PASI70 by 66.7% (20/30), PASI90 by 63.3% (19/30), while ACR50 by 56.7% (17/30) and ACR70 by 33.3% (10/30) of the patients. On the other hand, after 5 years of treatment with etanercept, PsARC was achieved by 64% (16/25), PASI70 and PASI90 by 68% (17/25), while ACR50 by 56% (14/25) and ACR70 by 32% (8/25). A significant improvement was also noted in the DAS-28 score throughout the 5 years of the study in both groups. Five patients were increased the dose of infliximab and 3 of them have shortened the interval infusion. Overall, 13 patients treated with infliximab and 6 treated with etanercept were withdrawn from the study, mostly because of adverse events. At the end of the 5 years of treatment, the survival of infliximab was 56.7% , while the survival rate for the etanercept was 76%.

Conclusion: Both anti-TNF blockers were effective, safe and well-tolerated in patients with PsA. The clinical improvement was maintained through the 5 years of the study with sufficient infliximab and high etanercept survival rate.

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1782

Entheses Ultrasound (US) Evaluation in Early Psoriatic Arthritis (ePsA) Patients Is Independent of Psoriasis Extension and Clinics.

Francesca Bandinelli[1], Francesca Bartoli[1], Diletta Bonciani[2], Francesca Prignano[2], Sergio Generini[1], Torello Lotti[2], Antonio Candelieri[3] and Marco Matucci-Cerinic[4], [1]University of Florence, Italy, Florence, Italy, [2]University of Florence, Florence, Italy, [3]University of Calabria, Italy, [4]University of Florence, Firenze, Italy

Purpose: To investigate the presence of lower limb entheseal abnormalities in patients with early psoriatic arthritis.

Method: 92 patients with early PsA (ePsA), defined as inflammatory joint symptoms and signs with a duration < 1 year , with psoriasis (69), past psoriasis (2) and without psoriasis (21), diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR) [1] were consecutively studied with US (My Lab 25 XVG US Esaote 7-18 MHz linear array transducer) of Achilles, quadriceps, patellar entheses and plantar aponeurosis.

Patients (51 female and 41 male, 51±15 years old) were scored according to the 0-36 Glasgow Ultrasound Enthesitis Scoring System (GUESS)[2] and with total Power Doppler signal (calculated with semiquantitative system, score 0-3), with total Psoriasis Area and Severity Index (PASI) and with Maastricht Ankylosing Spondylitis Enthesitis Index (MASES). We studied the correlation between GUESS and Power Doppler with clinical characteristic of patient (PASI, MASES, pain and fatigue visual analogic scale -VAS-, duration of symptoms).

Results: Intraobserver agreement was high (interclass correlation coefficient 0,99). All patients presented almost one alteration on tendons (GUESS >1). Mean GUESS and Power Doppler score were respectively in patients 6,6±3,3 and 0,95±1,5. The GUESS score was not correlated with duration of symptoms, pain and fatigue VAS, morning stiffness (correlation coefficient of Spearman >0,05).

US revealed the presence of enthesophytes, erosions, bursitis, thickness of tendons, in different percentage (table 1).

Major features		
Enthesophytes	85%	
Erosions	6%	
Bursitis	27%	
Thickness of tendon (1)	Quadriceps (>6,1 mm)	40%
	Proximal rotuleus (>0,4 mm)	74%
	Distal rotuleus (>0,4 mm)	60%
	Achilleon (>5,29 mm)	30%
	Plantar fascia (>4,4 mm)	11%

Conclusion: Entheseal abnormalities are present in all patients in ePsA. US is a reliable tool to disclose entheseal involvement and more available than clinical examination and symptoms.

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Markers of Bone Formation Are Increased in Psoriatic Arthritis Compared to Rheumatoid Arthritis at Baseline and Increase Further After 3 Years of Anti-TNF-α Therapy. Agnes Szentpetery[1], Chin Teck Ng[1], Barbara F. Murray[2], Jennifer J. Brady[2], Phil Gallagher[1], Susan Van der Kamp[1], Barry Bresnihan[1], Douglas J. Veale[1], Malachi J. McKenna[2] and Oliver FitzGerald[1], [1]St. Vincent's University Hospital, Department of Rheumatology, Dublin, Ireland, [2]St. Vincent's University Hospital, Department of Metabolism, Dublin, Ireland

Purpose: To evaluate changes in clinical responses, bone turnover markers and bone mineral density (BMD) measurements in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) prior to and 3 years after commencing anti-TNF-α therapy.

Method: RA and PsA patients were recruited following a decision to commence anti-TNF-a therapy. Clinical assessments including DAS28-CRP and HAQ were recorded. EULAR response criteria were applied. Markers of bone formation ((serum osteocalcin (OC1-49) serum procollagen type I Npropeptide (PINP) and serum bone alkaline phosphatase (bone ALP)) and of bone resorption (urine free deoxypyridinoline crosslinks (fDPD) and urine N-terminal crosslinking telopeptide of type I collagen (NTX-I)) were measured at baseline, 1 and 3 years. The results are reported as T-values. Bone density measurements (DXA) were obtained at baseline, 1 year and 3 years (spine and hips).

Results: 51 patients (28 RA, 23 PsA) out of 62 recruited completed 3 years of follow up. At baseline ESR and CRP levels were lower in PsA than RA (median ESR 10 v. 25 p=0.0017; median CRP 8.0 v. 21.5 p=0.004). DAS28 CRP level was lower in PsA at all time points during the study. After 3 years follow up DAS28 CRP and HAQ were lower in both PsA and RA than at baseline (median DAS28CRP PsA 2.85 v. 5.67, RA 3.35 v. 5.925 p<0.0001) (HAQ median PsA 0.5 v. 1.125 p=0.0192, RA 0.5 v. 1.31 p=0.0002). Bone ALP was higher at baseline and at 3 years in PsA compared to RA (median bone ALP at baseline 1.42 v. -0.03 p=0.0117). After 3 years of anti-TNF-αtherapy bone ALP increased in both diseases compared with baseline (median bone ALP PsA 3.1 v. 1.42 p=0.0001, RA 1.855 v. 0.05 p= 0.0002). PINP levels were also higher in PsA good responders (PsAGR) at 3 years compared to baseline (median PINP 0.88 v. -0.59 p=0.0266). There were no significant differences observed between RA and PsA in terms of bone density measurements at the different time points. In RA BMD and T-scores were lower at 3 years compared to baseline measurements (median BMD hip 0.931 v. 0.933 p=0.0436, median T-score hip -0.3 v. -0.1 p=0.0377; median BMD spine 0.97 v. 1.007 p=0.0325, median T score spine -0.9 v. -0.5 p=0.0447). In contrast, BMD and T-scores increased in PsAGR in the lumbar spine (median BMD 1.03 v. 0.96 p=0.0015; median T-score 0 v. -0.5 p=0.0039).

Conclusion: DAS28 CRP scores are higher in RA compared to PsA at all time points but clinical responses to anti-TNF-α therapy were similar in both diseases after 3 years follow up. Bone formation markers, in particular bone ALP is higher in PsA compared to RA at baseline and at 3 years but increases in both treatment groups after 3 years. Following anti-TNF-α therapy bone remodelling balance improves in both diseases with an increase in bone formation and a decrease in bone resorption. In PsA but not in RA axial bone density loss is reversed after 3 years of anti-TNF-α therapy.

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The Extended SPARCC MRI Spinal Inflammation Score: Assessment of Inflammation in Posterior Elements of the Spine Substantially Increases Discrimination. Walter P. Maksymowych[1], Sean M. Crowther[2], Suhkvinder S. Dhillon[2] and Robert GW Lambert[2], [1]Department of Medicine, University of Alberta, Edmonton, AB, [2]Department of Radiology, University of Alberta, Edmonton, AB

Purpose: Systematic evaluation has shown a high frequency of inflammatory lesions in the posterior elements of the spine on MRI which are responsive to treatment with anti-TNF. It is unclear whether formal scoring of these lesions enhances the performance of established MRI-based instruments for scoring inflammation in the spine. We aimed to assess the performance of the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spinal inflammation score when inflammation in posterior elements is additionally quantified.

Method: We scanned 32 patients recruited to randomized placebo-controlled trials of various anti-TNF therapies (12-24 weeks). Inflammatory lesions were detected by systematic review of consecutive sagittal STIR slices of the entire spine imaged in two halves and were recorded dichotomously (present/absent) using a custom-designed online scoring tool depicting the following posterior elements: pedicle, facet joint, processes (transverse and spinous), soft tissues. Two readers independently evaluated pre- and post-treatment films, blinded to diagnosis and time sequence, on a 3-monitor review station that permits simultaneous visualization of all spinal segments. Vertebral body inflammation was also quantified using the SPARCC MRI method for both clinical trials (the 6-DVU score: scoring limited to the 6 most severely affected disco-vertebral units) and observational studies (the 23-DVU score: all 23 DVU are scored) using an online scoring tool. Discrimination was assessed by Guyatt's effect size (ES). Convergent validity with clinical measures of disease activity was assessed using Spearman's correlation.

Results: The median number of spinal levels with inflammation in at least one posterior element per patient was 5.5 (mean (SD) = 6.7(5.3)). The spinous processes were the most commonly affected structure (median per patient = 3, mean (SD) = 3.7(2.9)). Discrimination between anti-TNF therapy and placebo was substantially enhanced when inflammation in posterior elements was scored and added to either the 6-DVU or 23-DVU scores. This was noted irrespective of whether inflammation was scored in each individual posterior element (All-PE score) or when inflammation was recorded as being present in at least one of the posterior elements at a particular spinal level (Any-PE score). Correlation with change in CRP was also superior when either the All-PE or Any-PE score was added to the SPARCC MRI 6-DVU or 23-DVU scores. No significant correlation was noted between change in BASDAI and any MRI score.

	6-DVU	**6-DVU +Any-PE**	**6-DVU + All-PE**	**23-DVU**	**23-DVU + Any-PE**	**23-DVU + All-PE**
Guyatt's ES	2.68	3.39	3.83	3.01	3.77	4.07
Correlation with CRP	0.43	0.51	0.60	0.50	0.51	0.59

Conclusion: The addition of a simple dichotomous method for scoring posterior element inflammation substantially enhances the discrimination provided by the SPARCC MRI spinal inflammation score which quantifies inflammation in the vertebral bodies. This method may be particularly valuable for proof-of-concept studies of new therapeutics in ankylosing spondylitis.

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Infliximab Withdrawal in Patients with Spondyloarthritis Who Presented Criteria of Clinical Disease Remission. An Open Study of Clinical Practise (REMINEA). V. Torrente[1], J. Gratacos[2], X. Juanola[3], R. Sanmartí[4], D. Suarez[5], M. Moreno[6] and REMINEA Group, [1]Hospital Sant Pau, Barcelona, Spain, [2]H Parc Taulí, Barcelona, Spain, [3]Hospital Universitari Bellvitge (IDIBELL), Barcelona, Spain, [4]H Clínic i Provincial, Barcelona, Spain, [5]Parc Taulí Hospital, Sabadell, Spain, [6]Parc Tauli Hospital, Sabadell, Spain

Purpose: Anti-TNF therapy (infliximab) has demonstrated good efficacy, especially in early-onset spondyloarthritis patients. However, the consequences of infliximab withdrawal in these patients are not yet determined, particularly in those who reach an excellent response.

Objective: To evaluate the percentage of patients under infliximab treatment who achieve criteria of clinical remission. To assess, after 1 year follow-up, the outcome after infliximab withdrawal in disease remission achieved patients and in the re-treated ones since they had a disease flare.

Methods: 107 patients (70%M) mean age 42 yrs (20-72) with spondylarthitis (82 with ankylosing spondylitis, 25 with undifferentiated spondylarthritis) who met criteria of anti-TNF therapy were included and treated with infliximab (5mg/Kg, 0,2, 6 and every 8 weeks infusions). The mean disease duration before treatment was 11 yrs (0.5-39), 50% of patients included had less than 10 yrs of disease evolution. Infliximab withdrawal was performed in those patients who presented persistent clinical remission (two consecutive visits, after the induction period) defined as both absence of peripheral arthritis/enthesitis and presence of a BADAI≤2 and a CRP≤0.8mg/dl. During the discontinuation treatment period (≈1yr) patients who presented a flare (BASDAI≥4) were re-treated with infliximab (5mg/Kg every 8 weeks.

Results: 36/107 patients (34%) achieved remission criteria. Remission patients compared to non-remission ones were significantly younger (39 vs 43 p=0.05) had a lesser disease evolution (9 vs 14, p=0.04) and more disease activity (CRP 3.4 vs 1.6 mg/dl, p=0.005). Over the treatment discontinuation period 21/36 patients (58%) presented a flare (62% during the first 6 months). After reintroduction of infliximab therapy 11/21 (52%) again reached clinical remission, and only 3/21 (14%) did not achieved a significant response (BASDAI≥4). No other problems associated to re-treatment were observed.

Conclusion: Infliximab as continuous therapy appears to be the best choice in this group of patients with spondylarthritis. However, we observed both high (34%) percentage of complete remission patients during 1yr follow-up, and good efficacy and safety of infliximab re-treatment in reactivated patients. In terms of cost-effectiveness, these findings seem to reinforce the infliximab withdrawal in clinical practise in patients who get persistent clinical remission.

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Achievement of a Patient Acceptable Symptom State (PASS) and of a Minimum Clinically Important Improvement (MCII) with Etanercept in Refractory Heel Enthesitis Related to Spondyloarthritis: Results of a Double Blind Placebo Controlled Study (HEEL).

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Purpose: To investigate the short-term symptomatic efficacy of etanercept in chronic heel enthesitis related to spondyloarthritis (SpA)

Method: Prospective, randomized, 12-week, placebo- controlled trial. *Study treatments*: etanercept 50 mg OW *vs* placebo. *Patients*: Adults, SpA (Amor criteria) with active and refractory heel enthesitis. *Outcome variables*: Apart from the conventional ones (*e.g.* visual pain [VAS scale 0-100], function [WOMAC function sub-scale, normalized unit 0-100]), the PASS concept was evaluated according to the following question: "*If you were to remain in the next several months as you were during the last 48 hours, would this be acceptable for you?*" and the MCII by "*Compared to when you started the study, how have you been during the last 48 hours*?" Such questions were asked at each visit after baseline. *Statistical analysis*: Time to reach a sustained PASS using the Kaplan Meier survival analysis and Log-Rank test; MCII using a GEE model.

Results: Of the 24 enrolled patients (males: 67%, age: 37±12 y, B27 positive: 71%), 12 received etanercept and 12 placebo. Groups were comparable at baseline concerning symptomatic activity of the disease (patient's global: 70±17, heel pain: 68±16, functional impairment: 47±20). Estimated percentage of patients achieving a sustained PASS after 3 months was 50% vs 0% (p=0.0168) in the etanercept and placebo group respectively and such status was achieved as soon as the first 4 weeks of therapy. Statistically significant difference between etanercept and placebo was reported for the MCII at week 12 (75% versus 22.2% patients very or moderately improved, p=0.020).

Conclusion: This study, the first one using a prospective, placebo-controlled design in patients with active and refractory heel enthesitis demonstrated a symptomatic clinically relevant and statistically significant effect of etanercept. In addition it shows the achievement of another treatment goal such as PASS and MCII, addressing "therapeutic success" at patient level

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Health-Related Quality of Life (Physical Component) in Ankylosing Spondylitis Is Independently Determined Both by Disease Activity and by Physical Function. Pedro Machado[1], Robert Landewé[2], Jürgen Braun[3], Kay-Geert Hermann[4], Benjamin Hsu[5], Daniel Baker[5] and Désirée M.F.M. van der Heijde[6], [1]Coimbra University Hospital, Coimbra, Potugal, and Leiden University Medical Center, Leiden, Netherlands, [2]University Hospital Maastricht, Maastricht, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Charité Medical School, Berlin, Germany, [5]Centocor Inc., Malvern, PA, [6]Leiden University Medical Center, Leiden, Netherlands

Purpose: Improvement in patients' quality of life is one of the ultimate goals in health care. In order to achieve that goal it is useful to understand the health concepts driving quality of life in ankylosing spondylitis (AS). Our aim was to investigate which factors determine the level of the physical component summary score of health related quality of life (QLPCS) in patients with AS.

Method: In this investigator-performed sub-analysis of the ASSERT database at baseline, in total 214 patients, representing an 80% random sample, were investigated. The Short Form 36 health survey questionnaire was used to assess QLPCS, physical function was assessed by the BASFI, spinal mobility by the linear definition of the BASMI (BASMI-lin), disease activity by the ASDAS-CRP or by the BASDAI, MRI inflammation by the ASspiMRI-a score and structural damage by the mSASSS. Correlations were performed by use of Spearman correlation analysis. Univariate regression analyses were used to examine for associations and to select the variables to enter in a linear regression analysis. C-reactive protein, disease duration, age, sex, body mass index and HLA-B27 status were also investigated. Non-normally distributed variables underwent a normalization procedure using the van der Waerden technique before entering in the linear regression analysis.

Results: QLPCS correlated moderately well with BASFI (Spearman's rho=-0.55), ASDAS (rho=-0.34) and BASDAI (rho=-0.48) and weakly with BASMI-lin (rho=-0.19) and age (rho=-0.18). In the linear regression analysis only BASFI, disease activity (either ASDAS or BASDAI) and sex remained significantly associated with QLPCS (table I). Results were similar using either ASDAS or BASDAI.

Table I: Best-fit model for QLPCS

	B (95% CI)	**Beta**	**p-value**
BASFI	-1.910 (-2.396, -1.425)	-0.501	<0.001
ASDAS	-1.450 (-2.317, -0.583)	-0.193	0.001
BASMI-lin	0.222 (-0.343, 0.787)	0.048	0.439
Age	-0.072 (-0.154, 0.010)	-0.099	0.085
Sex (male)	2.524 (0.595, 4.453)	0.144	0.011

Conclusion: Quality of life (physical component summary score) in patients with AS is independently determined both by disease activity and by physical function. Function and disease activity should be critical domains in the treatment of AS in order to maximize benefits in quality of life.

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Is Adalimumab An Efficacious Treatment for Enthesitis of the Achilles Tendon in Patients with Spondyloarthritis? Christopher Ritchlin[1], Philip Mease[2], Renee Perdok[3], Hartmut Kupper[4] and Frédéric Lavie[5], [1]University of Rochester, Rochester, NY, [2]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [3]Abbott Laboratories, Abbott Park, IL, [4]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [5]Abbott Laboratories, Rungis, France

Purpose: Adalimumab (ADA) significantly improved enthesitis for patients (pts) with ankylosing spondylitis (AS) in the ATLAS trial,[1] but the efficacy of ADA for spondyloarthritis (SpA) pts with enthesitis (including pts with peripheral SpA) has never been evaluated. This *post-hoc* analysis compared the effect of ADA vs. placebo (PBO) for enthesitis of the Achilles tendon in pts with peripheral and/or axial SpA who were enrolled in 1 of 3 different clinical trials.

Methods: ATLAS was a Phase III randomized controlled clinical trial comparing ADA with PBO in pts with AS.[1] ADEPT was a Phase III randomized controlled clinical trial comparing ADA with PBO in pts with psoriatic arthritis (PsA).[2] RHAPSODY was an open-label study assessing the effectiveness of ADA in pts with AS in typical European clinical settings.[3] In both ATLAS and ADEPT, only enthesitis of the Achilles tendon was assessed. Data from pts who had at least 1 Achilles tendon enthesitis in ATLAS and ADEPT were analyzed separately and as pooled data at available time points. Similar data from RHAPSODY were analyzed at baseline and at Weeks 2 and 12.

Results: Data from 309 pts in ATLAS (ADA, N=204; PBO, N=105), 310 pts in ADEPT (ADA, N=149; PBO, N=161), and 1,220 pts in RHAPSODY were analyzed. A greater percentage of pts with PsA in the ADEPT trial had enthesitis of the Achilles tendon than pts with AS in either the ATLAS or RHAPSODY trials (32.0%, 21.7%, and 18.4%, respectively). Results over time are presented in the table.

Patients With Enthesitis of at Least 1 Achilles Tendon at Different Time Points in ADEPT, ATLAS, and RHAPSODY

	Clinical Trial						
	ADEPT		**ATLAS**		**ADEPT+ATLAS**		**RHAPSODY**
Time Point	ADA N=149	PBO N=161	ADA N=204	PBO N=105	ADA N=353	PBO N=266	ADA N=1,220
Week 0	47 (31.5)	52 (32.5)	39 (19.1)	28 (26.7)	86 (24.4)	80 (30.2)	224 (18.4)
Week 2	47 (31.8)	54 (33.5)	NA	NA	NA	NA	98 (11.7)
Week 4	41 (27.5)	47 (30.1)	NA	NA	NA	NA	NA
Week 8	32 (21.9)	48 (31.2)	NA	NA	NA	NA	NA
Week 12	29 (20.4)[a]	52 (33.8)	26 (17.3)	9 (17.6)	55 (18.8)[a]	61 (29.8)	65 (8.1)

Data shown are n (%). [a]$p<0.05$ compared with PBO using Fisher's exact test.

NA=not applicable (enthesitis was not assessed at these time points in ATLAS or RHAPSODY).

Conclusion: These data demonstrate the efficacy of ADA on Achilles tendon enthesitis for pts with axial or peripheral SpA.

References: [1]van der Heijde D, et al. *Arthritis Rheum.* 2006;54:2136–46; [2]Mease PJ, et al. *Arthritis Rheum.* 2005;52:3279–89; [3]Rudwaleit M, et al. *J Rheumatol.* 2009;36:801–8.

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Sexual Functioning in Male Ankylosing Spondylitis Patients. Anthony So[1], Finbar (Barry) D. O'Shea[2] and R.D. Inman[2], [1]University of Toronto, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON

Purpose: Ankylosing Spondylitis (AS) is commonly associated with fatigue, pain, and stiffness, resulting in significant disability. Sexual functioning plays an important role as a contributor to quality of life factors. Sexual functioning in AS patients has not been studied extensively. This study assessed the sexual function of male AS patients and its correlation with to various measures of disease activity and severity.

Methods: The International Index of Erectile Function (IIEF) was used as a validated measure of sexual functioning, with a higher score reflecting better sexual function. Nocturnal Back Pain (NBP), Total Back Pain (TBP), Global Disease Activity (GDA), BAS-G (Bath Ankylosing Spondylitis Global score), BASDAI (BAS Disease Activity Index), BASFI (BAS Functional Index), and ASQoL (AS Quality of Life) surveys were self-administered to randomly selected AS patients. Spearman rank correlation was used to assess for correlation. Student t-test was used to compare morbidity measures between groups. P values less than 0.05 were considered significant.

Results: 27 Male AS patients were recruited, of whom 23 patients were on an anti-TNF agent and 4 were on NSAIDs. The mean age of the group was 39.6±12.2 years. 4 patients (all on an anti-TNF agent) reported no sexual activity. According to the Sexual Health Inventory for Men (SHIM), a sensitive marker for erectile dysfunction (ED) constructed from the IIEF, 10 of the 23 patients with sexual activity had ED (mild ED=6, mild-moderate ED=1, moderate ED=2 , and severe ED=1). Of the 23 patients, 3 were taking sildenafil or tadalafil, two were on anti-depressants, and one was on a β-blocker. IIEF scores negatively correlated with NBP (rho=-0.553, p=0.006), TBP (rho=-0.675, p<0.001), GDA (rho=-0.526, p=0.010), BAS-G (rho=-0.718, p<0.001), BASDAI (rho=-0.712, p<0.001), BASFI (rho=-0.612, p=0.002), and ASQoL (rho=-0.437, p=0.037). A subcomponent analysis of the IIEF demonstrated that different subcomponents correlated with different measures of morbidity. Significant differences were found between patients with and without ED in regards to NBP (p=0.01), TBP (p=0.003), GDA (p=0.013), BAS-G (p=0.003), BASDAI (p=0.001), and BASFI (p=0.001), but not ASQoL (p=0.057) nor age (p=0.172). The mean IIEF scores of patients on Biologics *vs* NSAIDs alone were 62.8±9.0 vs 38.5±11.7 respectively (p<0.001).

Conclusion: Sexual dysfunction is common in AS patients and the strongest correlation was with the degree of pain experience by the patient. Patients with ED had worse indicators of back pain severity compared to those without ED. Patients with sexual activity on biological therapy reported significantly higher IIEF scores, reflecting better sexual functioning, than those on non-biological therapy.

Disclosure: A. So, None; **F. (. D. O'Shea**, None; **R. D. Inman**, None.

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Update of the ASAS Recommendations On the Use of TNF-Blockers in Ankylosing Spondylitis. Désirée M.F.M. van der Heijde[1], Joachim Sieper[2], Walter P. Maksymowych[3], Maxime Dougados[4], Ruben Burgos Vargas[5] and Jürgen Braun[6], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Charite - Campus Benjamin Franklin, Berlin, Germany, [3]University of Alberta, Edmonton, AB, [4]Paris Descartes University, Medicine Faculty - Cochin Hospital, Paris, France, [5]Universidad Nacional Autonoma de Mexico, Mexico, Mexico, [6]Rheumazentrum Ruhrgebiet, Herne, Germany

Purpose: ASAS, the Assessment of SpondylArthritis international Society has published recommendation on the use of TNF-blockers (aTNF) in AS in 2003 with an update in 2006. The aim of the current work is to update the recommendations taking into account available literature, a survey among rheumatologistis worldwide and the expert opinion of the ASAS members.

Method: The literature on the management of AS was reviewed since the last review in 2005. A survey asking about the conceptual agreement with the current recommendations and the level of application in practice as well as the barriers in applying the recommendations was completed by 787 practicing rheumatologists in 13 countries in Europe, Asia, Middle-East, S-America and Canada. These data were presented to the ASAS members, a group of experts in the field of AS, in two sessions. Discussion and voting resulted in the following changes.

Results: The recommendation on the diagnosis is expanded to: 'Patients fulfilling the modified New York criteria or the ASAS criteria for axial SpA'. The latter criteria indicate that MRI can be used to define sacroiliitis on imaging. Inadequate response to NSAIDs is considered fulfilled if at least 2 NSAIDs are ineffacious (or not tolerated) over a 4-week period in total. Pretreatment with sulfasalazine in patients with predominantly peripheral symptoms is no longer mandatory. However, patients with predominantly peripheral symptoms 'Should normally have had a therapeutic trial of a DMARD, preferably sulfasalazine'. Patients with pure axial manifestations do not have to take DMARDs

before anti-TNF treatment can be started. The level and assessment of response is unchanged (improvement of >=50% in BASDAI or >=2 units), but the timeperiod to assess response has been extended to 'at least 12 weeks'. The recommendations on monitoring (ASAS core set for clinical practice and BASDAI) remain unchanged. There are no special recommendations with respect to safety for patients with AS as compared to other rheumatic diseases treated with aTNF.

Conclusion: The updated recommendations give the option to include patients at an earlier stage of the disease with sacroiliitis on MRI but without structural damage on radiographs. Moreover, the requests for pretreatment have been loosened both for the duration of treatment with NSAIDs and no longer a mandatory use of sulfasalazine in patients with predeominantly peripheral involvment. This is all in accordance with data from the literature, and the wishes from a large group of practicing rheumatologists worldwide and AS experts.

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Validation of the Assessment of Spondyloarthritis International Society (ASAS) Disease Activity Candidate Scores According to MRI Parameters of Axial Inflammation. Walter P. Maksymowych[1], Praveena Chiowchanwisawakit[2] and Robert GW Lambert[1], [1]University of Alberta, Edmonton, AB, [2]Siriraj Hospital, Mahidol University, Bangkok, Thailand

Purpose: Four candidate disease activity indices for AS (ASDAS1-4) have been developed by ASAS based on a Delphi exercise amongst ASAS experts followed by item selection according to the theoretical decision by ASAS members whether to start treatment with anti-TNF agents. Further validation using objective parameters of disease activity is desirable. MRI shows active inflammation in both the sacroiliac joints (SIJ) and spine that correlates with histopathological scores and is responsive to anti-TNF agents. We aimed to validate the candidate ASAS disease activity indices according to MRI parameters of axial inflammation and compare them with current methods for assessing disease activity.

Method: We studied 89 patients with AS by modified New York criteria followed prospectively who received either standard therapy (n = 53) or anti-TNF agents (n = 36). Clinical and lab assessments were collected at baseline, 3 months (for anti-TNF patients), and every 6 months. MRI of the SIJ and spine was conducted at baseline and at 3-12 months. Data on clinical, lab, and MRI was also available at baseline and 12-24 weeks on 30 AS patients recruited to placebo-controlled trials of anti-TNF agents. MRI quantification of axial inflammation was based on the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SIJ and Spine scoring methods with spinal inflammation being measured in all 23 spinal units. SPARCC SIJ and Spine scores were combined into a SPARCC Total axial inflammation score. Correlations of baseline and change scores between the ASDAS indices and SPARCC scores were assessed by the Pearson correlation coefficient. Discriminatory ability of the ASDAS indices was compared using the standardised mean difference between subgroups of patients with high versus low disease activity defined by the SPARCC scores (<10 and >30 = low and high activity, respectively, for both baseline and change scores).

Results: All the ASDAS change scores correlated significantly and similarly with change scores for MRI in the anti-TNF trial cohort (p = 0.02-0.006) but only change in ASDAS1 and ASDAS3 scores correlated significantly with MRI in the anti-TNF treated observational cohort. For baseline scores the weakest correlation was observed for ASDAS2. Discriminatory ability was also lowest for ASDAS2 according to baseline and change scores for MRI inflammation. None of the ASDAS indices outperformed the CRP.

	Baseline MRI correlation	**Change MRI* correlation**	**Change MRI** correlation**	**Baseline MRI SMD**	**Change in MRI SMD**
ASDAS1	0.32 (0.003)	0.37 (0.03)	0.49 (0.01)	0.76	0.66
ASDAS2	0.24 (0.03)	0.29	0.44 (0.02)	0.54	0.49
ASDAS3	0.32 (0.002)	0.41 (0.02)	0.46 (0.007)	0.71	0.60

ASDAS4	0.30 (0.005)	0.32	0.52 (0.006)	0.72	0.60
BASDAI	0.17	0.31	0.51 (0.002)	0.27	0.52
CRP	0.39 (<0.0001)	0.53 (0.001)	0.40 (0.02)	0.58	0.86
ESR	0.26 (0.005)	0.22	0.44 (0.02)	0.37	0.42
** observational cohort **clinical trial cohort p values provided in brackets*					

Conclusion: This analysis supports the construct validity of the ASDAS indices according to MRI scores for axial inflammation. The ASDAS2 performs less well and none of the indices outperforms the CRP.

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Associations with Radiographic Damage in Ankylosing Spondylitis in a Large Cohort. Finbar (Barry) D. O'Shea, Nigil Haroon, Reena Riarh and R.D. Inman, Toronto Western Hospital, Toronto, ON

Purpose: To study the radiographic damage in a large ankylosing spondyltis (AS) in relation to multiple clinical parameters using the modified Stoke AS Spinal Score (mSASSS).

Methods: The patients were drawn from the clinical database of the Spondylitis Clinic in a large teaching hospital. Patients are evaluated according to a standard protocol in which demographic, clinical, radiographic and laboratory variables are recorded at regular intervals. Mean and standard deviation (SD) were calculated for the various clinical variables. The mSASSS was correlated with the grade of sacroiliitis using Pearson correlation coefficients, and the mSASSS was examined in a number of different sub-groups.

Results: Data was available for 319 AS patients who all fulfilled modified New York criteria. 79.9% were male, 80.5% were HLA-B27 positive, and 22.3% had juvenile onset AS (defined as symptom onset ≤ 16 years old). Mean (+/-SD) BASDAI was 4.6 (+/-2.6), mean BASFI was 3.8 (+/-2.8), and mean mSASSS was 18.4 (+/-22.6). Mean age was 40.2 (+/-13.1). Mean ESR was 13.5 (+/-14.5), and mean CRP was 11.9 (+/-15.5). There was a significant difference between the mSASSS scores for males versus female patients, for HLA-B27 positive versus negative patients, and for Adult onset versus Juvenile onset patients – see Table 1. There was a good correlation between the total mSASSS score and the grade of sacroiliitis ($r=0.616$, $p<0.001$). Specifically, male patients ($r= 0.630$, $p<0.001$), and adult-onset patients ($r=0.653$, $p<0.001$), had the strongest correlation between severity of spinal and sacroiliac disease.

Conclusion: Male AS patients who are HLA-B27 +ve, have the highest radiographic scores according to the mSASSS. Radiographic changes in the spine correlate well with the severity of sacroiliitis. Juvenile onset AS patients have less severe radiographic damage in comparison to adult onset AS. These features should assist in the identification of patients at higher risk of radiographic damage.

	Mean mSASSS (+/-SD)	
Total Cohort (N=319)	18.4 (+/-22.6)	
Male	20.9 (+/-23.8)	
Female	8.2 (+/-12.6)	p<0.001
Adult onset	21.1 (+/-23.9)	
Juvenile onset	8.8 (+/-13.5)	p<0.001
B27+ve	18.5 (+/-22.7)	
B27-ve	11.5 (+/-16.2)	p=0.007

Table 1. mean (+/-SD) MSASSS for the different subgroups

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The Majority of Peripheral Spondyloarthritis Is 'Undifferentiated' at the Time of Diagnosis – Lessons From the ASAS Study On New Classification Criteria for Peripheral Spondyloarthritis. M. Rudwaleit[1], Désirée M.F.M. van der Heijde[2], R. Landewé[3], N. Akkoc[4], J. Brandt[5], J. Braun[6], CT Chou[7], M. Dougados[8], J. Gu[9], F. Huang[10], H. Mielants[11], I. Olivieri[12], E. Roussou[13], M. Ostergaard[14], S. Scarpato[15], R. Valle-Oñate[16], J. Wei[17] and J. Sieper[1], [1]Charité, Berlin, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Maastricht, Netherlands, [4]Izmir, Turkey, [5]Berlin, Germany, [6]Herne, Germany, [7]Taipei, Taiwan, [8]Paris, France, [9]Guangzhou, China, [10]Beijing, China, [11]Gent, Belgium, [12]Potenza, Italy, [13]London, United Kingdom, [14]Copenhagen, Denmark, [15]Scafati, Italy, [16]Bogota, Colombia, [17]Taichung, Taiwan

Purpose: The Assessment in SpondyloArthritis international Society (ASAS) has recently developed new classification criteria for axial SpA and new criteria for peripheral SpA. In the group of patients with peripheral symptoms only, we were interested to assess the frequencies of SpA subgroups.

Method: In a prospective international study involving expert rheumatologists from ASAS, patients with axial and/or peripheral symptoms, an age at onset <45 years, and no definite diagnosis at the time of referral were included. Among these, 266 patients had peripheral manifestations only. The clinical expert diagnosis (SpA vs no SpA) upon routine diagnostic work-up was taken as reference standard for diagnosis. Patients with peripheral SpA but without concomitant psoriasis, without inflammatory bowel disease (IBD), and without evidence of preceding infection (clinical or laboratory) were classified 'undifferentiated' peripheral SpA. The ASAS classification criteria for peripheral SpA (arthritis or enthesitis or dactylitis PLUS [≥1 of psoriasis, IBD, preceding infection, HLA-B27, uveitis, sacroiliitis by imaging (radiographs or MRI)] or [≥2 of arthritis, enthesitis, dactylitis, IBP, positive family history for SpA]) were compared with the ESSG and Amor criteria.

Results: Of the 266 patients, 86.6% had peripheral arthritis, 45.9% enthesitis, and 14.7% dactylitis (all were clinically assessed). A diagnosis of SpA was made in 176 patients (66.2%) in whom psoriasis was found in 9.1%, IBD in 3.4%, and evidence of preceding infection (i.e. reactive arthritis) in 5.7%. Radiographic sacroiliitis was found in 18.0% and active sacroiliitis on MRI in 12.5% but none of these patients had current back pain and only 1 patient had previous IBP. Thus, peripheral SpA not associated with psoriasis, IBD or preceding infection ('undifferentiated SpA) was diagnosed in 81.8% of all SpA patients. The ASAS classification criteria for peripheral SpA had a sensitivity of 75.0% and specificity of 82.2%. This was a better sens/spec balance than the ESSG criteria (sens. 55.1%, spec. 81.1%), ESSG modified for MRI (sens. 62.5%, 81.1%), Amor criteria (sens. 35.2%, spec. 97.8%), and Amor modified for MRI (sens. 39.8%, spec. 97.8%).

Conclusion: The majority of newly diagnosed peripheral SpA patients is 'undifferentiated' at the time of diagnosis. The new ASAS classification criteria for peripheral SpA performed well in patients with predominant peripheral manifestations, and appeared to be better balanced than the ESSG and Amor criteria.

Disclosure: M. Rudwaleit, None; **D. M. F. M. van der Heijde**, None; **R. Landewé**, None; **N. Akkoc**, None; **J. Brandt**, None; **J. Braun**, None; **C. Chou**, None; **M. Dougados**, None; **J. Gu**, None; **F. Huang**, None; **H. Mielants**, None; **I. Olivieri**, None; **E. Roussou**, None; **M. Ostergaard**, None; **S. Scarpato**, None; **R. Valle-Oñate**, None; **J. Wei**, None; **J. Sieper**, None.

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High Sensitivity C-Reactive Protein Outperforms Standard C-Reactive Protein in Disease Activity Assessment in Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Denis Poddubnyy[1], Martin Rudwaleit[1], Joachim Listing[2], Jürgen Braun[3] and Joachim Sieper[1], [1]Charité - Campus Benjamin Franklin, Berlin, Germany, [2]DRFZ, Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany

Purpose: This study was aimed at comparing high sensitivity C-reactive protein (hsCRP) measurement with routine C-reactive protein (CRP) evaluation as disease activity parameters in patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (SpA).

Method: 269 patients (153 with AS and 116 with non-radiographic axial SpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were included. hsCRP levels were measured using particle-enhanced immunoturbidimetric method (Roche) with the lowest detected level of 0.1 mg/l. hsCRP values were compared to results of routine turbidimetric CRP test with the lowest detected level of 6 mg/l.

Results: In the group of patients with AS (n = 153) hsCRP showed better than routine CRP correlation with clinical parameters: general pain level (Spearman's ρ = 0.340 for hsCRP vs 0.253 for routine CRP), spinal pain level (0.247 vs 0.177), night pain level (0.325 vs 0.253), intensity of morning stiffness (0.213, vs 0.168), and BASFI value (0.271 vs 0.238). Only hsCRP demonstrated significant correlation with the level of enthesitis-related discomfort (ρ = 0.173, p = 0.032) and the overall BASDAI value (ρ = 0.173, p = 0.034). In the group of patients with non-radiographic axial SpA (n = 116) neither hsCRP nor routine CRP demonstrated significant correlation with clinical parameters, except the correlation between the hsCRP level and the level of enthesitis-related discomfort in tender areas (ρ = 0.224, p = 0.018).

65 patients with AS (42.5%) and 61 patients with non-radiographic axial SpA (52.6%) had level of routine CRP <6 mg/l. In the group of patients with AS and level of routine CRP <6 mg/l there was a clear trend for an increased level of pain, stiffness, and functional impairment in patients with higher hsCRP concentration (table). Such trend was less pronounced in patients with non-radiographic axial SpA.

Table. Clinical parameters (median and IQR) in relation to a level of hsCRP in patients with the level of routine CRP <6 mg/l

	AS			**Non-radiographic axial SpA**		
	hsCRP, mg/l					
	0-1.9 (n=40)	2.0-3.9 (n=14)	≥4.0 (n=11)	0-1.9 (n=46)	2.0-3.9 (n=12)	≥4.0 (n=3)
Spinal pain, points NRS	3.5 (2.0-6.0)	6.0*(3.8-7.3)	5.0 (4.0-8.0)	5.5 (2.0-7.0)	5.5 (1.5-7.8)	6.0 (6.0-8.0)
Night back pain, points NRS	2.0 (1.0-5.0)	4.5*(3.0-6.3)	7.0*(3.0-7.0)	4.5 (2.0-7.0)	5.0 (0.8-7.8)	8.0 (5.0-10.0)
Morning stiffness, points NRS	3.0 (1.0-5.8)	5.5 (2.8-7.0)	5.0 (2.0-8.0)	4.0 (1.0-7.3)	2.0 (1.0-6.0)	6.0 (5.0-7.0)
BASDAI	2.8 (1.4-5.5)	3.9 (2.8-5.9)	3.6 (1.7-5.7)	3.6 (1.4-5.0)	4.7 (2.0-5.3)	3.6 (1.7-5.7)
BASFI	1.3 (0.2-4.7)	2.5 (1.4-3.7)	3.0 (1.0-5.9)	1.3 (0.3-3.7)	2.7 (1.1-4.3)	4.7 (4.0-5.4)

* p < 0.05 in comparison to the first tertile (hsCRP 0-1.9 mg/l)

Conclusion: High sensitivity CRP correlates better than standard CRP with clinical disease activity parameters in patients with AS and non-radiographic axial SpA. Within the normal range of routine CRP (<6 mg/l) parameters of disease activity tended to be higher with higher hsCRP levels. Therefore, hsCRP could be superior to standard CRP in assessing disease activity in axial SpA.

Disclosure: D. Poddubnyy, None; **M. Rudwaleit**, None; **J. Listing**, None; **J. Braun**, None; **J. Sieper**, None.

1795

Early Psoriatic Arthritis "Sine Psoriasis": Clinical Aspects and Sensitivity of the CASPAR Classification Criteria. Giovanni Ciancio, Matteo Colina, Cesare Savini, Valentina Foschi, Marcello Govoni and Francesco Trotta, Rheumatology Section, Ferrara, Italy

Purpose: Psoriatic arthritis (PsA) is a chronic and potentially disabling inflammatory arthritis. Skin psoriasis usually precedes joint disease in 70% of patients with PsA whereas it may occur at the same time in 15%.In about 10-30% of patients arthritis may precedes psoriasis even for many years. In these cases the recognition of the so-called psoriatic arthritis "*sine psoriasis*" represents a diagnostic challenge. Classification criteria for PsA (CASPAR criteria) were recently developed. They give a sensitivity and specificity of 0.914 and 0.987 respectively. Our purposes were to evaluate the clinical spectrum and to verify the sensitivity of the CASPAR criteria in patients with early psoriatic arthritis (PSA) "*sine psoriasis"*.

Methods: All patients with early PsA "sine psoriasis" (disease duration < 12 months) who consecutively attended our centre in the last 2 were recruited for study. The inclusion criteria were: 1) a clinical picture suggestive of PSA; 2) psoriasis in at least one first degree relative; 3) absence of other rheumatic diseases. All patients were evaluated for the presence of spinal involvement (SI) (inflammatory spinal pain and/or radiological sacroiliitis); peripheral arthritis (PA), dactylitis (D), tenosynovitis (T) and peripheral enthesitis (PE), documented by ultrasound and/or MRI. Laboratory evaluation included ESR, CRP, rheumatoid factor and anti-cyclic citrullinated peptide . The proportion of patients meeting CASPAR criteria (i.e., the sensitivity) was determined.

Results: Forty patients with early PsA *"sine psoriasis"* were studied (Tab.1). CASPAR criteria were satisfied by fourteen patients (sensitivity: 35%). Radiologic criteria were satisfied by only 1 patient.

Conclusion: The clinical spectrum of PSA "*sine psoriasis"* appears as wide as that of PSA. However CASPAR criteria have a very low sensitivity when applied to early PsA

"sine psoriasis".

Tab.1

N. Patients	W	M	Mean age +/- SD	Mean disease duration (weeks) +/- SD	-PA -T -PE	-PA -T -PE -SI	-PA -D -T	PA	-PA -D	-PA -PE -D -SI	-T -SI	-PA -SI
40	22	18	45.4± 13.2 yrs	23.8±7.8	14	3	8*	5	4*	2*	2	2

W=Women M=Men *Patients who fulfilled CASPAR criteria

Disclosure: G. Ciancio, None; **M. Colina**, None; **C. Savini**, None; **V. Foschi**, None; **M. Govoni**, None; **F. Trotta**, None.

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Ankylosing Spondylitis Diasease Activity Score (ASDAS): What Level Corresponds to Low Disease Activity and What Is An Important Improvement? Elisabeth Lie[1], Désirée M.F.M. van der Heijde[2], Till Uhlig[1] and Tore K. Kvien[1], [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands

Purpose: ASDAS is a newly developed ASAS endorsed disease activity score calculated from BASDAI questions 2, 3 and 6, patient global assessment, and CRP. Cut-points for ASDAS states and changes as well as response criteria based on the ASDAS are not yet established. Our objective was to examine how ASDAS relates to patient acceptable symptom state (PASS), minimal clinical important improvement (MCII) and levels of/changes in physician global assessment (PhGA).

Methods: AS patients were extracted from a multi-center treatment registry where patients (pts) with inflammatory arthropathies starting treatment with DMARDs and biologicals are followed longitudinally. 448 pts (69% male, 89% HLA-B27 pos, biologicals n=340, DMARDs n=66) were included in the baseline analyses while 243 pts had 3-month follow-up data. Patients were at each time point asked if they were in a satisfactory condition (yes/no), i.e. PASS, and pts were from 3 months onward asked if they had experienced a considerable improvement since start of therapy (yes/no), i.e. MCII. ASDAS levels/changes were examined across disease states and level of changes defined by PASS, MCII and PhGA (0-10 cm VAS). We performed receiver operating characteristic (ROC) curve analyses (maximum accuracy and 80% specificity approaches) to find cut-offs for ASDAS.

Results: At treatment start (baseline) mean(SD) ASDAS were 3.51(1.01) and 3.28(0.97) for pts on biologicals and pts on DMARDs, respectively, while mean(SD) 3-month changes were -1.31(1.24) and -0.31(0.97). 28%/58% of pts were in PASS at baseline/3 months, while 65% reported an important improvement on therapy. Among pts reporting/not reporting PASS at baseline and 3 months mean(SD) ASDAS were 2.96(0.95)/3.72(0.97) and 1.84(0.91)/3.00(1.14), respectively. Mean(SD) 3-month ΔASDAS were -1.71(1.07)/-0.20(0.97) in pts

reporting/not reporting significant improvement, and -1.85(1.15)/-0.59(1.06) for pts with ΔPhGA ≤-2/>-2, respectively. The results of the ROC analyses are shown in the table.

ROC analyses – ASDAS cut-points for state and change			
ASDAS state	**80% spec.**	**Max. accuracy**	**AUC (95% CI)**
Baseline PASS yes (vs. no)	2.96	3.15	0.71 (0.65-0.77)
3-month PASS yes (vs. no)	2.01	2.50	0.79 (0.74-0.84)
Baseline PhGA <4 (vs. ≥4)	3.05	3.40	0.70 (0.65-0.75)
3-month PhGA <4 (vs. ≥4)	3.55	3.55	0.92 (0.88-0.96)
ASDAS change			
3-month MCII yes (vs. no)	-0.88	-0.68	0.86 (0.81-0.91)
3-month ΔPhGA ≤-2 (vs. >-2)	-1.40	-1.27	0.79 (0.73-0.85)
3-month ΔPhGA ≤-4 (vs. >-4)	-2.00	-1.53	0.80 (0.73-0.88)

Conclusion: In this study, PASS corresponded to ASDAS levels of 2.01 to 3.15 depending on time for assessment and method. The ASDAS levels corresponding to PASS were considerably lower at baseline than at 3 months. MCII corresponded to ΔASDAS of -0.7 to -0.9 while >2 point improvement of PhGA corresponded to a larger ASDAS change. These data show how ASDAS relates to PASS, MCII and the PhGA, but further work is needed to define cut-points for ASDAS change and states.

Disclosure: E. Lie, None; **D. M. F. M. van der Heijde**, None; **T. Uhlig**, None; **T. K. Kvien**, None.

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A Prediction Model for Future Radiologic Damage in Ankylosing Spondylitis Based On a Prospective Cohort Analysis. Finbar (Barry) D. O'Shea, Nigil Haroon, Reena Riarh and R.D. Inman, Toronto Western Hospital, Toronto, ON

Purpose: Spinal ankylosis is a predominant and disabling feature of ankylosing spondylitis (AS). Identifying baseline predictors of radiological progression of AS can be helpful in prognostication and treatment decisions.

Methods: Patients with AS (modified New York criteria), attending the Spondylitis Clinic were prospectively enrolled in this study. At the baseline visit the BASDAI, BASFI and BASMI were noted and cervical and lumbar x-rays were taken. Patients were reviewed annually and X-rays repeated every 2 years. The x-rays were scored for mSASSS by 2 independent investigators with an ICC of 0.9. X-rays were arranged sequentially and scored for mSASSS after blinding. Partial correlation coefficients were calculated after correcting for disease duration at the baseline visit. Predictors of future radiological damage were identified using a linear regression model with the last mSASSS score as the dependant variable and a regression equation was obtained for prediction. The rate of change in radiologic damage was also calculated by dividing the change in mSASSS by the time interval between the X-rays.

Results: Eighty seven patients (12 female), 76% were HLA-B27 positive, 64% were receiving an anti-TNF agent. Each patient had X-rays repeated at least twice with a minimum interval of 2 years. At baseline, the mean age ± SD of the patients was 36.6 ± 12.9 years and mean ±

SD disease duration was 14.7 ± 9.5 years. The mean ± SD BASDAI, BASFI and BASMI were 4.8 ± 2.6, 4.1 ± 2.9 and 2.4 ± 2.0 respectively. The mean baseline and follow up mSASSS were 16.5 ± 21.8 and 18.5 ± 22.3 respectively in a mean interval of 2.7 ± 0.9 years. The mean change in mSASSS was 1.97 ± 2.9 at rate of 0.88 ± 1.6 units/year.

After correcting for disease duration, the baseline BASMI (R=0.314, p=0.04), ESR (R=0.447, p=0.001), and CRP (R=0.460, p=0.002) correlated with change in mSASSS. Baseline mSASSS, BASDAI, BASFI and age of onset did not significantly correlate with change in mSASSS. Regression analysis determined that the only two significant predictors of the final mSASSS score were baseline mSASSS and CRP. The model with mSASSS alone had and adjusted R^2 of 0.981 ($p < 0.01$) and the addition of CRP improved the model only minimally (R^2 of 0.983; $p < 0.01$). The regression equation for predicting mSASSS was 1.12 + 1.01 (baseline mSASSS) + 0.04 (baseline CRP). There was no difference in the rate of radiographic progression between patients who were or were not treated with anti-TNF agents. However there was a negative correlation between the duration of biologic intake and the rate of change in mSASSS (R=-0.297, p=0.03).

Conclusion: This prospective study demonstrates that baseline radiographic damage is the strongest predictor of future radiographic damage. A longer duration of anti-TNF therapy was associated with a slower rate of radiographic progression. The proposed model could have important clinical utility in defining prognosis in AS patients.

Disclosure: F. (. D. O'Shea, Abbott Immunology Pharmaceuticals, 5, Schering Canada, , 5 ; **N. Haroon**, Schering Global, 2 ; **R. Riarh**, None; **R. D. Inman**, Schering Canada, Amgen-Wyeth, Abbott, Sanofi-Aventis, 5 .

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No Progression of Chronic Sacroiliac Changes in Patients with Active, Non-Radiographic Axial Spondyloarthritis Treated with Adalimumab Over 52 Weeks. Hildrun Haibel[1], Valeria Rios[2], Kay-Geert Hermann[3], Christian Althoff[4], Martin Rudwaleit[5], Hartmut Kupper[6], J. Braun[7] and Joachim Sieper[8], [1]Department of Rheumatology, Charité CBF, Berlin, Germany, [2]Department of Rheumatology, Bellvitge University Hospital, Barcelona, Spain, [3]Charité Medical School, Berlin, Germany, [4]Charité–University Medicine Berlin, Berlin, Germany, [5]Charité - Campus Benjamin Franklin, Berlin, Germany, [6]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [7]Rheumazentrum Ruhrgebiet, Herne, Germany, [8]Charite - Campus Benjamin Franklin, Berlin, Germany

Purpose: To evaluate the progression of chronic changes, as observed in T1 sequences on MRI, over 52 weeks in a 12-week, placebo-controlled study of adalimumab with a 40-week, open-label extension in the treatment of patients with active axial spondyloarthritis (SpA) not yet fulfilling the modified New York Criteria who had previously demonstrated good clinical response.[1]

Methods: T1 sequences of MRIs of the sacroiliac joints (SIJ) were obtained at baseline, at Week 12 (placebo phase), and at Week 52 (40 weeks of open-label extension) in patients treated with adalimumab. MRIs were read in 1 batch blinded for both sequence and therapy regimen by 2 assessors employing a recently developed score for chronic changes. Fatty lesions were scored (0–8), sclerosis was read for each joint (0–2), and erosions were counted for each joint (0–24).

Results: Nine pairs each of MRIs for both the placebo and adalimumab groups were available at baseline and Week 12. In addition, 12 pairs of MRIs for the former placebo group and 14 pairs for the adalimumab group were available at baseline and Week 52. No changes were observed after 40 weeks (former placebo group) or 52 weeks of adalimumab treatment regarding fatty lesions, sclerosis, or erosions in the SI joints. Through analysis of the 12-week placebo-controlled data, significant reductions of fatty lesions were found in the adalimumab-treated patients vs. the placebo-treated patients (p=0.042). No significant changes and no differences between the two groups were found for erosions and sclerosis.

Conclusion: This was the first study analysing chronic SI-joint changes by MRI in patients treated with a TNF antagonist. These data indicate that fatty degeneration and erosions might be stopped. These findings need to be confirmed by longer observation periods. Furthermore, it has yet to be determined how and whether this affects also new bone formation.

Mean Scores for Chronic Changes in T1 sequences by MRIs of Sacroiliac Joints

	Baseline to Week 12 **Placebo Group**	**Baseline to Week 12** **Adalimumab Group**	**Baseline to Week 52** **All Patients**

	n=9		n=9		n=26	
	BL	**Wk 12**	**BL**	**Wk 12**	**BL**	**Wk 52**
Fatty Lesions	5.9	6.0	3.9	1.9[a]	4.9	4.8
Sclerosis	1.9	1.8	1.4	1.6	1.5	1.5
Erosions	2.9	2.2	1.0	0.6	1.6	1.7

[a]$p<0.05$.

[1]Haibel H, et al. Arthritis Rheum. 2008;58:1981–91.

Disclosure: H. Haibel, Schering-Plough, 8, Abbott Laboratories, 8 ; **V. Rios**, None; **K. G. Hermann**, None; **C. Althoff**, None; **M. Rudwaleit**, Schering-Plough, 5, Schering-Plough, 8, MSD, 5, MSD, 8, Abbott Laboratories, 5, Abbott Laboratories, 8, Pfizer Inc, 8, Pfizer Inc, 5, Wyeth Pharmaceuticals, 8, Wyeth Pharmaceuticals, 5 ; **H. Kupper**, Abbott Laboratories, 3, Abbott Laboratories, 1 ; **J. Braun**, Abbott Laboratories, 5, Wyeth Pharmaceuticals, 5, Schering-Plough, 5, Amgen, 5, Centocor, Inc., 5 ; **J. Sieper**, Abbott Laboratories, 2, Abbott Laboratories, 5, Abbott Laboratories, 8, Schering-Plough, 2, Schering-Plough, 5, Schering-Plough, 8, Wyeth Pharmaceuticals, 2, Wyeth Pharmaceuticals, 8, Wyeth Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Roche Pharmaceuticals, 8, Pfizer Inc, 8 .

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Ten Year Outcome of Spondyloarthritis Related Oligoarthritis Involving the Knee: What Are the Predictors? Alexander.N. Bennett[1], Helena Marzo-Ortega[2], Ai Lyn Tan[2], EM Hensor[2], Mike Green[2], Paul Emery[2] and Dennis McGonagle[2], [1]Defence Medical Rehabilitation Unit, London, United Kingdom, [2]University of Leeds, Leeds, United Kingdom

Purpose: To investigate longterm outcome of Spondyloarthropathy (SpA) related oligoarthritis involving the knee and establish predictors of outcome with a specific hypothesis that HLA-B27 and PsA would be linked to more severe MRI bone marrow oedema (BMO), and these variables would predict a poor longterm outcome.

Method: Patients with seronegative oligoarthritis involving the knee of suspected SpA origin were recruited. Assessment including ESSG SpA criteria, MRI, rheumatoid factor, and HLA-B27 were all performed at baseline, Patients where given standard treatments at the discretion of their treating rheumatologist and followed up at 10yrs. Outcome assessments included joint counts, ESSG SpA criteria, functional and symptomatic questionnaire, CRP, and radiographic assessment for knee OA.

Results: Forty-four patients were recruited, (Mean age 32.3yrs {range 15-59yrs}, 68% male) with a mean disease duration at baseline of 9.75months (1-48months). Twenty-six patients (59%) (mean age 42.6yrs, 61.5% female) returned for followed up after a mean of 10years (range 8.4-12.6yrs). The mean total bone marrow oedema score for the whole knee MRI was 2.86 (range 0-29). The patella was the most severely and frequently affected area by BMO. HLA-B27 and BMO were not predictive of 10yr outcome but PsA was. Ten patients (38%) had persistent clinical synovitis and 31% of affected knees' had secondary radiographic OA. Global outcome was poor or very poor in 69% of cases. PsA patients had significantly worse outcome compared to ReA.

Conclusion: SpA releated oligoarthrits involving the knee has significant long term clinical and radiological morbidity despite standard treatments. HLA-B27 and MRI BMO do not appear to be predictors of poor outcome as they are in axial-SpA. However PsA oligoarthritis has a significantly worse long term outcome than ReA.

Disclosure: A. N. Bennett, None; **H. Marzo-Ortega**, None; **A. L. Tan**, None; **E. Hensor**, None; **M. Green**, None; **P. Emery**, None; **D. McGonagle**, None.

ACR/ARHP Poster Session C

Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Pathogenesis, Animal Models and Genetics II

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

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Association of *FAM167A (C8orf13) - BLK* Region with Systemic Sclerosis. Ikue Ito[1], Yasushi Kawaguchi[2], Aya Kawasaki[1], Minoru Hasegawa[3], Jun Ohashi[1], Manabu Kawamoto[2], Manabu Fujimoto[3], Kazuhiko Takehara[3], Shinichi Sato[4], Masako Hara[2] and Naoyuki Tsuchiya[1], [1]University of Tsukuba, Doctoral Program in Life System Medical Sciences, Tsukuba, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Kanazawa University, Graduate School of Medical Science, Kanazawa City, Japan, [4]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Purpose: Association of single nucleotide polymorphisms (SNPs) in *FAM167A (C8orf13)* - B lymphoid tyrosine kinase (*BLK*) region with systemic lupus erythematosus (SLE) has been demonstrated in the Caucasian and Asian populations. Recent studies showed that many genes including *IRF5*, *STAT4* and *PTPN22* are shared susceptibility genes for multiple autoimmune diseases. This study was performed to examine whether the *FAM167A-BLK* region is also associated with susceptibility to systemic sclerosis (SSc).

Method: A two-tiered case-control association study was performed on 309 Japanese patients with SSc and 769 healthy controls. Tier-1 examined association of 16 tag SNPs encompassing the *FAM167A-BLK* region on 124 patients and 412 controls. Tier-2 analyzed additional 185 patients and 357 controls for a SNP rs13277113, selected based on the results of tier-1.

Results: At tier-1, rs13277113 A allele, previously shown to be associated with SLE, demonstrated significant association after correction for multiple testing (permutated P=0.024). Conditional logistic regression analysis revealed that this SNP could account for association of other SNPs. At tier-2, additional 185 patients and 357 controls were genotyped for rs13277113. When tier-1 and tier-2 samples were combined, rs13277113 A allele was significantly associated with SSc and its clinical subsets (Table 1). This association was not observed in the patients who did not possess any of the three major autoantibodies associated with SSc in Japanese: anti-topoisomerase I (anti-topo I), anti-centromere (ACA) and anti-U1 snRNP (anti-RNP) antibodies, suggesting that the genetic effect may be accounted for by autoantibody production.

Conclusion: The rs13277113 A allele is associated not only with SLE but also with SSc. The association was preferentially observed in autoantibody-positive patients. These findings indicate that the *FAM167A-BLK* region is a common genetic risk factor for SLE and SSc.

Table 1. Association of rs13277113 with SSc and its clinical subsets.

	n	Genotype, n (%)			A allele frequency	Allelic association	
		AA	AG	GG		OR (95% CI)	*P*
all SSc	309	179 (58)	107 (35)	23 (7)	0.75	1.45 (1.17-1.79)	6.1×10^{-4}
dcSSc	158	93 (59)	54 (34)	11 (7)	0.76	1.50 (1.14-1.98)	0.0041
lcSSc	151	86 (57)	53 (35)	12 (8)	0.75	1.39 (1.05-1.84)	0.021
anti-topo I, ACA or anti-RNP Ab positive	208	127 (61)	68 (33)	13 (6)	0.77	1.63 (1.27-2.10)	1.1×10^{-4}
anti-topo I, ACA and anti-RNP Ab negative	101	52 (51)	39 (39)	10 (10)	0.71	1.15 (0.84-1.59)	0.38
healthy controls	769	354 (46)	334 (43)	81 (11)	0.68	referent	

Disclosure: I. Ito, None; **Y. Kawaguchi**, None; **A. Kawasaki**, None; **M. Hasegawa**, None; **J. Ohashi**, None; **M. Kawamoto**, None; **M. Fujimoto**, None; **K. Takehara**, None; **S. Sato**, None; **M. Hara**, None; **N. Tsuchiya**, None.

1801

HLA-DPB1 and DPB2 Are Genetic Loci for Systemic Sclerosis -Genome-Wide Association Study in Koreans with Replication in North Americans. Xiaodong Zhou[1], Jong Eun Lee[2], Frank C. Arnett[1], Momiao Xiong[3], Min Young Park[2], Yeon Kyeong You[2], Eun Soon Shin[2], John D. Reveille[1], M. Mayes[4], Jin Hyun Kim[5], Ran Song[5], Ji Yong Choi[5], Ji Ah Park[5], Yun Jong Lee[5], Eun Young Lee[5], Yw Song[6] and Eun Bong Lee[5], [1]University of Texas Medical School at Houston, Houston, TX, [2]DNA Link Inc, Seoul, South Korea, [3]University of Texas School of Public Health, Huston, TX, [4]U.Texas Houston, Houston, TX, [5]Seoul National University College of Medicine, Seoul, South Korea, [6]Seoul National Univ, South Korean

Purpose: To investigate the most susceptible genetic loci in systemic sclerosis (SSc) with genome-wide association study (GWAS).

Methods: A genome-wide association study was performed in 137 patients with systemic sclerosis and 564 controls from Korea using the Affymetrix Human SNP Array 5.0. After fine mapping study, the results were replicated in 1,107 SSc patients and 2,747 controls from a US Caucasian population.

Results: The SNPs (rs3128930, rs7763822, rs7764491, rs3117230 and rs3128965) of HLA-DPB1 and –DPB2 on chromosome 6 formed a distinctive peak with log p-values ($p = 8.16 \times 10^{-13}$) for association with SSc susceptibility. Subtyping analysis of HLA-DPB1 showed that DPB1*1301 ($p = 7.61 \times 10^{-8}$) and DPB1*0901 ($p = 2.56 \times 10^{-5}$) were the most susceptible subtypes for SSc in Koreans. In US Caucasians, two pairs of SNPs, rs7763822/rs7764491 and rs3117230/rs3128965, showed strong association with SSc patients who had either circulating anti-DNA topoisomerase I ($p = 7.58 \times 10^{-17}/4.84 \times 10^{-16}$) or anti-centromere autoantibodies ($p = 1.12 \times 10^{-3}/3.2 \times 10^{-5}$), respectively.

Conclusion: Our GWAS in Koreans revealed that the region of HLA-*DPB1* and *–DPB2* contains the most susceptible loci to Korean SSc. The confirmatory studies in US Caucasians indicated that specific SNPs of the HLA-DPB1 and/or –DPB2 were strongly associated with US Caucasian SSc patients who were positive to anti-topoisomerase I or anti-centromere autoantibodies.

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1802

BANK1 Is a Genetic Risk Factor for Diffuse Cutaneous Systemic Sclerosis Having Additive Effects with IRF5 and STAT4. Philippe Dieudé[1], Mickael Guedj[2], Julien Wippf[3], Inga Melchers[4], Catherine Boileau[5], Yannick Allanore[3] and GFRS and DNSS co-workers, [1]Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [2]Université d'Evry Val d'Essonne, Evry, France, [3]Paris Descartes Univ, Paris, France, [4]University Medical Center, Freiburg, Germany, [5]Hôpital Ambroise Paré, AP-HP, Boulogne, France

Background: Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) share common genetic risk factors including *IRF5* and *STAT4* variants. Polymorphisms of the B-cell scaffold protein with ankyrin repeats gene, *BANK1*, were recently identified as SLE risk factors.

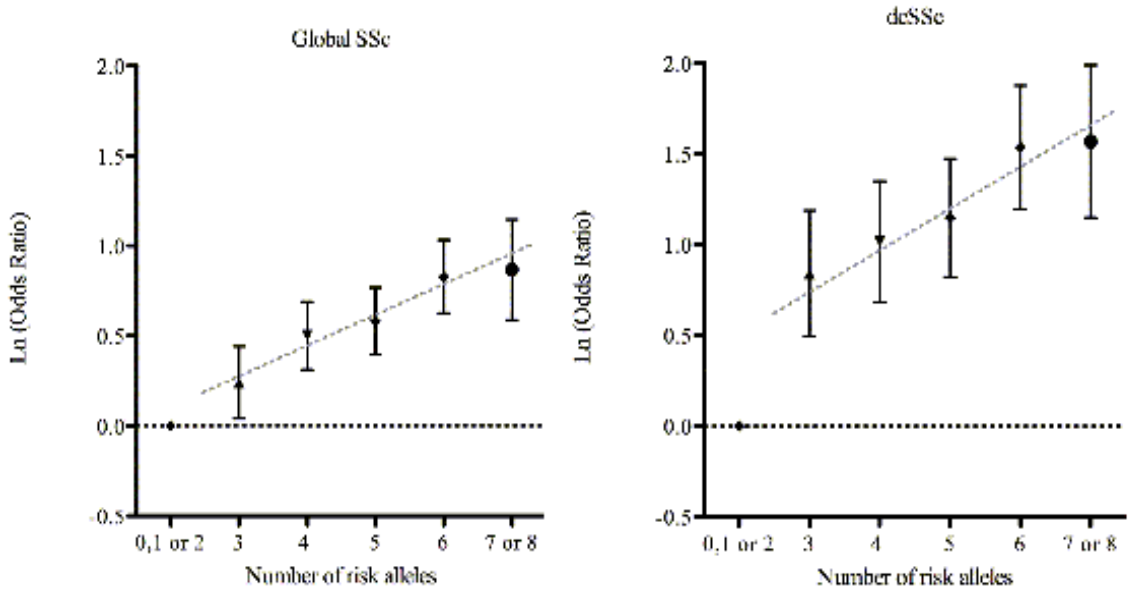
Purpose: To determine whether the functional *BANK1* rs3733197 and rs10516487 variants are associated with SSc in European Caucasians populations. To investigate the putative gene-gene interaction between *BANK1* and *IRF5* and *STAT4*.

Methods: *BANK1* SNPs were genotyped in 2407 individuals comprising a French set (874 SSc patients and 955 controls, previously genotyped for both *IRF5* rs2004640 and *STAT4* rs7574865) and a German set (421 SSc patients and 182 controls).

Results: The *BANK1* variants were found to be associated with the diffuse cutaneous SSc (dcSSc) in both samples providing an OR of 0.77 for the rs10516487 T rare allele in the combined populations compared to controls (95%CI [0.64-0.93]) and an OR of 0.73 (95%CI [0.61-0.87]) for the rs3733197 A rare allele. *BANK1* haplotype analysis found the A-T haplotype to be protective in dcSSc (P=0.0003, OR 0.70 [95% CI 0.57-0.86]) and the G-C haplotype to be a risk factor (P= 0.008, OR 1.25 [95% CI 1.06-1.47]). Significant differences were also observed when the limited cutaneous subset of SSc was compared to dcSSc both for rare alleles and haplotypes. The *BANK1*, *IRF5* and *STAT4* risk alleles risk alleles displayed a multiplicatively increased 1.43-fold risk of dcSSc (Figure).

Conclusion: Our results establish *BANK1* as a new SSc genetic susceptibility factor and *BANK1*, *IRF5* and *STAT4* act with additive effects.

Figure. Joint effects of risk alleles of *BANK1* (rs10516487 & rs3733197) *STAT4* (rs7574865) and *IRF5 (*rs2004640) on SSc and dcSSc susceptibility



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1803

Phenotype-Haplotype Correlation of IRF5 Gene in SSc : Association with Different Fibrotic Sub-Phenotypes and Severe Patterns.

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Background: Systemic sclerosis (SSc) is a complex multi-organ disease affecting the microvascular network, the immune system and connective tissue. The type 1 interferon (IFN) pathway has been postulated to play a key role in autoimmune diseases. Our original finding of an association between the *IRF5* rs2004640 and SSc have provided additional support for the pivotal role of IRF5 and the type 1 IFN pathway in autoimmune diseases. To date, additional *IRF5* variants have been convincingly identified as autoimmune genetic factor.

Purpose: To test for association with SSc the *IRF5* rs3757385, rs2004640 and rs10954213 variants. To investigate whether *IRF5* haplotypes determined by those 3 single nucleotide polymorphisms (SNPs) would be also involved in SSc and SSc sub-phenotypes genetic background.

Methods: *IRF5* single marker and haplotype analyses were performed in 1625 individuals of French Caucasian origin (743 SSc patients and 882 controls), all the individuals having a full genotyping information for the 3 *IRF5* SNPs investigated.

Results: The *IRF5* variants were found to be associated with SSc samples providing an OR of 1.27 for the rs3757385 C risk allele compared to controls (95%CI [1.10-1.47]), an OR of 1.34 for the rs2004640 T risk allele and an OR of 1.17 (95%CI [1.01-1.34]) for the A risk allele. *IRF5* haplotype analysis found the A-G-G haplotype to be protective in SSc ($P = 8.8x10^{-4}$, OR 0.78 95% CI [0.68-0.90]) and the C-T-A haplotype to be a risk factor ($P = 0.0024$, OR 1.23 95% CI [1.07-1.40]). In this sample, single marker analysis do not provided any significant differences when phenotype-genotype correlation was performed. Interstingly, the *IRF5* C-T-A risk haplotype frequency was strongly associated with the diffuse cutaneous SSc subset when compared to limited cutaneous SSc (50.9% vs 43.8%, $P = 0.008$). The frequency of the *IRF5* A-G-G protective haplotype was found to be significantly decreased in SSc patient with fibrosing alveolitis compared to those without (24.1% vs 29.6%, $P = 0.018$). The risk haplotype aws also found to be associated with a severe phenotype defined by the presence of renal crisis and/or CVF <75% and/or HTAP and/or ulcerations($P = 0.045$)

Conclusion: Our results establish *IRF5* as a new SSc genetic susceptibility factor influencing the SSc fibrotic phenotype and a severe disease.

Disclosure: P. Dieudé, None; **K. Dawidowicz**, None; **M. Guedj**, None; **C. Boileau**, None; **Y. Allanore**, None.

1804

Genotype-Phenotype Correlation in Systemic Sclerosis: STAT4 rs7574865 Is a Relevant Marker for Interstitial Lung Disease.

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Purpose: Two recent large studies (Rueda et al, Hum Mol Genet. 2009 and Dieude et al Arthritis Rheum 2009) have showed that rs7574865, a variant allele of *STAT4,* confers an increased risk for systemic sclerosis (SSc). However, genotype-phenotype correlation analyses revealed discrepancies for subphenotype associations.

Objectives: We sought to assess whether combined analyses clarified the contribution of rs7574865 to the phenotypic heterogeneity of SSc.

Method: We pooled the SSc and control populations from the 2 available studies providing an overall sample of 2190 SSc patients and 4104 controls all of European Caucasian origin.

Results: STAT4 being associated with various auto-immune diseases (AID), we stratified SSc patients according to the co-occurrence of another AID in the French sample. However, we could not identify any difference for allele or genotype frequencies between SSc patients with (n=72) or without (n=801) *STAT4* associated AID and thus included the whole French population in the subsequent analyses. The pooled data confirmed the association of *STAT4* rs7574865 T allele with SSc providing an OR of 1.39 ($P = 2.48 \times 10^{-13}$, 95%CI [1.2-1.51]). When subphenotypes related to cutaneous subsets, auto-antibody status or pulmonary involvement were queried, comparisons to controls provided evidence of association of T allele for all of them with the higher values of ORs for lung involvement. When comparisons were performed within SSc patients comparing those with *versus* without the clinical trait, significant findings were observed for lcSSc compared to dcSSC ($P = 0.045$ OR 1.16 95%CI [1.01-1.33]) and more strongly for fibrosing alveolitis compared to lack of lung involvement with an OR of 1.69 (95%CI: 1.07-2.69; p=0.025) for TT genotype

Conclusion: The common rs7574865 polymorphism of *STAT4* is strongly associated with SSc and contributes to its phenotypic heterogeneity. It seems to particularly predispose to interstitial lung disease and may be useful for risk stratification of SSc patients. In addition, STAT4 pathways may offer new therapeutic approaches.

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1805

The FAS -670A>G Polymorphism Influences the Susceptibility to Systemic Sclerosis Phenotypes.

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Purpose: To investigate the possible role of the FAS -670A>G functional polymorphism in the genetic predisposition to systemic sclerosis (SSc) susceptibility or clinical phenotype.

Methods: A total of 2900 SSc patients and 3186 healthy controls were included in this study. We analyzed the genotype and allele frequencies of the FAS -670A>G polymorphism in 9 distinct ethnic cohorts. Six case-control sets of European ancestry; a Spanish cohort: 228 SSc patients and 265 controls; a Dutch cohort: 203 SSc patients and 277 controls; a German cohort: 313 SSc patients and 247 controls; an Italian cohort: 323 SSc cases and 89 controls; a British cohort: 269 SSc patients and 182 Swedish patients. In addition, three distinct ethnic cohorts resident in the USA were considered in the FAS -607A genotyping; 1047 US white SSc patients and 692 controls, 159 US Hispanic SSc patients and 137 controls and 176 US African SSc patients and 194 controls. Genotyping was performed using Taqman 5´allelic discrimination assay.

Results: In the British, Italian and American white cohort we observed an association of the FAS -670G allele with lcSSc (respectively p=0.049; OR 1.25; 95%CI; 1.00-1.60 and p=0.045; OR 1.43; 95%CI; 1.00-207 and p=0.036; OR 1.18; 95%CI 1.01-1.39). A meta-analyses comprising all 9 cohorts revealed an association with both the FAS -670G allele and FAS -670GG genotype (both; p=0.036 allele; OR 1.10 95%CI 1.01 to 1.21 and genotype OR 1.13 95%CI 1.01 to 1.27) and the lcSSc phenotype. In a meta-analyses considering only Caucasian individuals we found that both the FAS -670G allele as well as the FAS -670GG genotype were associated with lcSSC (genotype; p= 0.017; OR; 1.16 95%CI 1.03 to 1.31 and allele p= 0.020;OR 1.12; 95%CI 1.02-1.24). In addition, a recessive model of the -670GG genotype revealed a strong association with SSc, lcSSc and ACA+ lcSSc (respectively, p=0.004; OR 1.23; 95%CI 1.07 to 1.41, p=0.0003; OR 1.33; 95%CI 1.14 to 1.56) and p=0.0002; OR 1.45; 95%CI 1.19 to 1.76)

Conclusion: Our data show that the FAS -670A>G polymorphism plays a role in lcSSc susceptibility, a trend observed in other auto-immune diseases as well.

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1806

Activin-Smad Pathway Is Activated in Systemic Sclerosis. Kae Takagi, Yasushi Kawaguchi, Yuko Ota, Takahisa Gono, Akiko Tochimoto, Yasuhiro Katsumata, Chikako Fukasawa, Masako Hara and Hisashi Yamanaka, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Systemic sclerosis is a chronic disease of unknown etiology characterized by autoimmunity, vascular damage, and progressive fibrosis of the skin and internal organs. However, it has not been elucidated how the fibrosis is achieved. The pathogenesis of fibrosis is not well understood and then there are not any effective treatments. It has been reported that overproduction of collagen, fibronectin, other many extracellular matrix and cytokines such as transforming growth factor b(TGF-b) and connective tissue growth factor (CTGF) in fibroblast cultured from SSc patients skin. TGF-b is thought to be the most important mediator, which induce fibrosis in SSc patient. Activin is a member of the TGF-b superfamily and initially discovered as inducers of follicle-stimulating hormone release. Recently wide varieties of functions of activins have been reported. Particularly, activin has the important functions to repair a tissue in acute and chronic inflammatory diseases, and to induce fibrosis in liver and renal tissue. Previous report was suggested the activin receptor 1B (ACR1B) also known as ALK4/5 mRNA was highly expressed in SSc patient. Then, we have investigated how activin is involved in the development of fibrosis in SSc.

Method: Serum activin levels were measured by an ELISA assay. The expression of activin was determined by RT-PCR and immunohistochemistry in fibroblasts cultured from skin of SSc patients and healthy controls (HC). The production of procollagen type I was measured by an ELISA assay, and gene expression of COL1a was quantitated using real-time PCR. Ligand induced activation of the Smad signaling pathway was examined by Western blot analysis.

Results: Serum activin levels were significantly higher in SSc patient than HC. Activin expression was also higher in cultured SSc fibroblasts. Activin stimulation induced phosphorylation of Smad2/3 and CTGF expression in SSc fibroblasts. Procollagen production and Col1a mRNA was also increased by activin stimulation. The basal level of Smad2/3 phosphorylation was higher in cultured SSc fibrobrast,

and treatment of ALK4/5 inhibitor SB431542 abrogated phosphorylation of Smad2/3 and CTGF expression. Treatment of ALK4/5 inhibitor also attenuated collagen production induced by activin. The mechanism for activation of activin pathway in SSc fibroblast is speculated using autocrine activin production.

Conclusion: Activin play a critical role in collagen production of SSc fibroblast. Inhibition of activin-smad pathway would be a new approach for treatment of SSc.

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1807

The PPAR Gamma Agonist Rosiglitazone Reverses the Persistent Fibrotic Phenotype of Scleroderma Fibroblasts. Xu Shi-wen[1], Andrew Leask[2], Mark Eastwood[3], Liaquat Suleman Verjee[4], Christopher P. Denton[1] and David Abraham[1], [1]UCL Medical School, London, United Kingdom, [2]University of Western Ontario, London, ON, [3]University of Westminster, London, United Kingdom, [4]London, United Kingdom

Purpose: The transcription factor peroxisome proliferator-activated receptor (PPAR)γ plays an important role in controlling cell differentiation. The aim of the present study was to examine whether PPARγ expression was reduced in scleroderma (SSc) fibroblasts and whether PPARγ agonists could suppress the persistent fibrotic phenotype of SSc fibroblasts.

Method: Fibroblasts (n=6) were obtained from control and SSc tissue. The effect of PPARγ agonist rosiglatizone (20 μM) on the phenotype of normal and SSc fibroblasts was assessed using Western blot, cell migration and 3D-collagen matrix contraction analyses. Results were verified using PPARγ knockout dermal fibroblasts and normal dermal fibroblasts transfected with PPARγand control siRNA.

Results: PPARγ protein expression was significantly reduced in SSc fibroblasts compared to normal control ($p<0.05$). Rosiglitazone reduced the characteristic overexpression of α-SMA, Col-1 and CTGF protein and elevated PPARγ expression by lesional SSc fibroblasts ($p<0.05$). Moreover, rosiglitazone alleviated the enhanced ability of SSc fibroblasts to migrate and to contract collagen gel lattices ($p<0.05$). TGFβ-induced Smad3 phosphorylation and CTGF protein expression was impaired in PPARγ knockout fibroblasts and normal fibroblasts treated with specific PPARγ siRNAs ($p<0.05$). Basal fibroblast activity was unaffected by rosiglitazone.

Conclusion: Reduced PPARγ expression by lesional SSc fibroblasts appears to contribute to the persistent fibrotic phenotype of this cell type. The PPARγ agonist rosiglitazone may represent a novel, selective treatment for SSc.

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1808

Augmentation of IL-21 Receptor by Endothelin-1 Via Endothelin Receptor B in Skin Fibroblasts From Systemic Sclerosis. Yasushi Kawaguchi, Kae Takagi, Akiko Tochimoto, Yuko Ota, Yasuhiro Katsumata, Takahisa Gono, Masako Hara and Hisashi Yamanaka, Tokyo Women's Medical University, Tokyo, Japan

Purpose: Endothelin (ET)-1 is a vasoconstrictive agent which is involved in endothelial dysfunction in patients with systemic sclerosis (SSc). Recently, it is reported that ET receptor antagonist is a useful treatment for Raynaud's phenomenon and pulmonary arterial hypertension in patients with SSc, and currently we are able to select a selective antagonist for ET receptor A (ETRA) or a dual antagonist for ETRA and ETRB. However, the effects of ET-1 on skin fibroblasts derived from patients with SSc (SSc fibroblasts) remain to be elucidated. In this study, we sought to determine key mediators induced by ET-1 through ETRA and/or ETRB in SSc fibroblasts.

Method: The expression of ETRA and ETRB in skin fibroblasts was estimated by immunohistochemistry using antibodies against a specific for ETRA or ETRB. We comprehensively analyzed ET-1-induced genes by skin fibroblasts from SSc patients and healthy donors using DNA microarray using Affymetrix GeneChip Human U133 Plus 2.0 Array. Recombinant ET-1, BQ123 as selective ETRA antagonist, BQ788 as selective ETRB antagonist, and PD145065 as dual ETRA and ETRB antagonist were purchased in Sigma. A quantitative analysis of mRNA was performed by a real-time RT-PCR method using a specific TaqMan probe. IL-6, TGF-beta and procollagen type I were measured by commercial ELISA kits.

Results: Both ETRA and ETRB were expressed in skin fibroblasts constitutively. In addition of optimal ET-1 and BQ-123 in culture media, IL-21 receptor (IL-21R) mRNA was over-expressed in SSc fibroblasts using DNA microarray. This phenomenon was confirmed by real-time RT-PCR. On the other hand, the stimulation of ET-1 with BQ788 or PD145065 failed to induce IL-21R gene expression in SSc fibroblasts. Those findings strongly suggest that IL-21R expression is dependent upon ET-1 signal transduction through ETRB alone. It was reported that IL-21 induced collagen production in intestinal fibroblasts from inflammatory bowel disease. In the next experiments, we investigated whether exogenous IL-21 could induce the fibrogenic mediators and procollagen production in skin fibroblasts. The addition of recombinant IL-21 increased the production of IL-6, TGF-beta, and procollagen type I in culture media of SSc fibroblasts. These phenomena were augmented by pre-stimulation with optimal ET-1.

Conclusion: ET-1 induced IL-21R through ETRB in SSc skin fibroblasts, and the addition of IL-21 increased the production of IL-6, TGF-beta and procollagen type I, suggesting that blocking ETRB as well as ETRA may play an important role in treatment for systemic sclerosis.

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1809

Cytokines Produced by Type I Collagen (CI)-Stimulated PBMC From Patients with Systemic Sclerosis (SSc) but Not Localized Scleroderma (LS) Inhibit Matrix Metalloproteinase (MMP-1) Expression in SSc Dermal Fibroblasts. Monica Brown[1], Arnold E. Postlethwaite[2], Linda K. Myers[3] and Karen Hasty[4], [1]University Tennessee Health Science Center, LeBonheur Children's Medical Center, Memphis, TN, [2]Univ Physicians Found Inc, Memphis, TN, [3]UT Medical Group Inc, Memphis, TN, [4]Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute of Allergy and Infectious Diseases (contract N01-AR-902242), the NIAMS US Department of Veterans Affairs, TN

Purpose: Patients with SSc in contrast to patients with LS have cellular immunity to a variety of autoantigens, including CI. How immunity to autoantigens contributes to disease pathogenesis is not understood. Fibroblasts grown from explants of lesional skin of patients with SSc but not from non-lesional skin exhibit a transient resistance to TNFa-induced stimulation of MMP-1, the major collagenase of human dermal fibroblasts, that is reversed after multiple population doublings, suggesting this is an acquired phenotype. The purpose of this study is to test the hypothesis that PBMC from SSc patients cultured with CI will synthesize cytokines/factors that will induce fibroblast resistance to expression of MMP-1.

Methods: In preliminary studies, PBMC from ten adult SSc patients were isolated and cultured with bovine CI for 6 days. The supernatants were pooled and added to cultures of SSc dermal fibroblasts and incubated for 21 days with periodic media renewal. The response of the fibroblasts was determined by induction of MMP-1 by TNFa. The pooled supernatant was further assayed for cytokine content using an antibody array. To compare juvenile and adult disease, supernatants from cultures of PBMC, incubated with and without CI, from six juvenile patients with LS or SSc and four adult patients with limited or diffuse cutaneous SSc were also analyzed.

Results: Pooled supernatants from PBMC co-cultured with CI from ten adult SSc patients induced MMP-1 resistance to TNFa stimulation in the fibroblasts similar to cultures of low passage fibroblasts taken from lesional skin of adult SSc patients. Assay of the supernatant showed distinct cytokines were induced by incubation with CI. Supernatants from PBMC, cultured without collagen, from adult and juvenile patients with SSc as well as juvenile patients with LS significantly increased levels of MMP-1 by 2-3 fold over media/collagen controls, with or without TNFa stimulation ($p<0.05$). However, when PBMC from juvenile or adult SSc but not juvenile LS patients were cultured with collagen, the supernatants induced marked resistance to TNFa upregulation of MMP-1 in SSc fibroblasts ($p<0.05$). Array analyses showed CI induced production of a variety of cytokines in PBMC from patients with SSc that were not found in LS CI-stimulated PBMC supernatants.

Conclusion: CI induces production of soluble cytokines/factors by PBMC that inhibit MMP-1 synthesis by dermal fibroblasts. These cytokines/growth factors are specific for adult and juvenile SSc and are not elevated by CI-stimulated PBMC from LS patients. Identification of the involved cytokines and the associated regulatory pathways should provide a better understanding of the pathogenesis of fibrosis in SSc.

Disclosure: M. Brown, LeBohneur Children's Medical Center, 2 ; **A. E. Postlethwaite**, arGentis pharmaceuticals, 5, 9, National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute of Allergy and Infectious Diseases , 2, National Institute of Arthritis and Musculoskeletal and Skin

Diseases, 2, US Department of Veterans Affairs, 3 ; **L. K. Myers**, National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute of Allergy and Infectious Diseases, 2, National Institute of Arthritis and Musculoskeletal and Skin Diseases (Scor), 2 ; **K. Hasty**, The US Department of Veterans Affairs , 2 .

1810

Rac Inhibition Reverses the Fibrotic Phenotype of Scleroderma Fibroblasts. Andrew Leask[1], Xu Shi-wen[2], Mark Eastwood[3], Christopher P. Denton[4] and David Abraham[4], [1]University of Western Ontario, London, ON, [2]University College London, London, United Kingdom, [3]University of Westminster, London, United Kingdom, [4]UCL Medical School, London, United Kingdom

Purpose: Rac GTPase plays a key role myofibroblast formation and is required for bleomycin-induced skin fibrogenesis. The aim of the present study was to examine whether rac1 activity was elevated in scleroderma (SSc) fibroblasts and whether rac antagonists could suppress the persistent fibrotic phenotype of SSc fibroblasts.

Method: Fibroblasts (n=6) were obtained from control and SSc tissue. The effect of rac antagonist NSC 23766 (100mM) on the phenotype of normal and SSc fibroblasts was assessed using Western blot, cell migration and 3D-collagen matrix contraction analyses. Results were verified by overexpressing rac1 in normal and rac1 knockout dermal fibroblasts. The mechanism underlying the effects of rac1 on fibroblasts was evaluated using inhibitors of specific signal transduction pathways.

Results: Rac1 activity was significantly elevated in SSc fibroblasts compared to normal controls ($p<0.05$). NSC 23766 reduced the characteristic overexpression of a-SMA, Col-1 and CTGF protein in lesional SSc fibroblasts ($p<0.05$). Moreover, NSC 23766 alleviated the enhanced ability of SSc fibroblasts to contract collagen gel lattices ($p<0.05$). NSC 23766 also reduced elevated Akt phosphorylation in SSc fibroblasts. In an Akt/PI3-kinase-dependent fashion, overexpressing rac1 caused elevation of a-SMA, Col-1 and CTGF expression and matrix contraction in normal and rac1 knockout fibroblasts ($p<0.05$). Basal fibroblast activity was unaffected by NSC 23766.

Conclusion: Elevated rac activity in lesional SSc fibroblasts appears to contribute to the persistent fibrotic phenotype of this cell type, via an Akt-dependent mechanism. Targeting rac/Akt may represent a novel, selective treatment for SSc.

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1811

Functional Regulation of Fibrosis in Vitro and In Vivo by CUTL1 Isoforms. Tetsurou Ikeda[1], Maria Fragiadaki[2], Xu Shiwen[3], Markella Ponticos[4], Patricia Garcia[4], Korsa Khan[3], Christopher P. Denton[3], Osamu Hosono[1], Chikao Morimoto[1], David Abraham[4] and George Bou-Gharios[2], [1]Univ of Tokyo/Inst of Med Scie, Tokyo, Japan, [2]Renal medicine, Imperial College of London, United Kingdom, [3]UCL Medical School, London, United Kingdom, [4]Royal Free and University College Medical School, London, United Kingdom

Purpose: Tissue scarring occurs after injury following the release of several mediators including TGF-beta, PDGF, CTGF, Wnt and ET1. These factors stimulate fibroblasts to differentiate into myofibroblasts characterized by the expression of α-smooth muscle actin and the excessive production of extracellular matrix molecules such as type1 collagen (COL1). Prolonged or abnormal production of these cytokines results in irreversible fibroblast stimulation (fibrosis), a major cause of keloid and

Scleroderma (SSc). In SSc patients COL1 is deposited in many organs including the lung, kidney and skin. The data from knock-in mice, overactive TGF-beta signalling show the same fibrogenic pathology as in SSc, supporting a key role for cytokines in the pathogenesis of fibrosis. COL1 expression is controlled in vivo by an enhancer containing 5 DNase Hypersensitive sites encompassing pivotal regulatory sites.

Analysing these sites we found cis-element consensus site for the transcription factor CUTL1. CUTL1 is known as both activator and repressor of gene transcription. But the role of CUTL1 in for the normal regulation COL1 or in fibrosis is unknown.

Methods: NIH 3T3 cell lines having Empty vector (EV) and sh-CUTL1(sh-C) vector were selected by puromycin. Transient transfection of CUTL1 and short CUTL1expression vectors were performed on the NIH3T3 cells and normal human fibroblast cells. Western blots were performed to check protein level of the ET1, CTGF, Wnt and COL1. Reporter assay of human COL1A enhancer+proximal vector or proximal vector only were apply to EV, sh-C cells and transiently transfected with CUTL1 and short CUTL1 over-expression vectors. EMSA(electorophretic mobility shift assay) and ChIP assay were done to verify its binding ability to the promoter of COL1A.Wound

healing assay were performed on sh-CUTL1 cell lines. Bosentan(both ET1 and ET-2 receptors antagonist) were used. SSc lung fibroblasts were used too.

Results: Over-expression of CUTL1 and short CUTL1 increased protein level of ET1,Wnt, beta-catenin, CTGF and COL1. EMSA and ChIP results showed the CUTL1 can bind to 1095 ,1609 of enhancer sites and proximal site. Wound healing assay indicated that sh-CUTL1 reduced the cell mobility ($p<0.05$). Bosentan treatment of sh-CUTL1 reduced the protein level of COL1 compared to control. CUTL1 isoforms expression was increased in the SSc compare to control.

Conclusion: CUTL1 isoforms up-regulated the protein level of ET1,CTGF, Wnt and COL1.Treatment of Bosentan on the sh-CUTL1 showed the synergistic reduction of collagen protein. These results indicated that CUTL1 up-regulates fibrosis related cytokines and COL1. In the SSc fibroblasts, CUTL1 isoforms were increased compare to control. More over, sh-RNA of CUTL1 in SSc showed the reduction of COL1. These results indicated that CUTL1 isoforms are the new pathway via TGF-beta in fibrosis.

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1812

Dysregulated Pro- and Antiangiogenic Chemokine Expression in Systemic Sclerosis. Bradley J. Rabquer[1], Yong Hou[1], Pei-Suen Tsou[1], G. Kenneth Haines Haines III[2], Michele L. Gerber[1], James R. Seibold[1] and Alisa E. Koch[3], [1]University of Michigan, Ann Arbor, MI, [2]Yale University, New Haven, CT, [3]Veteran's Administration and University of Michigan, Ann Arbor, MI

Purpose: Systemic sclerosis (SSc) is characterized by microvascular abnormalities and leukocyte infiltration. Chemokines are a family of small proteins that have leukocyte activation and chemoattractant properties. Also, some chemokines have angiogenic or antiangiogenic effects. Monokine induced by interferon-γ (IFN-γ) (MIG/CXCL9) and IFN-inducible protein 10 (IP-10/CXCL10) are CXC chemokines that are antiangiogenic. Their effects are mediated by a shared receptor, CXCR3, which is expressed on endothelial cells (ECs). In contrast, CXCL16 is a proangiogenic chemokine with a unique receptor, CXCR6, which is also expressed on ECs. In this study we sought to determine the expression of MIG, IP-10, CXC16, and their receptors in SSc skin and serum.

Methods: Biopsies from proximal (less involved) and distal (more involved) skin and serum were obtained from patients with SSc and normal (NL) volunteers. Immunohistochemistry was performed to determine the expression of MIG, IP-10, CXCL16, CXCR3, and CXCR6 in SSc and NL skin. ELISAs were performed to determine the concentration of MIG, IP-10, and CXCL16 in SSc and NL serum.

Results: MIG is highly expressed in the stratum spinosum of the epidermis of distal SSc skin (52%, n=21 patients), proximal SSc skin (52%, n=21), and normal skin (48%, n=10). Similarly, IP-10 is also highly expressed in the stratum basalis layer of the epidermis of distal SSc skin (100%, n=21 patients), proximal SSc skin (100%, n=21), and normal skin (100%, n=10). The levels of MIG and IP-10 were also significantly increased in SSc serum (876 pg/ml and 495 pg/ml, respectively, n=21 patients) compared to normal serum (126 pg/ml and 263 pg/ml, respectively, n=8, both $p<0.05$). In contrast, the expression of their receptor, CXCR3, is significantly decreased on ECs in distal SSc skin (21%, n=21) and proximal SSc skin (25%, n=21) compared to NL skin (54%, n=10, both $p<0.05$). In addition, the expression of CXCL16 is significantly decreased on the surface of ECs in distal SSc skin (20%, n=21) and proximal SSc skin (18%, n=21) compared to NL skin (45%, n=10, both $p<0.05$), while being significantly increased in SSc serum (4.6 ng/ml, n=21) compared to normal serum (3.3 ng/ml, n=9, $p<0.05$). However, the expression of its receptor CXCR6 is significantly increased on the surface of ECs in distal SSc skin (15%, n=19) and proximal SSc skin (16%, n=19) compared to NL skin (4%, n=8, both $p<0.05$).

Conclusion: Antiangiogenic MIG and IP-10 are highly expressed in SSc skin and serum, whereas the expression of their receptor, CXCR3, is downregulated in SSc skin. In contrast, angiogenic CXCL16 is upregulated systemically in SSc serum, while the expression of its receptor, CXCR6, also is upregulated in SSc skin. These results indicate that despite an abundance of pro- and antiangiogenic chemokines in SSc serum, that chemokine receptor expression in SSc skin is regulated in an effort to promote angiogenesis in the avascular SSc skin.

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1813

Specific Histone Deacetylases (HDACs) Modulate Fibrosis and Angiogenesis in Systemic Sclerosis (SSc). Hossein Hemmatazad, Britta Maurer, Hanna Maciejewska Rodrigues, Renate E. Gay, Beat A. Michel, Steffen Gay, Oliver Distler and Astrid Jüngel, Center of Experimental Rheumatology, Zurich Center of Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland

Purpose: Recently, we have shown that Trichostatin A (TSA) does not only inhibit the activity of HDACs but also modulates significantly the transcriptional expression of two isoforms of HDACs, HDAC3 and 7. While the expression of HDAC7 is almost completely down-regulated by TSA, HDAC3 expression is up-regulated. Furthermore, we demonstrated that silencing of HDAC7 has anti-fibrotic effects in skin fibroblasts from patients with SSc. However, there are reports indicating that silencing of HDAC7 affects angiogenesis in human umbilical vein endothelial cells (HUVECs). Since microvascular damage is characteristic for SSc, we investigate here the role of HDAC3 in fibrosis and in angiogenesis in human uterine microvascular endothelial cells (HUMECs).

Method: Over-expression of HDAC3 in SSc skin fibroblasts and HUMECs was achieved by transfecting a HDAC3-expression vector/plasmid into cells using Amaxa nucleotransfection. An empty vector was used as control. Gene expression patterns of collagen types I and III, connective tissue growth factor (CTGF) and intercellular adhesion molecule-1 (ICAM-1) were analyzed by Sybr Green Real-time PCR. To assess the expression on the protein level, antibodies against collagen types I and III, CTGF and ICAM-1 were used for Western blot. Endothelial capillary sprouting was assessed using tube formation assay.

Results: After over-expression of HDAC3 in skin fibroblasts from patients with SSc, the transcription of collagen types I and III was reduced by 38 ± 16 % and 25 ± 20 % (n=6 each, $p<0.05$) respectively. These changes could be confirmed on the protein level by Western blot. In addition, the mRNA expression of other pro-fibrotic molecules such as CTGF remained unchanged in cells over-expressing HDAC3, while the expression of ICAM-1 was significantly reduced (50 ± 20 %, n=4, $p<0.05$). Western blot confirmed the results on the protein level. Over-expression of HDAC3 did not affect the expression levels of HDAC7, suggesting that HDAC3 exerts its anti-fibrotic effects independently of HDAC7. Using the tube formation assay, over-expression of HDAC3 did not inhibit the angiogenesis in HUMECs. However, in HDAC3 over-expressing cells, the accumulative length and number of tubes were increased to 204 ± 46 and 185 ± 52 % ($p<0.05$), after 18h of seeding the cells on Matrigel, compared to cells transfected with the empty vector.

Conclusion: Based on the fact that the altered angiogenesis is a major factor in the pathogenesis of SSc, we could show here that the over-expression of HDAC3 improves angiogenesis and has anti-fibrotic effects in SSc.

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1814

Inhibiting B-Cell Activation by Skin Fibroblasts and Pulmonary Epithelial Cells: a New Treatment for Systemic Sclerosis ? Antoine Francois[1], Isabelle Couillin[2], Dominique Wachsmann[3], Jean Sibilia[4] and Jacques-Eric Gottenberg[5], [1]EA 3849 Laboratoire de Physiopathologie des Arthrites, Illkirch Graffenstaden, France, [2]UMR-IEM 6218 Molecular Immunology and Embryology, F-45071 ORLEANS Cedex 2, France, [3]Illkirch - Graffenstaden, France, [4]Hautepierre, Strasbourg, France, [5]University Hospital of Strasbourg, Strasbourg, France

Purpose: B lymphocytes might play a role in the induction of skin and pulmonary fibrosis in systemic sclerosis. BAFF and APRIL, key cytokines for B-cell activation, are increased in serum and skin from patients with systemic sclerosis. Lung fibrosis induced by bleomycin (BLM) is decreased in CD19-/- mice. We therefore investigated whether an increase of these cytokines could be observed in the activated skin fibroblasts isolated from SSc patients and in the bleomycin model of systemic sclerosis.

Method: Quantitative RT-PCR and ELISA were performed to evaluate BAFF mRNA induction and BAFF release by skin fibroblasts isolated from patients with SSc and subsequently stimulated with TLR ligands : BLP for TLR2, poly I:C for TLR3, LPS for TLR4, IFNs I, IFN-γ and TNF-α. BAFF levels were also evaluated in the broncho-alveolar lavages (BAL) and lung lysates from bleomycin-treated mice 1, 7, 10 or 14 days after administration of BLM (15mg/kg) (n=4 mice per group).

Results: Skin fibroblasts isolated from SSc patients synthesized and released BAFF in response to poly I:C (25 fold, 500pg/mL), LPS (10 fold, 200pg/mL) and IFNs I (15 fold, 200pg/mL) stimulation. BLP, IFN-γ and TNF-α had no effect. Interestingly BAFF secretion by skin fibroblasts seemed to be disease specific as this cytokine was not detected in activated normal skin fibroblasts culture supernatants. No

increase of APRIL expression was observed compared to controls skin fibroblasts. We also found a major increase of BAFF expression in BAL and lungs from bleomycin-treated mice (5000 pg/ml in BAL vs 340 pg/mL in controls after 14 days). Interestingly, BAFF increase was higher in BAL than in lungs, which suggests that alveolar epithelial cells are the main contributors to BAFF secretion.

Conclusion: Taken together, these data suggest that resident cells may participate through BAFF release to B cells-induced fibrosis in skin and lung from patients with SSc. BAFF might thus be a relevant therapeutic target in systemic sclerosis.

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1815

Measurement of Total Serum Activin A in Patients with Systemic Sclerosis. Vasiliki-Kalliopi K. Bournia[1], Haralampos M. Moutsopoulos[2] and Panayiotis G. Vlachoyiannopoulos[2], [1]School of Medicine,National University of Athens, Greece, [2]School of Medicine, National University of Athens, Athens, Greece

Purpose: Activin A is a member of the transforming growth factor-β superfamily that has been implicated in the pathogenesis of inflammatory diseases and has been shown to enhance hepatic, pulmonary, kidney and pancreatic fibrosis. Recently, evidence of elevated circulating levels of activin A was reported in patients with pulmonary hypertension. Our aim was to assess the levels of total Activin A in sera from patients with Systemic Sclerosis.

Method: Sera were obtained from 40 patients with systemic sclerosis (SSc) and 39 age and gender matched healthy controls (**patients:** mean age 58,6 years, range 23-74 years, mean disease duration 13,15 years, lcSSc=15, dcSSc=25 / **controls:** mean age 58,4 years, range 24-75 years). Female patients and controls were also matched for menstrual cycle phase. All participants provided written informed consent prior to blood sampling. The samples were stored at -80°C until assayed. Levels of total serum Activin A were analyzed using a commercial solid phase sandwich ELISA kit (OXFORD BIO-INNOVATION LTD, product code: MCA1426KZZ). All samples were assayed in duplicate and the mean was calculated.

Results: Total serum activin A levels were higher in the patient group as compared to the control group (median 522.8 pg/ml vs 431.4 pg/ml, Mann-Whitney-U-test, p= 0.0131). The non parametric Kruskal-Wallis test was used to determine significant differences in total serum activin A levels between the subgroups of SSc patients with (n=8, median 567.3 pg/ml) or without pulmonary arterial hypertension (PAH)(n=32, median 499.8 pg/ml) and controls (p= 0,0167). Dunn's multiple comparison test was used to compare serum activin A levels in subgroups. A significantly higher Activin A serum level was shown for patients with PAH compared to controls ($p<0.05$). In addition we compared activin A levels in the subgroup of SSc patients with disease of recent onset (<5 years) (n=8, median= 669,8 pg/ml) to SSc patients with established disease (> 5years) (n=32, median= 511,7 pg/ml) and to controls (Kruskal-Wallis test, p= 0.0057). Significantly higher activin A serum levels were shown for SSc patients with disease duration of less than 5 years compared to controls (Dunn's multiple comparison test $p<0.05$).

Conclusion: Elevated total serum activin A levels in SSc patients with pulmonary involvement and in particular in those with pulmonary arterial hypertension could indicate a possible role of this molecule in the pathogenesis of systemic sclerosis and especially in the initial disease stages.

Disclosure: V. K. K. Bournia, None; **H. M. Moutsopoulos**, None; **P. G. Vlachoyiannopoulos**, None.

1816

Activation of Scleroderma-Like Signaling Pathway: Importance of PDGFR-NADPH Oxidase Complex and Receptor Integrity. Tatiana Spadoni[1], Silvia Svegliati[1], Lucia De Gennaro[1], Gianluca Moroncini[1], Enrico Avvedimento[2] and Armando Gabrielli[1], [1]Università politecnica delle Marche, Ancona, Italy, [2]Università "Federico II", Napoli, Italy

Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by widespread vascular changes and progressive fibrosis of the skin and internal organs. We have demonstrated the presence of stimulatory immunoglobulins binding to PDGF receptor in serum of SSc patients. These autoantibodies from SSc patients show functional agonistic activity as demonstrated by induction of tyrosine phosphorylation and production of reactive oxygen species (ROS). Moreover isolated IgG from SSc patients induced myofibroblast conversion and type I collagen expression in normal human fibroblasts. The scope of this study is to elucidate the cellular and molecular changes elicited by the

PDGFR autoantibodies in normal cells and to assess the molecules engaged in the membrane complex recognised by SSc IgG and their role in the generation of PDGFR signalling and ROS.

Method: The interaction between SSc IgG, PDGFR and the subunits of the NADPH oxidase complex was evaluated by immunoprecipitation of extracts from stimulated and unstimulated fibroblasts and HeLa cells, constitutively devoid of PDGFR, stably transfected with different alpha and beta PDGFR recombinant DNA constructs, with purified SSc IgG and monoclonal anti-PDGFR antibodies. Immunocomplexes were characterized by specific immunoblotting with anti PDGFR, Nox-2 and Ha-Ras antibodies. The stably trasfected cell lines were used to determine the regions of PDGFR recognized by the different IgG and the importance of receptor integrity on signalling transduction.

Results: We have found that SSc IgGs from several different patients selectively immunoprecipitate gp91 phox, the NADPH oxidase Nox-2 subunit, in addition to PDGFR. SSc IgG stabilized a membrane-associated complex made of PDGFR and NADPH oxidase with the consequence of lengthening ROS/Ras activation. The recombinant receptors devoid of the cytoplasmatic domain are bound to gp91 but the lack of tyrosine phosphorylation sites impairs the transduction of the signalling.

Conclusion: SSc IgGs interact with the extracellular part of the PDGFR and prolong the formation of a stable PDGFR/NADPH oxidase complex on the cell membrane, leading to a persistent ROS production and appearance of the disease pathological signatures.

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1817

The Interplay of Vascular Function, Low Grade Inflammation and Innate Immunity in Raynaud's Phenomenon and Systemic Sclerosis. Marina E. Anderson, Theresa Barnes, Paula Pyrkotsch, Janette Lamb, Emma Naylor, Steven W. Edwards and Robert J. Moots, University of Liverpool, Liverpool, United Kingdom

Purpose: The pathophysiological processes underlying systemic sclerosis (SSc) are incompletely understood, despite considerable morbidity and risk of early mortality in this multi-system disease. However, preliminary work from our department suggests that, in addition to well-described vascular, fibrotic and immunological abnormalities, low-grade inflammation and innate immunity play a role. Our aim was to investigate the link between inflammation, innate immunity and vasculopathy in this disease.

Method: In our cohort of patients with limited and diffuse cutaneous SSc (lcSSc and dcSSc), primary RP (PRP), undifferentiated connective tissue disease (UCTD) and healthy control subjects, we studied three groups of parameters:

1) **NK cells and neutrophils:** peripheral blood

2) **Markers of inflammation and vascular activation:** peripheral blood

3) **Vascular physiology:**

a) Macrovascular function: Applanation tonometry

b) Microvascular morphology: Digital nailfold video capillaroscopy

c) Microvascular function: Digital iontophoresis of acetylcholine (ACh, endothelial-dependent vasodilatation) and nitroprusside (NP, endothelial-independent vasodilatation) measured by laser Doppler imaging.

Spearman's rank correlation coefficient was used to examine the relationship between the three groups of parameters.

Results: Having determined, in 40 subjects (9 controls, 5 PRP, 4 UCTD & 22 SSc), that there are significant differences between the studied subject groups of

1) markers of apoptosis (annexin V), activation (CD16) & adhesion (CD11b & CD18) on isolated **neutrophils**

2) markers **of endothelial activation** (VCAM-1, E-selectin & ET-1) and inflammation (IL-6) in sera , and

3) tests of **vascular function / morphology**,

we correlated our findings to examine the relationship between variables.

Significant correlations between markers of neutrophil / endothelial activation and vascular morphology / function are shown in table 1.

Table 1: Correlations between markers of neutrophil / endothelial activation and vascular morphology / function

	Spearman's rho correlation coefficient (p)	
lcSSc	Annexin V vs ACh iont	-0.929 (<0.001)
	Annexin V vs NP iont	-0.857 (0.007)
	CD11b vs Loops/mm	0.700 (0.036)
All disease groups	Annexin V vs ACh iont	-0.591 (0.016)
	Annexin V vs NP iont	-0.544 (0.029)
	E-selectin vs Loops/mm	-0.419 (0.024)
	ET-1 vs Appl tonometry	0.620 (0.018)
	IL-6 vs ACh iont	-0.388 (0.034)
	IL-6 vs Loops/mm	-0.414 (0.026)

Significant correlations were also seen between IL-6, ET-1 and cellular adhesion molecules in the disease states.

Conclusion: We demonstrated that 1)neutrophil apoptosis and 2)markers of both neutrophil and endothelial adhesion / activation are associated with micro- and macro-vascular function and morphology in RP and SSc, suggesting that low-grade inflammation, innate immunity and the micro-/macro-circulation play an integrated role in the pathogenesis of SSc.

Further work is underway to further characterise the role of both the innate immune system and the vasculature, and the interplay of these two systems in SSc, with the ultimate aim of identifying new markers of disease activity and severity.

Disclosure: M. E. Anderson, Actelion Pharmaceuticals, 2 ; **T. Barnes**, None; **P. Pyrkotsch**, Actelion Pharmaceuticals, 2 ; **J. Lamb**, Actelion Pharmaceuticals, 2 ; **E. Naylor**, None; **S. W. Edwards**, None; **R. J. Moots**, None.

1818

Upregulated Versican in Monocytes From Patients with Systemic Sclerosis: Role in Amplification of Monocytes-Chemoatrractant Protein-1 (MCP-1) Activity at Site of Fibrosis. Hidekata Yasuoka[1], Ayako Masuda[1], Yukie Yamaguchi[2], Takashi Satoh[1] and Masataka Kuwana[1], [1]Keio University School of Medicine, Tokyo, Japan, [2]Division of Pulmonary, Allergy, and Critical Care of Medicine, University of Pittsburgh, Pittsburgh, PA

Purpose: Pathologic features of systemic sclerosis (SSc) in early disease phase include infiltration of lymphocytes and monocytes surrounding small vessels, which may contribute to the subsequent fibrotic process. Phenotypic and functional alteration of circulating monocytes have been reported in SSc patients, but their roles in the pathogenesis of SSc are largely unknown. In this study, we identified molecules that preferentially expressed by SSc monocytes using DNA microarray analysis and examined their roles in the fibrotic aspect of SSc.

Methods: Peripheral blood samples were obtained from 36 patients with SSc (22 diffuse and 14 limited) and 32 healthy controls (HC). Circulating monocytes were isolated as CD14+ cells using the MACS™ sorting system. Pooled RNA samples derived from SSc and HC monocytes were applied to Oligo GEArray® system to evaluate expression profiles of 330 genes related to extracellular matrix and adhesion molecules, chemokines, and endothelial cell biology. Candidate genes defined by >1.5 fold increase of the expression level in SSc versus HC monocytes were further subjected to semi-quantitative RT-PCR combined with densitometry and TaqMan™ quantitative RT-PCR for confirmation. Protein expression of genes of interest in monocytes was evaluated by immunoblots or ELISA using culture supernatants of unstimulated monocytes and by 3-color fluorecent immunocytostaining. Chemoattractant activity of MCP-1 was assessed in cultures of monocytes in a TransWell® system in the presence or absence of the condroitin sulfate (CS) chain.

Results: By screening with oligo DNA microarray system, type I collagen, versican, MCP-1, IL-8, MMP-2 and CCR1 were selected as candidate genes preferentially expressed by SSc monocytes. The subsequent analyses by semi-quantitative and quantitative RT-PCR revealed that MCP-1 and versican were upregulated 3.5 and 4.8 times in SSc monocytes compared with HC monocytes, respectively. Protein expression analysis of culture supernatants from 14 SSc and 11 HC monocytes showed upregulated protein expression of versican ($p = 0.03$) and a trend toward increased expression of MCP-1 ($p = 0.2$) in SSc versus HC monocytes. Immunocytostaining analysis on SSc monocytes demonstrated colocalization of MCP-1 and versican in the Golgi apparatus. Since versican functions as a reservoir of various chemokines, through binding to its CS chain, we further examined the role of the CS chain on activity of MCP-1, one of fibrogenic chemokines. Binding of MCP-1 to the CS chains resulted in protection of MCP-1 from protease attack, and enhanced MCP-1-induced monocyte migration in a dose-dependent manner.

Conclusion: Increased expression of versican in complexed with MCP-1 in SSc monocytes may contribute to the pathogenesis of SSc by amplifying fibrogenic activity of MCP-1 in the affected tissues where monocytes are recruited.

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1819

Mesenchymal Stem Celles From Bone Marrow of Patients with Systemic Sclerosis: Properties and Pathogenic Perspectives. N. Del Papa[1], N. Quirici[2], C. Scavullo[2], L. Corti[2], M. Introna[3], W. Maglione[1], D. Comina[1], N. Vaso[1], F. Onida[4] and G. Lambertenghi Deliliers[4], [1]G. Pini Hospital, Milano, Italy, [2]1Università degli Studi di Milano, Milano, Italy, [3]OORRBG, Bergamo, Italy, [4]Fond.Osp. Magg. Policlinico e Università di Milano, Milano, Italy

Purpose: Bone marrow-derived mesenchymal stem cells (MSCs) are currently being studied to evaluate their potential role in the pathogenesis and/or management of autoimmune diseases. Several studies suggest that systemic sclerosis (SSc) may be seen as a stem cell disorder, however it is unclear whether MSCs from SSc patients are defective. Aim of the study was to evaluate the biological properties of bone marrow (BM) derived MSCs in patients with SSc, focusing on their phenotype and functional characteristics.

Method: BM samples were obtained from 28 SSc patients and 17 healthy donors. The MSCs were purified according to their adherence to the plastic (PA) and by positive selection for the expression of the low-affinity nerve growth factor receptor (L-NGFR), the p75 antigen known to be expressed in early MSCs. The stromal compartment was then analyzed in its progenitor number and functional properties by various assays. In addition, the anti-proliferative effects of normal and SSc MSCs were evaluated by co-culture experiments with SSc cutaneous fibroblasts.

Results: Phenotype analysis showed a decrease in the percentage of $NGFR^+$ cells with respect to normal marrows (nBM) (0.53±0.43% *vs* 1.17±0.64%; P=0.001). Furthermore, SSc $NGFR^+$ cells showed increased levels of CD105 surface expression, the TGF-b receptor (25.6±10.3% *vs* 13.8±5.9%; P=0.03). Proliferation ability was always impaired in comparison to healthy subjects both in the whole PA stromal compartment and in $NGFR^+$ cells, with a 1 to 4 log lower cell expansion. The clonogenic efficiency, evaluated by a CFU-F assay, was impaired both in the whole PA fraction (16.1±20.4 colonies/$1x10^6$ cells *vs* 34.2±18.3 in controls; P=0.01) and in the $NGFR^+$ cells (7±12.8 colonies/$1x10^5$ cells *vs* 69±61; P=0.011). Long-term BM culture assays showed that the impaired stromal growth poorly supported hematopoiesis, with a decrease in hematopoietic precursors during culture. Co-culture assays showed a inhibition of fibroblast proliferation, higher when fibroblasts were cultured with nBM MSCs (% of inhibition: 40±6.5% with nBM MSCs *vs* 26.3±8.6% with SSc MSCs; P=0.04).

Conclusion: The analysis of the SSc BM stromal compartment showed that MSCs are impaired in their number and functional properties, with an increased expression of the TGF-b receptor, suggesting that MSCs are involved in the pathogenic mechanisms of SSc. In addition, we show for the first time an anti-proliferative effect of MSCs on SSc cutaneous fibroblasts, even if it was lower in the presence of SSc BM MSCs. Our results arise relevant questions on BM MSCs as a therapeutic tool in Scleroderma. MSCs therapy is already considered for treating severe acute graft versus-host disease, which bears many similarities to SSc. The ability of MSCs to inhibit SSc fibroblast proliferation opens up exciting prospects for their use in anti-fibrotic strategies.

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1820

Faecal-Calprotectin as a Biomarker in Systemic Sclerosis. Kristofer Andréasson[1], Agneta Scheja[1], Tore Saxne[1], Bodil Ohlsson[2] and Roger Hesselstrand[1], [1]Dept of Clinical Sciences, Section of Rheumatology, Lund University, Lund, Sweden, [2]Dept of Clinical Sciences, Section of Gastroenterology and Hepatology, Lund University, Malmö, Sweden

Purpose: In systemic sclerosis (SSc), involvement of the gastrointestinal (GI) tract is frequent and its assessment distal to the oesophagus complicated in clinical practice. Faecal calprotectin (F-calprotectin), also known as S100A9/A8, is a validated biomarker in inflammatory bowel disease. In this study we analysed F-calprotectin to explore the mechanisms of GI involvement in SSc and to test its potential as a biomarker of GI involvement in SSc.

Method: The study comprised 77 consecutive SSc patients (65 female, 12 men). Mean disease duration, defined as years from first non Raynaud manifestation, was 9 (S.D.=7) years. Levels of calprotectin in stool and plasma were measured with ELISA (Bühlmann laboratories AG, Switzerland). F-calprotectin >50 µg/ml was considered pathologically increased. P-calprotectin was compared with the median (0.83 µg/ml) for healthy controls. Patients were subjected to a clinical, radiological and biochemical examination and their medical records studied. Statistical correlations were done with parametric tests using the logarithm of F-calprotectin and P-calprotectin.

Results: A majority of the patients had increased levels of F-calprotectin (median 125; interquartile range (IQR) 45-213 µg/ml). A significant relationship was noted between patients' reported proton pump inhibitor-usage and F-calprotectin ($r=0.50$; $p<0.001$) and the number of medications prescribed for GI dysfunction including malnutrition ($r=0.34$; $p=0.002$). Patients with radiological evidence of oesophageal dysfunction had higher levels of F-calprotectin than those without (mean 141 *vs* 60 µg/ml; $p=0.015$). F-calprotectin correlated with the estimated pulmonary arterial pressure (PAP; $r=0.47$; $p<0.001$), but not with finger arterial pressure or nailfold capillary density. Patients showing signs of diastolic dysfunction had higher F-calprotectin values ($p=0.006$). There was a weak relationship between F-calprotectin and vital capacity ($r=-0.25$; $p=0.027$) but no correlation with modified Rodnan Skin Score, limited or diffuse skin involvement or NSAID-usage. P-calprotectin was higher than previously reported in healthy controls (median 1.5; IQR 0.7-1.9 µg/ml), correlated with other markers of systemic inflammation, e.g. orosomucoid ($r= 0.58$; $p<0.001$), but did not show any significant relationship with F-calprotectin ($r=0.22$; $p=0.061$).

Conclusion: Patients with SSc have increased levels of calprotectin in faeces, which suggests presence of an inflammatory process in the GI tract. F-calprotectin correlates with clinically relevant GI manifestations and may prove to be a useful non-invasive marker of GI involvement in SSc.

Disclosure: K. Andréasson, None; **A. Scheja**, None; **T. Saxne**, None; **B. Ohlsson**, None; **R. Hesselstrand**, None.

ACR/ARHP Poster Session C

VASCULITIS I

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1821

Possible Genetic Association of HLA-A*2601 and B39 with Ocular Behçet's Disease in Japan. Toshikatsu Kaburaki[1], Misuko Takamoto[1], Jiro Numaga[1], Hidetoshi Kawashima[1], Makoto Araie[1], Yuka Ohnogi[1], Shinji Harihara[2], Shoji Kuwata[3] and Fujio Takeuchi[1], [1]The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]The University of Tokyo Graduate School of Science, Tokyo, Japan, [3]Teikyo University Chiba Medical Center, Teikyo University School of Medicine, Chiba, Japan

Purpose: Behçet's disease (BD) is known to be associated with HLA-B*51 in many different ethnic groups. Recently, several HLA-A alleles including HLA-A*2602 have been proposed as a candidate gene for BD susceptibility in several ethnic groups. To confirm the association of the HLA-A*26 allele and the other HLA class I alleles to BD, we studied HLA-A and -B polymorphisms in Japanese ocular BD patients.

Method: Seventy-nine Japanese BD patients who suffered from uveitis and 104 healthy controls were enrolled for analysis of polymorphisms of HLA class I. Statistical analysis was performed with Fisher's exact test and odds ratio (OR) with 95% confidential interval (95%CI). The significance (p value) was corrected by the numbers of alleles compared.

Results: The phenotype frequencies (PF) of HLA-A*2601 were significantly higher in BD patients (36.7%) than in controls (14.4%) (p=0.0110, OR=3.44, 95%CI=1.69-7.02). The PF of HLA-B*5101 was also significantly more frequent in BD patients (45.6%) than in controls (18.3%) (p=0.00240, OR=3.75, 95%CI=1.92-7.29). The PF of the HLA-A*2601 is significantly increased in the group of BD without HLA-B*5101 (53.5% Vs 14.1%, $p=7.50x10^{-5}$, OR=7.00, 95%CI=2.97-16.46), whereas the PF of HLA-A*2601 is not increased in the group of BD with the HLA-B*5101 (16.7% Vs 15.8%). The PF of the BD patients carrying the HLA-A*2601 or HLA-B*5101 is extremely increased comparing to the frequency in the control (74.7% Vs 29.8%, $p=6.64x10^{-8}$,OR=6.95, 95%CI=3.60-13.41). Whereas the association with the HLA-A*2602 in Japanese BD was reported previously, we could not detect the association of HLA-A*2602 in our BD cases (6.3% Vs 3.8%). The PF of the HLA-B39 is significantly increased in the BD-group without HLA-A*2601 and HLA-B*5101 (30.0% Vs 4.1%, p=0.0491, OR=10.00, 95%CI=2.23-44.82). The PF of the HLA-A*2601 is significantly associated with severe ocular disease (p=0.023) and poor visual prognosis corresponding the best corrected-visual acuity of 0.1 or less in the worse eyes (p=0.0113).

Conclusion: Our results indicate that HLA-A*2601 is associated with BD independently from the HLA-B*5101, indicating that HLA-A*2601 is the additional susceptibility gene in the patients of BD in Japan. HLA-A*2601 might be a disease marker for the severity of ocular disease. Moreover, HLA-B39 might be a possibility of another susceptibility gene for ocular BD.

Disclosure: T. Kaburaki, None; **M. Takamoto**, None; **J. Numaga**, None; **H. Kawashima**, None; **M. Araie**, None; **Y. Ohnogi**, None; **S. Harihara**, None; **S. Kuwata**, None; **F. Takeuchi**, None.

1822

Localized Vasculitis of the Gastrointestinal Tract: A Case Series. Carlo Salvarani[1], Kenneth T. Calamia[2], Cynthia S. Crowson[3], Dylan V. Miller[3], Aaron W. Broadwell[2], Gene G. Hunder[3], Eric L. Matteson[3] and Kenneth J. Warrington[3], [1]Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [2]Mayo Clinic Jacksonville, Jacksonville, FL, [3]Mayo Clinic, Rochester, MN

Purpose: Localized vasculitis of the gastrointestinal tract (LVGT) occurring in isolation is unusual. The objective of this study is to describe the clinical features and outcomes of patients with LVGT.

Method: Medical records of 608 patients diagnosed with vasculitis involving the intraabdominal vasculature and/or abdominal viscera between 1/1996 and 12/2007 were reviewed. Only patients with histopathological confirmation or typical angiographic findings of vasculitis were included; patients with evidence of vasculitis outside the abdomen were excluded.

Results: We identified 18 cases with LVGT over the 12-year study period. The patients were predominantly Caucasian (89%) and female (67%). Mean age at diagnosis: 53.6 (±16.9) years. Most presented with abdominal pain (94%). Other symptoms included nausea (56%), vomiting (44%), diarrhea (44%) and abdominal angina (44%). GI bleeding (17%) was uncommon.

At presentation, mean hemoglobin was 12.7 (±1.6) g/dL, mean ESR was 30.6 mm/hour (±23.6) and mean CRP was 20.2 mg/L (±22; nl <8.0mg/L). ANCA, cryoglobulins and RF were negative in all patients tested. ANA and hepatitis C antibody were positive each in 1. Hepatitis B surface antigen was absent in all tested. Abdominal computed tomography (CT) scan findings included: bowel wall thickening, 3 (25%); bowel infarction, 2 (17%); liver infarcts, 2 (17%); splenic infarcts, 3 (25%). Conventional angiography was performed in 14 (78%) patients, 6 patients (33%) had CT angiography and 6 patients (33%) magnetic resonance (MR) angiography. Findings are listed in the table. Eleven patients (61%) underwent surgical intervention. Histologic confirmation of necrotizing vasculitis was recorded in 5 (28%) of patients, most commonly from gallbladder or small intestine specimens.

Corticosteroid therapy was administered to 10 patients (56%), 4 of whom also received other immunosuppressive agents. Mean follow-up was 12.6 (± 26.6) months. No evidence of vasculitis in other districts was observed during the follow-up. Eight patients (44%) died during the follow-up period (mean survival from diagnosis 6.7 (± 11.6) months) and of these, 3 deaths were related to vasculitis.

Conclusion: This largest series of LVGT reported to date reveals this uncommon form of vasculitis to be associated with significant morbidity and mortality. Laboratory tests are nonspecific; imaging is particularly helpful in assessing patients with suspected LVGT. Optimal treatment remains to be defined.

Table . Angiogram findings

Angiogram findings	No. of patients (%) (N= 15)				
Artery	aneurysm	stenosis	thickening	dilatation	occlusion
Celiac	3 (20)	7 (46.7)	2 (13.3)	2 (13.3)	2 (13.3)
Hepatic	1 (6.7)	5 (33.3)	0	3 (20)	3 (20)
Gastric	1 (6.7)	1 (6.7)	0	0	0
Splenic	2 (13.3)	4 (26.7)	0	0	3 (20)
Superior mesenteric	3 (20)	10 (66.7)	2 (13.3)	6 (40)	2 (13.3)
Inferior mesenteric*	0	5 (35.7)	1 (7.1)	4 (28.6)	1 (7.1)
Right renal	1 (6.7)	4 (26.7)	0	3 (20)	0
Left renal	1 (6.7)	3 (20)	0	1 (6.7)	0

* N = 14

Disclosure: C. Salvarani, None; **K. T. Calamia**, None; **C. S. Crowson**, None; **D. V. Miller**, None; **A. W. Broadwell**, None; **G. G. Hunder**, None; **E. L. Matteson**, None; **K. J. Warrington**, None.

1823

Identification of KIAA1529 as a Novel Susceptibility Gene for Behçet's Disease. Amr H. Sawalha[1], Yiping Fei[2], Ryan Webb[3], Beth L. Cobb[4], Jonathan Wren[5], Haner Direskeneli[6] and Güher Saruhan-Direskeneli[7], [1]University of Oklahoma, Oklahoma Medical Research Foundation, Department of Veterans Affairs Medical Center, Oklahoma City, OK, [2]University of Oklahoma, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Oklahoma Medical Research Foundation, JK Autoimmunity, Inc., [5]Oklahoma Medical Research Foundation, [6]Marmara University, Istanbul, [7]Department of Physiology, Istanbul Faculty of Medicine, Istanbul University

Purpose: Behçet’s disease is a chronic vasculitis characterized by recurrent oro-genital ulcers, skin lesions, uveitis, recurrent venous thrombosis and arterial aneurysms. The disease also affects the brain, joints, and in some cases the gastrointestinal tract. Behçet’s disease is poorly understood, and treatment options currently available are nonspecific and frequently ineffective. There is clear evidence to suggest a genetic contribution to the pathogenesis of Behçet’s disease. The genetic association with HLA-B51 is the only established and repeatedly confirmed genetic association with this disease. The association in the HLA region, however, accounts for less than 20% of the genetic risk for Behçet’s disease.

Method: We have performed a genome-wide association scan (GWAS) in a cohort of 152 Behçet’s disease patients and 172 ethnically-matched healthy controls using DNA pooling and the Affymetrix 500K arrays, followed by TaqMan® genotyping in individual samples in candidate susceptibility loci.

Results: We identified 5 novel candidate genes for Behçet’s disease (*KIAA1529*, *CPVL*, *LOC100129342*, *UBASH3B*, and *UBAC2*). Cluster analysis of the GWAS data identified 14 SNPs in the *KIAA1529* locus (9q22) that are associated with Behçet’s disease. Among the associated SNPs, the Behçet’s disease risk allele in rs2061634 located within *KIAA1529* leads to the change in the amino acid at position 995 to cysteine (S995C) in the *KIAA1529* protein (odds ratio= 2.04, 95%CI= 1.45-2.88, P value= $4.2X10^{-5}$). By identifying genes specifically and consistently co-expressed with *KIAA1529* over 3,651 human 2-color microarray datasets from NCBI’s GEO, we used an algorithm to

infer function using a "guilt by association" method. The 20 genes most closely matching *KIAA1529*'s expression trends (i.e., up and down-regulated with it) were analyzed for commonalities using a literature mining software (IRIDESCENT). Through these analyses, we predict that the transmembrane protein KIAA1529 is expressed on the nuclear membrane and is involved in nuclear trafficking.

Conclusion: We identified the genetic association between Behçet's disease and *KIAA1529* (Behçet's disease associated gene 1, *BDAG1*). Determining the functional consequences of the identified missense polymorphism might help to better understand the pathogenesis of this debilitating disease.

Disclosure: A. H. Sawalha, None; **Y. Fei**, None; **R. Webb**, None; **B. L. Cobb**, None; **J. Wren**, None; **H. Direskeneli**, None; **G. Saruhan-Direskeneli**, None.

1824

Efficacy of Infliximab in Patients with Different Types of Refractory Uveitis. Laura Niccoli, Carlotta Nannini, Emanuele Cassarà, Daniela Chindamo, Michele Bertoni, Giampaolo Gini, Ivo Lenzetti and Fabrizio Cantini, Hospital of Prato, Prato, Italy

Purpose: To evaluate the long-term efficacy and safety of infliximab (IFX) in patients with different types of sight threathening uveitis resistant to corticosteroid (CS) with associated immunosuppressants. Primary outcome measure was visual acuity (VA) at the end of follow up. Secondary measures were the proportion of relapse-free subjects through months 12.

Method: Open-label, single-center, 12-month, prospective, follow up study on 20 consecutive patients, 13 with Beh□et's disease (BD), 2 with Vogt-Koyanagi-Harada (VKH) disease and 5 with idiopathic posterior uveitis (IPU), who had failed at least one immunosuppressants in addition to CS. At baseline patients received prednisone 1 mg/Kg/day with rapid tapering, IFX infusions (5 mg/Kg) over a 12-month period. Non-responders after the third infusion withdrew from the study. Patients were evaluated for visual VA, ocular inflammation degree, number of ocular attacks, and incidence of adverse events (AEs).

Results: At 12-month visit, 10/13 (77%) BD patients achieved a complete remission with no relapse. All patients suspended corticosteroids at week 22. Mean VA improved from 0.2±0.6 to 0.5±0.2 ($p<0.001$), and ocular attacks dropped from 40 in the year before therapy to 5 after IFX cessation ($P<0.001$), 2/13 (15%) patients showed no improvement.

Two females with VKH disease, achieved a complete disease remission after the second infusion and CS were suspended with no relapse after the sixth. IFX monotherapy allowed maintaining the remission in both patients with improvement of VA (median VA before IFX 0.45, median VA after IFX 0.85).

Five IPU patients had inactive disease after the fourth infusion, and the remission was maintained over a median follow-up of 12 months. None of the patients required additional treatment with local CS. Median VA (9 eyes) improved from 0.15 at baseline to 0.8 ($p:0.001$) at the end of follow-up. No serious adverse events were recorded.

Conclusion: Infliximab is rapidly effective and safe in a high proportion BD patients, and both in VKH and IPU patients with refractory posterior uveitis, and may be helpful to prevent recurrences.

Disclosure: L. Niccoli, None; **C. Nannini**, None; **E. Cassarà**, None; **D. Chindamo**, None; **M. Bertoni**, None; **G. Gini**, None; **I. Lenzetti**, None; **F. Cantini**, None.

1825

Catastrophic Primary Central Nervous System Vasculitis. Carlo Salvarani[1], Robert D. Brown Jr.[2], Kenneth T. Calamia[3], Teresa J. H. Christianson[2], John Huston III[2], James F. Meschia[3], Caterina Giannini[2], Dylan V. Miller[2] and Gene G. Hunder[2], [1]Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic, Jacksonville, FL

Purpose: Primary Central Nervous System Vasculitis (PCNSV) is an uncommon and heterogeneous condition that affects the brain and spinal cord. Recently, we reported 101 patients with PCNSV seen over a 21-year period (1983-2003). Although most patients responded to therapy, an increased mortality was observed. This study was undertaken to identify the subset of patients who appear to have a catastrophic clinical course in the context of the largest cohort of consecutive patients with PCNSV studied to date.

Methods: The present study extends the previous cohort and includes 131 patients with PCNSV seen over the 25 year period of 1983 to 2007. PCNSV diagnosis was based on brain/spinal cord biopsy or angiograms. Intracranial internal carotid artery and proximal anterior, middle, and posterior cerebral arteries were considered large cerebral vessels. The modified Rankin Scale was used to identify catastrophic disease: patients with Rankin 5 (severe disability) or 6 (stroke death) at diagnosis and/or Rankin 5 or 6 at last follow-up (patients with Rankin < 5 at diagnosis must develop a score of 5 or 6 within 6 months after the diagnosis). We compared patients with catastrophic disease to those without.

Results: 11 cases had catastrophic PCNSV. Cerebral angiography was performed in 10 patients and showed bilateral, multiple, large-vessel changes in 9. Three cases had positive CNS biopsy. Compared with the 120 patients without, the 11 patients with catastrophic vasculitis more frequently had paraparesis/quadriparesis at presentation (36.4% vs 2.5%, $p < 0.001$), angiographic presence of bilateral, large-vessel vasculitis (90% vs 52.9%, $p = 0.04$), and MRI evidence of cerebral infarctions (100% vs 51.4%, $p = 0.004$); those infarctions were more frequently multiple and bilateral (77.8% vs 37.6%, $p = 0.03$) and more frequently involved both the cortex and subcortex on initial MRI (66.7% vs 25.7%, $p = 0.02$). Parenchymal and meningeal gadolinium-enhancing lesions occurred less frequently (0% vs 42.2%, $p = 0.01$). Other differences in those with catastrophic PCNSV that were not statistically significant included a higher frequency of persistent neurological deficit or stroke at presentation (63.6% vs 36.7%) and more patients were treated initially with cyclophosphamide or azathioprine (63.6% vs 47.5%). Cerebrospinal fluid abnormalities and the frequency of relapses/recurrences were similar in the two groups. No patients with catastrophic PCNSV showed a lymphocytic histopathological pattern. Survival of the patients with catastrophic PCNSV was significantly reduced ($p < 0.001$).

Conclusion: Catastrophic PCNSV appears to form a clinical subset of PCNSV characterized by bilateral, multiple, large-cerebral vessel lesions and multiple cerebral infarctions.

Disclosure: C. Salvarani, None; **R. D. Brown**, None; **K. T. Calamia**, None; **T. J. H. Christianson**, None; **J. Huston**, None; **J. F. Meschia**, None; **C. Giannini**, None; **D. V. Miller**, None; **G. G. Hunder**, None.

1826

Defective FOXP3 Expression in Patients with Acute Kawasaki Disease and Restoration by Intravenous Immunoglobulin Therapy.

Biagio Olivito[1], Andrea Taddio[2], Gabriele Simonini[1], Cristina Massai[1], Sara Ciullini[1], Eleonora Gambineri[1], Maurizio de Martino[1], Chiara Azzari[1] and Rolando Cimaz[1], [1]University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [2]Institute of Child Health, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy

Purpose: The acute phase of Kawasaki disease (KD) is characterized by an impaired immunoregulation and a link between CD4+CD25+FOXP3+ regulatory T cells (Tregs) and Intravenous Immunoglobulin (IVIG) has recently been suggested. We therefore investigated FOXP3 expression in patients with KD, comparing the expression pattern during the acute phase and after defervescence. A possible association of the FOXP3 SNP 543 (rs2232367) with KD was also evaluated.

Methods: FOXP3 expression was evaluated on 8 children with KD and 15 healthy children by flow cytometry and Real-Time Taqman polymerase chain reaction. FOXP3 SNP 543 was genotyped by denaturing high-performance liquid chromatography (DHPLC) and sequencing on DNA samples from 58 additional children with KD and 114 healthy donors.

Results: The percentage of Tregs was significantly ($p=0.0002$) lower during the acute phase of KD than in sex-and age-matched healthy donors (median % ± SD: 4.8 ± 1.3 vs 7.7 ± 1.7) and a similar tendency was revealed for FOXP3 mRNA transcripts ($p<0.0001$). FOXP3 expression increased significantly, at both protein and mRNA levels, after intravenous immunoglobulin (IVIG) treatment (at least 48 hrs; median 9.5 days, range 2-30) and achieving complete remission of disease. Of the 58 patients screened, only one female subjects (1.7%) carried the presence of 543 SNP in heterozygosis (C>T; for a total of 1 allele out of 88), with no difference between KD patients and controls (0/203 alleles).

Conclusion: Our data reinforce the notion of an impaired immunoregulation in KD, suggesting also a role of IVIG treatment in modifying the Tregs compartment. FOXP3 SNP 543 do not seem to be involved in susceptibility to KD in Italian children.

Disclosure: B. Olivito, None; **A. Taddio**, None; **G. Simonini**, None; **C. Massai**, None; **S. Ciullini**, None; **E. Gambineri**, None; **M. de Martino**, None; **C. Azzari**, None; **R. Cimaz**, None.

1827

Frequency of Fibromyalgia , Depression and Sleep Disorders in Wegener Granulomatosis. Rula Hajj-Ali[1], William S. Wilke[1], Leonard H. Calabrese[2], Gary S. Hoffman[3], Tiffany Clark[1] and C. A. Langford[1], [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]Cleveland Clinic, OH

Purpose: Morbidity and mortality for Wegener granulomatosis (WG) has dramatically improved. Nonetheless, patient surveys have revealed that despite remission, patients often complain of diffuse pain and fatigue. We hypothesized that there is an increased frequency of fibromyalgia (FM), depression, and sleep disorders in patients with (WG) that may contribute to the fatigue and pain.

Method: The frequency of FM, depression and sleep disorders in 55 patients with WG was assessed by 3 validated instruments: the London Fibromyalgia Epidemiologic Study Screening Questionnaire (LFESSQ), Epworth Sleepiness Scale (ESS), and the Brief Patient Health Questionnaire (BPHQ-9).Questionnaires were administered prospectively to patients who met the ACR criteria for WG and who have been followed at the Center for Vasculitis Care and Research at Cleveland Clinic for at least 2 visits. Eligibility included age of >18 years and duration of WG for at least 3 months. Pain in all 4 items and on both sides of the LFESSQ was used to identify fibromyalgia. BPHQ-9 score of ≥ 10 were used to indicate moderate depression. An ESS score of ≥10 was used to indicate abnormal sleepiness. Fatigue was captured quantitatively by the visual analogue scale (FVAS) and qualitatively by the LFESSQ fatigue questionnaire. Disease activity and damage were captured by using the Birmingham Vasculitis Activity for WG (BVAS/WG) and the Vasculitis damage index (VDI). Furthermore we assessed the correlation between VDI, BVAS/WG, disease duration, gender and BPHQ9, LFESSQ ESS, FVAS and evaluated correlations between ESS, BPHQ -9 and fatigue (FVAS).

Results: Patients mean age was 52 years, 60 % were males , and mean disease duration was 104 months. Based on the LFESSQ, 23.64 % of patients had fibromyalgia, 21.8 % had moderate depression defined as BPHQ-9 ≥ 10 , and 29 % had sleep abnormalities per ESS scores of ≥ 10. 76.4 % reported fatigue and 47.3% indicated that fatigue significantly limited their activities. There was no correlation between the score of the BPHQ-9, ESS, LFESSQ, FVAS, and VDI, BVAS-WG, or disease duration. There was no difference in BPHQ-9, LFESSQ, and ESS based on gender. Comparison of the WG cohort to the general population, revealed WG patients have a significantly greater frequency of fibromyalgia (LFESSQ 23.6 vs. 13 p=0.02) and depression (21.8 vs. 7.6 p< 0.001). There was a strong correlation between FVAS (fatigue) and BPHQ-9 (depression) [correlation coefficient of 0.73 (95% CI: 0.54, 0.92)].The correlation between FVAS and ESS was significant but not as strong as with the BPHQ 0.36 (95% CI: 0.10, 0.62).

Conclusion: Fibromyalgia and depression occur more often in WG compared to the general population. The association is not related to disease activity, damage or disease duration. Fatigue is very common and significantly limits the normal daily activities. Depression and sleep disorders contribute to fatigue in WG patients. Further studies with larger numbers of patients will be necessary to confirm these observations.

Disclosure: R. Hajj-Ali, None; **W. S. Wilke**, None; **L. H. Calabrese**, None; **G. S. Hoffman**, None; **T. Clark**, None; **C. A. Langford**, None.

1828

Comprehensive Analyses of Serum Peptides in Microscopic Polyangiitis. Yukiko Takakuwa[1], Manae S. Kurokawa[2], Seido Ooka[1], Kouhei Nagai[2], Mitsumi Arito[2], Kayo Masuko[2], Naoya Suematsu[2], Kazuki Okamoto[2], Shoichi Ozaki[1] and Tomohiro Kato[2], [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]St.Marianna University Graduate School of Medicine, Kawasaki, Japan

Purpose: Microscopic polyangitis (MPA), one of systemic vasculitides, is charactered by necrotising vasculitis of small vessels. We comprehensively analyzed serum peptides from MPA patients by proteomics techniques to find disease-specific peptides that would be a candidate disease marker, or that would be useful for elucidation of the pathogenesis.

Method: Peripheral blood was obtained from 26 patients with MPA before treatment and 1 or 6 weeks after start of the treatment, and from 27 patients with systemic lupus erythematosus (SLE) before treatment. Serum peptides were isolated by using magnetic beads with hydrophobic carriers. Then the peptides were detected comprehensively and quantitatively by mass spectrometer. Peptides increased or decreased significantly by the treatment, and those differently expressed between MPA and SLE before treatment, were selected by using ClinProt software. Amino acid sequences of a part of the increased/decreased peptides were identified by MS/MS analysis and protein data base searching.

Results: We detected peptides with 1523m/z, 1737m/z, 2503m/z, and 7767m/z whose ion intesities were high before the treatment but were low after the treatment. Similarly, peptides with 1625m/z, 2115m/z, and 7160m/z whose ion intesities were low before the treatment but were high after the treatment were detected. Interestingly, the peptides with 1523m/z, 1737m/z, and 2503 m/z were specifically detected in the serum samples from the MPA patients before the treatment, not in those from the SLE patients. The peptide with 1523m/z (p1523) was identified as C-terminal 13 amino acids (AA) of apolipoprotein A-I (ApoA1). Serum concentration of ApoA1 was found to be low in the MPA group before the treatment (5.9 mg/dL on average), which recovered into the normal range (11.9-16.5 mg/dL) 6 weeks after start of the treatment (12.9 mg/dL on average) by ELISA. A chemically synthetic peptide of p1523 was found to increase secretion of IL-6 and IL-8 from microvascular endothelial cell lines.

Conclusion: We made a surveillance of serum peptides in the patient with MPA and found several peptides whose abundance was changed depending on the disease activity. Of the peptides, p1523, the C-terminal 13 AA of ApoA1, was increased in peripheral blood of the patients with active MPA. Our results suggest that the peptide promotes the inflammation and migration of neutrocytes to the inflamed sites, by increasing secretion of IL-6 and IL-8, which leads to exacerbation of the vasculitis.

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1829

The Relationship Between Markers of Platelet Activation and Inflammation with Disease Activity in Wegener's Granulomatosis.

Gunnar Tomasson[1], Michael P. LaValley[1], Kahraman Tanriverdi[1], Javier D. Finkielman[2], John C. Davis Jr.[3], Gary S. Hoffman[4], W. Joseph McCune[5], E. William St. Clair[6], Ulrich Specks[2], Robert Spiera[7], John H. Stone[8], Jane E. Freedman[1] and Peter A. Merkel[1], [1]Boston University, Boston, MA, [2]Mayo Clinic, Rochester, MN, [3]Genentech, Inc, South San Francisco, CA, [4]Cleveland Clinic, Cleveland, OH, [5]University of Michigan, Ann Arbor, MI, [6]Duke University Medical Center, Durham, NC, [7]HSS, New York, NY, [8]Massachusetts General Hospital, Boston, MA

Purpose: There is an increased occurrence of venous thromboembolic events (VTEs) in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). The objective of this study was to determine if measures of platelet activation or inflammation are associated with disease activity in Wegener's granulomatosis (WG).

Methods: Study subjects were participants in a clinical trial. Soluble CD40 ligand (sCD40L), C-reactive protein (CRP), interleukin (IL) -6, IL-8, monocyte chemoattractant protein 1 (MCP-1), P-selectin, and vascular endothelial growth factor (VEGF) were measured with commercially available ELISA kits. PR3-specific ANCA were measured by capture ELISA. Plasma samples were obtained at baseline (active disease), at remission, and prior to, during, and after first flares. Disease activity was assessed by the Birmingham Vasculitis Activity Score for WG (BVAS/WG). Association of biomarkers with disease activity was determined with conditional logistic and linear regression. To provide a graphical representation of change in marker levels at baseline, remission and at times surrounding flares, a non-parametric smoothing curve was generated for selected markers using the LOESS algorithm (Figure).

Results: 180 subjects underwent 2044 visits over a mean follow-up of 27 months; markers were measured in 563 samples. Longitudinally, all markers, other than IL-6, were associated with disease activity. Strongest associations for active disease at baseline vs. remission were observed for PR3- ANCA (OR= 9.41; 4.03-21.99), sCD40L (OR=4.72; 95%CI: 2.47-9.03), P-selectin (OR=6.26; 95%CI: 2.78-14.10), and inversely for MCP-1 (OR=0.36; 95%CI: 0.22-0.57). BVAS/WG increased 0.80 (95%CI:0.44-1.16), 0.83 (95%CI: 0.42-1.25) and 0.81 (95%CI: 0.48-1.15) per unit increase in PR3-ANCA, sCD40L and P-selectin respectively, and decreased 1.54 (95% CI: 2.12 -0.96) per unit increase in MCP-1.

Conclusion: Selected measures of platelet activation correlate with disease activity in WG. Thrombosis and inflammation in AAV might have related underlying biologic processes. Future studies of this relationship might lead to insights into the pathophysiology of AAV and discovery of clinically useful biomarkers.

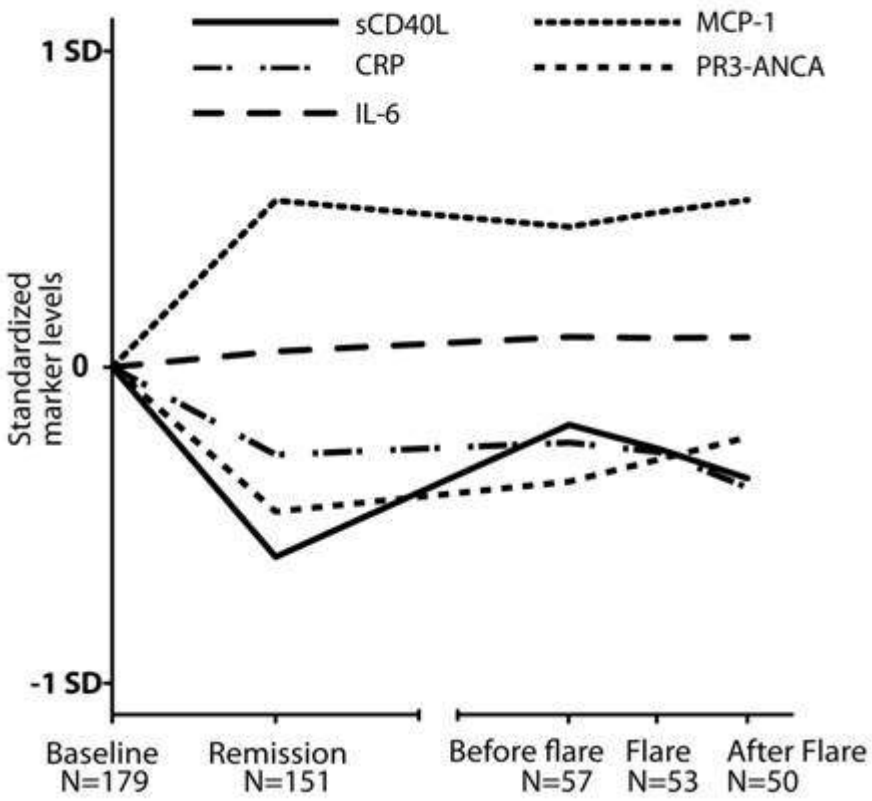

Figure. Non-parametric smoothing of selected marker levels at several time points. The x-axis represents different study visits and the y-axis represents standardized marker levels after subtraction of the baseline value (all baseline values set to zero).

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1830

Pulmonary Involvement in Microrcopic Poliangiitis: Focus On Prevalence and Outcome of Pulmonary Fibrosis. Maria A. Kokosi[1], Athanasios G. Tzioufas[2], Sophie P. Toya[2], Kyriaki A. Boki[3], Alexandra Zormpala[1], Haralampos M. Moutsopoulos V[2] and George E. Tzelepis[2], [1]Laikon General Hospital, Athens, Greece, [2]Medical School-Univ of Athens, Athens, Greece, [3]Sismanogleion General Hospital, Athens, Greece

Purpose: We sought to determine the type of pulmonary involvement in microscopic polyangiitis (MPA), focusing primarily on pulmonary fibrosis (PF), its prevalence, temporal relationship with other disease manifestations, and outcome.

Methods: Thirty three patients (16 men) with biopsy proven p-ANCA positive MPA (age 63.5 years) participated in the study. Pulmonary involvement was assessed with standard methods, including radiographic imaging (chest radiographs and high resolution CT), pulmonary function testing, bronchoscopy and bronchoalveolar lavage, and lung biopsy if indicated. All-cause mortality was analysed by the Kaplan-Meier method and was compared between MPA patients with and without PF.

Results: At the time of diagnosis, renal involvement was detected in all patients, with renal biopsies being consistent with segmental necrotizing glomerulonephritis in all patients. The most common respiratory symptom was hemoptysis, found in 9 (27%) of patients. Pulmonary fibrosis was present in 12 (36%) of patients at time of diagnosis, whereas one patient developed PF while on therapy, approximately 10 years from disease diagnosis. In 7 patients with PF, respiratory symptoms related to fibrosis preceded other disease manifestations by a period (median) of 13 months (range 5-120 months). Patients were followed up for a period of 38±30 months (mean±SD). Presence of PF was associated with increased mortality (p=0.02), with 6 deaths occurring in the fibrotic group and 1 in the nonfibrotic group. In the fibrotic group, most deaths were related to PF.

Conclusion: Pulmonary fibrosis occurs frequently in MPA, may precede other disease manifestations by a variable length of time, and has a poor prognosis.

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1831

Human Neutrophil Peptide as a Potential Inflammatory Mediator in Behçet's Disease. Joong Kyong Ahn[1], Ji-Min Oh[1], Ji Young Chai[2], Eun-Kyung Bae[1], Jaejoon Lee[1], Chan-Hong Jeon[3], Jinseok Kim[4], Hoon-Suk Cha[1] and Eun-Mi Koh[1], [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Jesang Hospital, Seongnam-Shi Gyeonggi-Doe, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea, [4]Cheju National University College of Medicine, Cheju, South Korea

Purpose: Behçet's disease (BD) is a systemic vasculitis of unknown etiology, characterized by orogenital ulcers, uveitis, and arthritis, which is more prevalent in Korea, China, Japan and Turkey. Neutrophil hyperactivity plays an important role in the pathogenesis of BD. Human neutrophil peptides (HNPs) are released into the extracellular milieu from neutrophils during inflammation, resulting in stimulation of cell adhesion, release of chemokines, induction of reactive oxygen species and T cell chemotaxis. In this study, we examined the expression of HNP-1 in the peripheral blood of BD patients and aim to show that HNP-1 expression level is associated with clinical features of BD.

Method: Our patients fulfilled the diagnostic criteria of the international BD study group. ELISA and real-time PCR were performed to measure HNP-1 protein level in the sera and HNP-1 mRNA level in peripheral blood mononuclear cells in BD patients and healthy control (HC).

Results: There was no significant difference in the serum HNP-1 protein level between BD patients (n=20) and HC (n=19)(2.20 ± 0.45 vs. 2.04 ± 0.42 ng/ml, p=0.796). However, the level of HNP-1 mRNA was significantly higher in BD patients (n=56) compared to HC (n=36)(0.52 ± 0.11 vs. 0.20 ± 0.04, p=0.007). The level of HNP-1 mRNA was significantly higher in BD patients with arthritis than those without arthritis (0.97 ± 0.24 vs. 0.29 ± 0.08, p=0.014). Based on organ involvement, patients were grouped into vascular BD (n=21), Behçet's arthritis (n=20), ocular BD (n=7), intestinal BD (n=5), CNS BD (n=3). The mean HNP-1 mRNA levels of each group were 0.37 (±0.14), 0.74 (±0.21), 0.20 (±0.13), 0.81 (±0.53), and 0.33 (±0.28), respectively. High level of HNP-1 mRNA was observed not only in the patients with arthritis but also in the patients with intestinal involvement. However because of the small patient number, this difference did not reach statistical significance (p=0.157). In BD patients, the HNP-1 mRNA and protein level had a positive correlation with leukocyte counts (r=0.333, p=0.018; r=0.615, p=0.019). No significant correlations were found between HNP-1 mRNA level and ESR or CRP.

Conclusion: The HNP-1 mRNA is overexpressed in the peripheral blood mononuclear cells of BD patients, especially in patients with the clinical manifestations of arthritis and intestinal ulcers. Considering its role in the innate and adaptive immune responses, these findings suggest that HNP-1 may play an important role as a potential inflammatory mediator in BD.

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Testicular Vasculitis: Findings Differentiating Isolated From Systemic Disease in 75 Patients. José Hernández-Rodríguez[1], Carmela D. Tan[2], Curry L. Koening[3], Atul A. Khasnis[2], E. René Rodríguez[2] and Gary S. Hoffman[2], [1]Hospital Clínic. IDIBAPS. University of Barcelona, Barcelona, Spain, [2]Cleveland Clinic, Cleveland, OH, [3]University of Utah, Salt Lake City, UT

Purpose: Testicular vasculitis (TV) may be recognized as part of a systemic vasculitis (SV), such as polyarteritis nodosa (PAN) or Wegener's granulomatosis (WG), or exist as single-organ/isolated (testicular) vasculitis (ITV). The current study sought to identify clinical and histologic features that distinguish SV from ITV. The distinction is deemed important because it is already well established that in other forms of single organ vasculitis surgical therapy alone may be curative.

Method: We identified patients with biopsy-proven TV from pathology databases from our institution and from an English language PubMed search. Patients were included if there was data available to confidently determine TV extent. Data recorded included clinical, laboratory and histologic features, treatment and clinical follow-up.

Results: 75 patients with TV (mean age 41 yrs; range 4-78) were included (8 from our institution). 75% of patients presented with painful testicular swelling/mass, 10.5% with a painless swelling/mass and 4% with epididymal swelling/mass or inguinal pain. 10.5% had no testicular complaints and vasculitis was discovered at autopsy or in interventions for incomplete testicular descent or vasectomy repair. Constitutional and/or musculoskeletal (systemic) symptoms were reported in 36% patients. Vasculitis involved the testicle in 81% of cases, the epididymis in 43% and the spermatic cord in 33%. Forty-three (57%) patients had ITV and 32 (43%) had SV. 7/8 (88%) patients from our institution had ITV. No differences between ITV and SV patients were found in regards to age, presenting testicular features, duration of testicular symptoms or time of follow-up. Compared to ITV patients, SV patients presented more often with systemic symptoms (100% vs. 12%; p=0.0001), elevated ESR (94% vs. 24%; p=0.0001) and anemia (53% vs. 3%; p=0.0001). Neoplasm was more frequently suspected in ITV than in SV (68% vs. 25%; p=0.002). Only 2 ITV patients received corticosteroids for a short period of time, whereas 96% of SV patients were treated (p=0.0001) and 65% also received cytotoxic agents. ITV was diagnosed more often by orchiectomy (77% vs. 41%; p=0.002) and less frequently by testicular biopsy (2% vs. 31%; p=0.0006) than SV. Non-granulomatous inflammation affecting medium-sized vessels occurred in most patients with both ITV and SV (>70%). Testicular carcinoma occurred concomitantly in 2 ITV patients. Among SV, PAN was the most frequently diagnosed (66%), followed by WG (16%).

Conclusion: TV occurs as ITV in men usually presenting with a testicular mass in the context of normal laboratory results and the absence of systemic symptoms. In most ITV patients a testicular neoplasm is initially suspected and TV is an unexpected finding. After surgical removal, ITV does not require systemic therapy. PAN is the systemic vasculitis most frequently associated with testicular involvement.

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1833

Characteristics of Wegener Granulomatosis (WG) Patients According to ANCA Status: Data From the FVSG Database. Raphaèle Seror[1], Christian Pagnoux[1], Philippe Guilpain[1], Loïc Guillevin[1] and French Vasculitis Study Group, [1]National Referral Center for Necrotizing Vasculitides and Systemic Sclerosis, Hôpital Cochin, Paris, France

Purpose: To study and compare the characteristics of anti-$PR3^+$, anti-MPO^+ and $ANCA^-$ WG patient subgroups.

Methods: Systematic retrospective study of the FVSG-database patients, diagnosed with WG according to the ACR and Chapel Hill Nomenclature classification criteria, and whose ANCA-test results were available. Their characteristics at diagnosis and outcomes were analyzed and compared according to their ANCA status.

Results: Among the 454 WG patients (261 (57.5%) male; mean±SD age = 51.3±16.2 years) of known ANCA status, 402 (88.5%) were $ANCA^+$ by immunofluorescence, with a cytoplasmic (n=315), perinuclear (n=56) or nonspecific (n=31) labeling pattern; enzyme-linked immunosorbent assay-determined specificities were: 280 anti-$PR3^+$, 48 anti-MPO^+ and 4 had both.

Compared to the 52 $ANCA^-$ patients, $ANCA^+$ patients had significantly higher median [IQR] creatinine levels (100 80–190] vs. 77 [67–100] µmol/l; p<0.001) and median [IQR] BVAS (21 [15–28] vs. 14 [11–20]; p<0.001). Multivariate analyses retained rhinitis (p=0.005) and elevated creatinine level ≥140 µmol/l (p=0.004) as being significantly associated with ANCA-positivity. Comparing anti-MPO^+ to anti-$PR3^+$ WG patients, the former were more frequently febrile (62% vs. 45%; p=0.01), and had arthralgias (55.3% vs. 34.0%; p=0.008) and cutaneous involvement (27.5% vs. 12.8%; p=0.03), but lower frequencies of myocardial infarction (1.8% vs. 8.5%; p=0.03) and recent-onset hypertension (6.3% vs. 14.9%; p=0.01).

During a mean±SD follow-up of 4.4±4.4 years, 239 (52.6%) patients relapsed and 12.3% died; relapse (48.1% of ANCA$^-$, 45.8% of anti-MPO$^+$, and 53.8% of anti-PR3$^+$ patients; NS) and mortality rates (13.5% of ANCA$^-$, 12.5% of anti-MPO$^+$, and 8.8% of anti-PR3$^+$ patients; NS) were comparable, regardless of ANCA status.

Conclusion: ANCA$^-$ WG patients were at lower risk of having renal involvement than ANCA$^+$ patients. Anti-MPO$^+$ WG patients were at higher risk of cardiovascular complications than anti-PR3$^+$ patients. However, mortality and relapse rates of our WG patients seemed to be independent of ANCA status.

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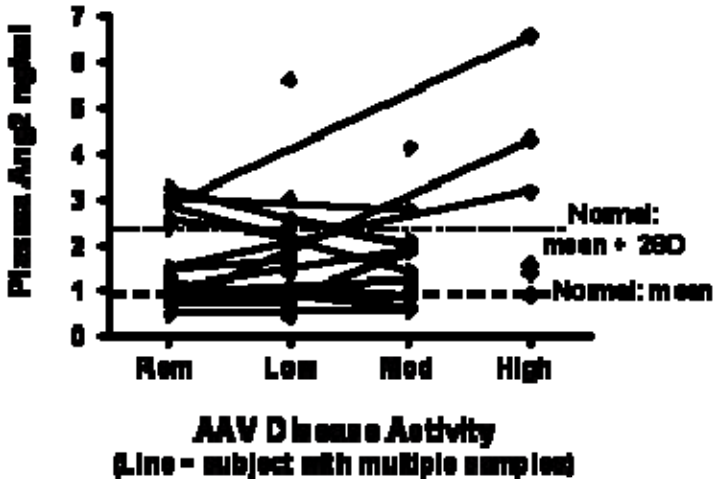
Angiopoietin-2 as a Biomarker in ANCA-Associated Vasculitis. Paul A. Monach[1], Philipp Kumpers[2], David Cuthbertson[3], Simon Carette[4], Gary S. Hoffman[5], Nader A. Khalidi[6], Carol A. Langford[5], Philip Seo[7], U. Specks[8], S.R. Ytterberg[8], Marion Haubitz[2] and Peter A. Merkel[9], [1]BU, Boston, MA, [2]Medical School Hannover, Germany, [3]University of South Florida, FL, [4]Toronto Western Hospital, Toronto, [5]Cleveland Clinic, Cleveland, OH, [6]Hamilton, [7]Johns Hopkins University, Baltimore, MD, [8]Mayo Clinic, Rochester, MN, [9]Boston University, Boston, MA

Purpose: To explore angiopoietin-2 (Ang-2) as a biomarker of active ANCA-associated vasculitis (AAV). Ang-2 is an inducible mediator of endothelial activation and vascular permeability. We have shown that circulating levels of Ang-2 are elevated in AAV prior to treatment and drop to normal levels after treatment. The present study was conducted to i) confirm the association of elevated Ang-2 with AAV at different levels of clinical disease activity and ii) evaluate changes in Ang-2 over time in patients transitioning between clinical remission and mildly-active disease.

Methods: 108 plasma samples from 59 patients with Wegener's granulomatosis or microscopic polyangiitis were selected from a repository linked to comprehensive longitudinal clinical data. Disease activity at each visit was assessed using BVAS, BVAS/WG, and physician global assessment (PGA). Ang-2 was measured by ELISA. Generalized linear models (GLM) were used to study the association of Ang-2 levels with activity measures while controlling for subject-specific effects.



Results: Active AAV, using any index, was associated with higher levels of Ang-2. This association was driven by subjects with highly active disease (Figure): mean Ang-2 levels were 2.99, 1.43, 1.42, and 1.49 ng/ml (normal = 1.0 ± 0.7 ng/ml) in high, moderate, low, or absent (remission) disease activity (p=0.0002). Among subjects with multiple assessments, most of whom transitioned between low activity and remission, Ang-2 levels tended to be stable relative to baseline (Figure).

Conclusion: Ang-2 levels are associated with highly-active AAV but not partially-treated or smoldering AAV. Assessing the value of Ang-2 as a predictor of relapse will require more study of longitudinal cohorts.

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1835

Oral Cyclophosphamide Therapy Diminishes Ovarian Reserve in Women with Wegener's Granulomatosis. Megan E. B. Clowse[1], Susannah Copland[1], T.C. Hseih[1], S.C. Chow[1], Gary S. Hoffman[2], Peter A. Merkel[3], Robert Spiera[4], John C. Davis Jr.[5], Steven R. Ytterberg[6], W. Joseph McCune[7], E. William St. Clair[8], U. Specks[6], J. H. Stone[9] and WGET Research Group, [1]Duke University, Durham, NC, [2]Cleveland Clinic, Cleveland, OH, [3]Boston University, Boston, MA, [4]Hospital for Special Surgery, New York, NY, [5]Genentech, Inc, South San Francisco, CA, [6]Mayo Clinic, Rochester, MN, [7]University of Michigan, Ann Arbor, MI, [8]Duke University Medical Center, Durham, NC, [9]MGH, Boston, MA

Purpose: Daily oral cyclophosphamide (CYC) is a standard treatment for severe Wegener's granulomatosis (WG). Monthly IV CYC for lupus leaves a third of women with ovarian failure. We hypothesized that the larger cumulative dose of CYC used to treat WG would result in a higher rate of diminished ovarian reserve.

Method: The Wegener's Granulomatosis Etanercept Trial (WGET) was a 180-patient randomized, placebo-controlled trial of etanercept therapy for this disease. Patients also received either CYC for severe WG or methotrexate for mild WG. All women under age 50 at enrollment were tested at the beginning and end of the study for plasma levels of anti-mullerian hormone (AMH) and follicle stimulating hormone (FSH). Diminished ovarian reserve was defined as a plasma AMH<1.0ng/ml and/or FSH>20mIU/ml. AMH is produced by the ovary and decreases with oocyte decline.

Results: This analysis included 42 women, ranging in age from 14-46 years (mean 32 ± 9). Baseline blood samples were available in 40 subjects. Daily oral CYC was administered during WGET to 28 women with a cumulative dose of 27 ± 23 grams (range 1-107 grams).

Women with exposure to CYC had a high rate of diminished ovarian reserve and a low mean AMH level (see table). For women with normal ovarian function at baseline, 6/8 who received CYC during the trial developed diminished ovarian reserve *vs*. 0/4 without CYC ($p<0.05$). The change in AMH was inversely correlated with cumulate CYC dose (regression coefficient -0.08, $p=0.01$), indicating a 0.8ng/ml decline in AMH for each 10g of CYC received.

Eighteen women, all but 2 under the age of 32, had not had a child prior to enrollment in the trial. Of these, 14 received CYC either before or during the trial and 13 of these had diminished ovarian reserve by the end of the study.

Conclusion: Diminished ovarian reserve occurred in 91% of women with WG treated with daily CYC. Compared to reports of patients with lupus treated with IV CYC, women with WG treated with daily CYC had a dramatically higher rate of ovarian dysfunction.

Table: AMH and diminished ovarian reserve based on CYC exposure.

	N	AMH** Mean ng/ml (SD)	Diminished Ovarian Reserve N (%)
Baseline evaluation (n=40)			
No prior CYC	16	2.5 (2.4)*	8 (50%)*
Prior CYC	24	0.6 (1.2)	20 (83%)

Final Evaluation (n=42)			
No CYC	9	1.9 (2.1)*	5 (56%)*
CYC prior to/during WGET	33	0.3 (0.5)	30 (91%)

* p<0.05 comparing no CYC vs CYC groups

** AMH declines with oocyte loss; AMH<1.0 is associated with decreased fertility.

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1836

Prevalence of Monozygotic Twins with Behçet's Syndrome. Seval Masatlioglu[1], F. Gogus[2], E. Seyahi[3], I. Fresko[3], E. Tahir-Turanli[4] and Hasan Yazici[3], [1]Istanbul, Turkey, [2]University of Gazi, Ankara, Turkey, [3]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [4]Istanbul Tecnical of University, Istanbul, Turkey

Background: Case reports about monozygotic twins with Behçet's syndrome (BS) have been very few (1-3). We considered this could have been due to in utero deaths. We are not aware of previous formal, systemic studies on monozygotic twin studies in this disorder.

Purpose: 1. To seek for the frequency of monozygotic twin births in BS and compare it to a healthy population sample from the same geography; 2. To seek for concordance/discordance if such monozygotic twins existed.

Methods: 1705 (1039 M/ 666 F) consecutive patients attending a dedicated BS outpatient clinic were questioned about a monozygotic twin(s). Similarly 7782 (3848 M/ 3913 F) consecutive medical school students were asked about having a monozygotic twin during their initial school registration. Monozygotic twins thus identified among both patients and controls were individually seen at the clinic. In addition, for BS patients, probands and twins were HLA, DNA and blood group typed to further confirm twin ship and being a carrier of HLA B51. All discordant monozygotic twins were contacted 8 years later for new emergence of disease.

Results: There were 6 (4 M/ 2F) (0.35%) patients among the BS and 28 (0.35%) among the controls who had a monozygotic twin. Of the 6 pairs of monozygotic twins 2 were concordant and 4 discordant. This was reconfirmed by DNA, HLA and blood groups analysis. 2 concordant patients and siblings were HLA B51 positive. Of the 4 discordant monozygotic twin pairs 2 pairs were carriers of HLA B51. The other 2 were HLA B51 negative. The syndrome had developed within 12 and 18 months in the 2 concordant twins and the organ systems involved were quite similar in both families. None of the monozygotic twin siblings of the remaining 4 probands developed the syndrome after 8 years of follow up.

Conclusion: The frequency of monozygotic twin births in BS is not different than that in the general population. The persistence of discordance after 8 years of follow up among the monozygotic twins of 4 probands gives some support for environmental factors operative in BS.

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3) Kobayashi T, et al. Monozygotic twins concordant for intestinal Behçet's disease. J Gastroenterol 2005;40:421-5.

Disclosure: S. Masatlioglu, None; **F. Gogus**, None; **E. Seyahi**, None; **I. Fresko**, None; **E. Tahir-Turanli**, None; **H. Yazici**, None.

1837

Cardiovascular Outcomes in a Cohort of 100 Patients with Wegener`s Granulomatosis. Vidya Nadig, Sriharsha Subramanya, Eamonn S. Molloy, Carol A. Langford and Rula A. Hajj-Ali, Cleveland Clinic, Cleveland, OH

Purpose: There is a growing body of evidence, based on surrogate markers of atherosclerosis, that patients with vasculitides, including Wegener`s Granulomatosis (WG) have an increased risk of cardiovascular disease. However there is little data confirming the link between vasculitis and overt cardiovascular events . The aim of this study was to examine the frequency of cardiovascular outcomes in patients with WG and to assess the relationship between WG disease activity and cardiovascular events.

Method: We examined a cohort of 100 patients with a diagnosis of WG according to the American college of Rheumatology criteria. Data were collected regarding ischemic events- Unstable Angina(UA), Non ST elevation myocardial infarction(NSTEMI), ST elevation MI(STEMI), transient ischemic attacks(TIAs) and ischemic stroke. We also collected data regarding WG disease activity by using the Birmingham Vasculitis activity score(BVAS-WG), a validated outcome measure used to assess disease activity, within one month of the ischemic event, when available.

Results: The male to female ratio was 1.2 :1 and the age of onset of disease ranged from 17-78 years of age. There were a total of 2 STEMI`s, 5 NSTEMI`s, 1 UA, 2 TIA`s, 3 Ischemic strokes. Among these events, BVAS-WG scores were available within 1 month of the cardiovascular event in 8 patients. Of these, 6 patients (75%) had active WG (BVAS-WG >0) . Among these 6 patients, the median interval between occurrence of the ischemic event and the diagnosis of WG flare was 0 days (range -3 to + 7 days).

Conclusion: Our results support the hypothesis that WG is associated with a high frequency of cardiovascular disease. Furthermore, the strong temporal relationship between WG flares and the occurrence of cardiovascular events raise the possibility of an etiologic link, potentially attributable to the pro-inflammatory milieu associated with active WG. These data suggest that it is advisable to proactively address modifiable risk factors in patients with WG and to be cognizant of the potential for ischemic heart disease during a disease flare.

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1838

Rituximab- Peg-IFN a /Ribavirin Compared to Peg-IFN a /Ribavirin in Mixed Cryoglobulinemia Vasculitis. David Saadoun[1], Damien Sene[2], Benjamin Terrier[3], Jeremie Sellam[4], Alexandre Karras[5], Laurent Perard[6], François Blanc[7], Pascale Ghillani[8], Michelle Rosenzwacj[9], Zahir Amoura[2] and Patrice P. Cacoub[10], [1]Pitie-Salpetriere Hospital, Paris, France, [2]Pitie salpetriere, Paris, France, [3]Pitie Salpetriere, France, [4]Saint Antoine hospital, Paris, France, [5]George Pompidou European Hospital, Paris, France, [6]Hôpital Edouard Herriot, Lyon, France, [7]Hôpital Lapeyronie, Montpellier, France, [8]Hôpital Pitié-Salpetrière, Paris, France, [9]Pitie Salpetriere, Paris, France, [10]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris

Purpose: To compare Rituximab plus Peg-IFN a /ribavirin to Peg-IFN a/ribavirin in patients with mixed cryoglobulinemia (MC) vasculitis.

Method: The outcome of ninety three consecutive patients with hepatitis C (HCV) associated MC from a single university hospital was analyzed. The efficacy and tolerance of Rituximab (375mg/m² w0, w1, w2 and w3) plus Peg-IFN a/ribavirin (n=38) was compared to Peg-IFN a/ribavirin alone (n=55) in patients with HCV-MC vasculitis.

Results: The mean age was 59.9 ± 11.7 years. Main clinical symptoms of MC vasculitis included arthralgia (38.7%), purpura (66.6%), peripheral neuropathy (72%), glomerulonephritis (33.3%) and central nervous system and gastrointestinal tract involvement (8.6%). Cryoglobulin was of type II in 78 (83.9%) with a mean level of 0.97 ± 1.2 g/l. Overall clinical, immunological and virological response rate were 73.1%, 52.7% and 59.1%, respectively. Compared with antiviral therapy alone, Rituximab plus Peg-IFN a/ribavirin had a shorter time for clinical remission (5.4 ± 4 versus 8.4 ± 4.7 months, p=0.004), a higher efficacy on kidney involvement (i.e membrano-proliferative glomerulonephritis) (80.9% versus 40% of complete response), and a higher efficacy on immunological response (68.4% versus 43.6%, p<0.01). The analysis of B-subpopulation showed that Rituximab specifically targets naive B-cells while antiviral therapy act on memory B cells. Treatment was well tolerated with 10% of discontinuation due to antiviral therapy.

Conclusion: Rituximab combined with antiviral therapy, shorten the time of clinical remission, increase the efficacy on kidney involvement and cryoglobulin clearance and synergizes the immunological effect of antiviral therapy in mixed cryoglobulinemia vasculitis.

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1839

Primary Systemic Vasculitis in Patients with Severe Alpha1-Antitrypsin (α1-AT) Deficiency - Report On Five Cases and Incidence Estimates. Mårten Segelmark[1] and Aladdin Mohammad[2], [1]Lund University Hospital,, Lund, Sweden, [2]Lund University Hospital, Lund, Sweden

Purpose: The aetiology of primary systemic vasculitis (PSV) [Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and polyarteritis nodosa (PAN)] is unknown. Environmental and genetic factors are postulated. The association between proteinase-3 ANCA positive small vessel vasculitis and a heterozygote state for the PiZ allele of α_1-AT was established in the beginning of the 1990s. In 1996 we reported nine Swedish patients with the combination of severe α_1-AT deficiency (PiZZ) and systemic vasculitis [1,2]. Since then very little have been published concerning this subject. In this study we describe five new cases with severe α_1-AT deficiency and systemic vasculitis and compare incidence rates with the background population.

Methods: Case records were reviewed for all new patients with the combination of PSV and PiZZ diagnosed at our department between 1996 and 2008. The diagnosis was confirmed by clinical, serology and histopathology data and patients were classified according to an algorithm based on the American College of Rheumatology classification criteria 1990 and the Chapel Hill Consensus Conference definitions 1994. The level of α_1-AT was measured and the α_1-AT phenotype was determined by electrophoretic focusing. The incidence rate among population with homozygote's α_1-AT deficiency was calculated using the estimated number of people living with α_1-AT deficiency in our area.

Results: Table 1 shows demographic and clinical data of the five patients diagnosed with PSV in our area during the study period. All patients responded well to therapy, however, three of them have experienced less severe relapses. The prevalence of the PiZZ phenotype of α_1-AT in Swedish population is 0.06%, corresponding to a total number of 720 individuals in the county of Skåne (population 1.2 million), where four of the patients resided. The annual incidence of PSV in patients with PiZZ phenotype carriers of α_1-AT deficiency was calculated to 42.7 per 100.000 (95% CI 0.9-84.6) which should be compared to the figure 2.1 reported previously by us from this area.

Conclusion: Individuals with the PiZZ phenotype of a_l-AT in this study exhibited a more than 20-fold increased incidence rate compared with the general population. Severe α_1-AT deficiency should be considered as an important genetic risk factor for PSV.

Table 1

Patient	Sex	Age at diagnosis, Yrs	Diagnosis	Clinical presentation	Histopathology	ANCA
1	M	16	PAN	Abdominal pain, diarrhea, weight loss. Acute intestinal perforation	Small Intestine: necrotizing lesion at medium sized arteries	Neg.
2	F	46	WG	Long standing facial pain and pulmonary infiltrate. Later severe pulmonary haemorrhage and acute renal failure	Not done	PR3+
3	F	49	WG	Skin vasculitis, arthralgia, nasal symptoms	Not done	PR3+
4	F	71	WG	Uremic symptoms (s-creatinine >1200µmol/l), minor stroke, arthralgia, otitis.	Kidney: Crescentic GN	PR3+
5	M	66	MPA	Prodromal symptoms of fatigue and arthralgia. High s-creatinine	Kidney: Crescentic GN	MPO+

References:
1.Mazodier et al. QJM 1996;89:599-611.
2.Elzouki et al. QJM 1996;89:877.

Disclosure: M. Segelmark, None; **A. Mohammad**, None.

1840

Decreased Numbers of Circulating Dendritic Cells and Defective Suppressive Function of T Regulatory Cells in ANCA-Associated Vasculitis. Marie Rimbert[1], Mohamed Hamidou[2], Xavier Puéchal[3], Marie Audrain[2], Cecile Braudeau[2], Luis Teixeira[4] and Régis Josien[1], [1]CHU and INSERM U643, Nantes, France, [2]CHU, Nantes, France, [3]Centre Hospitalier Du Mans, Le Mans, France, [4]AP-HP Hôpital Cochin, Paris, France

Purpose: Anti-neutrophil-Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV) are small vessel vasculitis including Wegener's granulomatosis, microscopic polyangiitis and Churg –Strauss syndrome. Even if the role of the ANCA in the inflammatory process is well known, AAV pathogenesis is still unclear. Dendritic cells (DC) play a pivotal role in controlling the immune response in both physiological and pathological conditions. DC also control T regulatory cells (Treg) function which are critically involved in autoimmune diseases. The aim of our study was to assess the frequency and phenotype of peripheral blood DC subsets and the frequency and suppressive function of $CD4^+$ $CD25^+$ $CD127^{low/-}$ T cells (Treg) in patients with AAV either during the acute phase or remission.

Method: Blood samples from 19 untreated patients in acute phase (BVAS>6), 17 patients in remission (with low dose steroids <10mg and without immunosuppressive treatment) rand 18 age-matched healthy controls were analysed. DC and Treg were measured by flow cytometry and DC were characterised for maturation and homing potential with CD86, CCR7 and CD62L. Suppressive function of FACS-sorted Treg was determined by coculture assay.

Results: We observed significant decrease in total DC numbers in acute phase versus healthy control and remission (8 DC/µL vs 20 DC/µL, p<0,0001; 8 DC/µL vs 15 cells/µL p=0.0006). DC numbers were also reduced in patients in remission as compared healthy control (15 cells/µL vs 20 DCs/µL; p= 0.0391). This diminution was observed at the same extent in pDC and mDC. Levels of CD86 and CCR7 were not significantly different between the 3 groups. However, a significant increase in CD62L expression levels was observed on DC from acute phase patients as compared to remissions and controls. Treg numbers were slightly but significantly reduced in AAV patients as compared to healthy controls. In contrast, Treg from acute phase patients exhibited a dramatic decrease of suppressive activity as compared to controls group (8% vs 78%. p<0.001) and remission group (8% vs 36%. p=0.0364). Treg suppressive function from the remission group was also reduced as compared to control group (36% vs 78%. p=0.0004).

Conclusion: We conclude that DC numbers as well as Treg suppressive activity are significantly reduced during AAV in a disease activity-specific manner. The decrease in DC numbers may reflect their recruitment in secondary lymphoid organs as suggested by the increase in CD62L expression on DC. The decrease in Treg suppressive function might be related to changes in DC function and might be an important defective tolerance checkpoint in AAV.

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1841

Strictly and Persistently Single-Organ Localized Wegener's Granulomatosis (WG) Is Rare: Study of the 18 Patients From the FVSG Cohort. Muriel Stubbe[1], Christian Pagnoux[2], François Lifermann[3], Patrick Jego[4], Nadine Méaux-Ruault[5], Jean Cabane[6] and Loïc Guillevin[7], [1]UZ Gent, Ghent, Belgium, [2]National Referral Center for Necrotizing Vasculitides and Systemic Sclerosis, Hôpital Cochin, Paris, France, [3]Centre Hospitalier Général de Dax, Dax, France, [4]CHU de Rennes, Rennes, France, [5]CHU de Besançon, Besançon, France, [6]Hôpital Saint Antoine, Paris, France, [7]National Referral Center for Necrotizing Vasculitides and Systemic Sclerosis, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris, Université Paris Descartes, Paris, France

Purpose and Background: It remains unclear whether patients with WG strictly localized to 1 organ have a distinct disease subset or are diagnosed at an early phase. Hence, whether or not they should be treated aggressively remains debated.

Objective: To study patients with single-organ localized WG that did not progress to more generalized forms throughout their entire follow-up.

Methods: Among 545 WG patients entered in the FVSG database, only 18 with such single-organ localized and non-progressing disease were identified: 8 with ENT involvement, 6 with lung nodules and 4 with ocular involvement.

Results: Nine (50%) were female. Mean age at diagnosis was 41.3 yr. Ten (56%) had PR3-ANCA and 4 (22%) had MPO-ANCA. Mean follow-up from diagnosis and start of therapy was 77.6 [12–238] mo. Twelve (67%) achieved sustained (6 partial and 6 complete) remissions with first-line therapy: corticosteroids (CS) and IV cyclophosphamide (CYC) for 9 or oral CYC for 3, co-trimoxazole (CTX) alone for 1 or combined with CS for 3, and CS alone for 2. Azathioprine or methotrexate maintenance therapy was prescribed with no difference in terms of efficacy or safety. Six (33%) patients relapsed (2 once, and 4 had ≥2 relapses) and required different immunosuppressive regimen(s). Relapses occurred in patients treated with CS alone, or combined with oral or IV CYC. Second-line therapies were: IV CYC (n=3), IV immunoglobulins (n=1), mycophenolate mofetil (n=1) and oral CYC (n=1). Rituximab was also prescribed as 3rd- or 4th-line therapy. At the last evaluation, 9 (50%) had complete and 8 had partial remissions (4 grumbling ENT manifestations, 1 persistent exophthalmia, 1 tracheal stenosis, 2 lung nodules); 1 patient had just relapsed; 15 (83%) were still on maintenance therapy.

Conclusion: Strictly and persistently single-organ localized WG is highly unusual. The majority of our patients received aggressive induction therapy. However, CTX alone or combined with CS was effective in a few patients. Identification of the characteristics of these patients with single-organ localized disease at diagnosis and at higher risk of disease progression might help decide their treatment intensity.

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1842

Efficacy and Tolerance of Rituximab with or without Peg-Interferon alpha2b-Ribavirin in Severe Hepatitis C Virus-Related Vasculitis: a Long-Term Follow-up Study of 32 Patients. Benjamin Terrier[1], David Saadoun[1], Damien Sène[1], Jeremie Sellam[2], Laurent Perard[3], Brigitte Coppéré[3], Alexandre Karras[4], François Blanc[5], Matthias Buchler[6], Emmanuelle Plaisier[7], Pascale Ghillani[8], Michelle Rosenzwacj[9] and Patrice Cacoub[1], [1]Pitié-Salpétrière, Paris, France, [2]Saint-Antoine, Paris, France, [3]Hôpital Edouard Herriot, Lyon, France, [4]George Pompidou European Hospital, Paris, France, [5]Hôpital Lapeyronie, Montpellier, France, [6]Bretonneau, Tours, France, [7]Tenon, Paris, France, [8]Hôpital Pitié-Salpetrière, Paris, France, [9]Pitie Salpetriere, Paris, France

Purpose: To report on the long-term follow-up of a cohort of patients treated with rituximab (RTX) +/- Peg-interferon (IFN) a2b-ribavirin in hepatitis C virus (HCV)-related vasculitis.

Method: Thirty-two patients HCV RNA+ with HCV-vasculitis were included: antiviral-naïve patients (n=9) and antiviral-resistant or relapser patients (n=11) treated with RTX and Peg-IFNa2b-ribavirin, and antiviral-intolerant patients (n=12) treated with RTX alone.

Results: RTX and Peg-IFNalpha2b-ribavirin induced a clinical complete (CR) and partial (PR) response in 80% and 15% of cases, respectively; an immunological CR and PR in 67% and 33%, respectively; and a sustained virological response in 55%. RTX alone induced a clinical CR and PR in 58% and 9% of patients, and immunological CR and PR in 46% and 36%, respectively. B cell depletion was achieved in 96%, and B cell recovery began after a median delay of 12 months. After a mean follow-up of 23±12 months, 22% experienced a clinical relapse, and 34% an immunological relapse. All relapses were associated with the absence of virological control, and in 78% with an increase in the number of B cells. Six patients were retreated with RTX: 100% were clinical CR, and immunological CR and PR were noted in 50% each. RTX was well-tolerated overall.

Conclusion: RTX is an effective treatment for severe and/or refractory HCV-vasculitis. Relapses were consistently associated with the absence of virological control. RTX seems to have the same clinical and immunologic efficacy after repeated infusions.

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1843

A Novel 60 Kda Reactivity in Cyclic Neutropenia: High Titer Classic ANCA Pattern and Negative Anti-Peroxidase-3. Camila E. Rodrigues[1], Eloisa Bonfá[1], Elvira R.P. Velloso[2], Flávia K. Teixeira[1], Vilma S.T, Viana[1], Cleonice Bueno[1], Andréa Kondo[2] and Rosa M.R. Pereira[1], [1]Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil, [2]Hematology Division, Facudade de Medicina da USP, São Paulo, Brazil

Purpose: To evaluate the presence of antineutrophil cytoplasmic antibodies (ANCA) in patients with chronic neutropenia.

Method: Twenty-two patients with hematological disorders under granulocyte-colony stimulating factor treatment for neutropenia (10 with aplastic anemia, 2 cyclic neutropenia, 1 myelodysplastic syndrome, 1 auto immune pancytopenia and 8 chronic myeloid leukemia with imatinib mesylate neutropenia induced) were enrolled in the study. Patient's charts were extensively reviewed for demographic, clinical, laboratorial and therapeutic data. ANCA were detected by indirect immunofluorescence (IIF) using isolated human neutrophils and ELISA (myeloperoxidase and proteinase-3). Characterization of the antigenic specificity of these antibodies was performed by Western blot using crude extract of human neutrophils as source of antigen. Exclusion criteria were drug use that induces neutropenia (except for imatinib) or ANCA.

Results: Among the 22 patients, an evident predominance of female gender (63.6%) and white race (86.3%) was observed. The mean age was 49 (from 17 to 79) years and mean disease duration was 38 months. Of note, ANCA were detected in two (9.1%) patients and both had cyclic neutropenia. These two sera displayed the classic ANCA pattern with high titer reactivity (1/1.260 and $\geq$ 2.520, respectively). The longitudinal evaluation of several frozen sera samples showed a persistent high titer classic ANCA pattern. Sera were uniformly negative for anti-peroxidade-3 and anti-mieloperoxidase antibodies. Western blot analysis revealed that serum from these two patients showed a common reactivity to a protein fraction with molecular weight of 60 kDa. One of these two patients during follow-up of 4 years had an additional diagnosis of large granular lymphocytic proliferation and none developed signs and symptoms compatible with Wegener granulomatosis.

Conclusion: A novel 60 kDa reactivity autoantibody is described in cyclic neutropenia which is characterized by high titer classic ANCA pattern with a uniformly negative anti-peroxidase-3 reactivity. The underlying inducing stimulus of this abnormal humoral response is not associated with granulocyte-colony stimulating factor treatment.

Disclosure: C. E. Rodrigues, None; **E. Bonfá**, CNPQ, 2 ; **E. R. P. Velloso**, None; **F. K. Teixeira**, None; **V. S. T. Viana**, None; **C. Bueno**, None; **A. Kondo**, None; **R. M. R. Pereira**, CNPQ, 2 .

1844

Clinical Spectrum of Type 1 Cryoglobulinemia: Retrospective Analysis of 8 Year Single Center Experience. Cassandra M. Calabrese[1], Manju Gupta[2] and Leonard H. Calabrese[3], [1]Ohio University of Osteopathis Medicine, Athens, OH, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH

Purpose: Cryoglobulins are immunoglobulins that precipitate from serum at temperatures below 37°C and may be symptomatic or associated with wide spread vasculitis. Cryoglobulins are classified into types I, II and III based on immunochemical composition. Type I cryoglobulinemia is the most clinically rare and has been described in few small-series case reports in the past 25 years. This study was intended to describe a large clinical series of patients with type I cryoglobulinemia from the clinical, pathologic and etiologic perspectives and to determine the influence of recently introduced biologic therapeutics on clinical outcomes.

Method: After receiving IRB approval, the laboratory records of the Clinical Pathology Department were reviewed for the 8 year period starting Jan 1, 2000 through Dec 31 2007. All samples with detected monoclonal cryoglobulins (type I) were included in the analysis. Both print and electronic medical records were reviewed and from them extracted standardized information on the etiology, clinical manifestations, immunologic features and outcomes.

Results: Over this 8 year period, more than 16,000 clinical samples were analyzed for cryoglobulins. Approximately 400 of these samples were strongly positive (> 500ugr/cc) and screened for immunochemical composition. From these records a total of 19 patients were found to have type I cryoglobulinemia (freq = 1.11/1,000 samples). Of these patients, 18 had adequate medical records for examination. The most common clinical manifestations were cutaneous involvement and cold-induced symptoms (61% and 31% respectively). Renal, hepatic and articular involvement was also observed (22%, 22% and 17%, respectively). Overall, 83% had hematologic disorders and only 11% were HCV infected, which is consistent with traditional views of the disease. 8 of our patients were treated with the B cell depleting agent rituximab with varying responses, and a single patient treated with thalidomide experienced complete remission of his cryoglobulinemia.

Conclusion:

1. Type I cryoglobulinemia is an extremely rare form of blood disorder.

2. The most common etiology appears to be within the spectrum of hematologic disorders and in contrast to previous reports is uncommonly associated with HCV infection.

3. Patients diagnosed with type I cryoglobulinemia since the year 2000 have frequently been treated with newer biologic therapeutic agents with varying responses. Thalidomide was used to induce a complete clinical and laboratory remission in a single patient and should be further evaluated in clinical trials.

Disclosure: C. M. Calabrese, None; **M. Gupta**, None; **L. H. Calabrese**, None.

1845

Efficacy and Safety of TNF-Alpha Antagonists in the Management of Behçet's Syndrome: A Systematic Review. Gulen Hatemi, Vedat Hamuryudan, Sebahattin Yurdakul and Hasan Yazici, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

Purpose: There is growing evidence on the efficacy of TNF-alpha antagonists in BS mainly based on open studies or case series. This systematic review aims to analyze the current literature on the efficacy and safety of TNF-alpha antagonists in BS patients.

Methods: We performed a systematic literature search covering articles in PubMed until May 2009 and searched the abstracts from the annual meetings of EULAR, ACR and International Conferences on Behçet's Disease.

Results: The literature search yielded 187 published articles and 31 meeting abstracts. Among these 97 articles and 17 abstracts were included in the analyses. Infliximab was used in 98 of these studies, etanercept in 11 of them and adalimumab in 5. The only RCT was the one comparing etanercept to placebo in 40 patients with mucocutaneous and joint involvement. Etanercept had a medium effect size on oral ulcers and papulopustular lesions (0.59 and 0.51 respectively) and a small effect size on genital ulcers and arthritis (0.33 and 0.24 respectively). In 14 open studies evaluating the efficacy of infliximab for eye involvement, 110/124 patients showed an immediate response and 57/97 patients had a sustained remission. Case series showed a rapid onset of response, improvement in visual acuity, suppression of retinal vasculitis, vitritis, retinitis, cystoid macular edema, decrease in the number of uveitis attacks and corticosteroid use. Relapses were observed when the drug was stopped and long term treatment with either infliximab or other immunosuppressives was required for maintenance. In an open study etanercept showed a significant improvement in visual acuity which tended to decrease after stopping the treatment. The only open study and 4 case reports for neurologic involvement showed a good clinical response and regression in MRI findings. One open study and 11 case reports on the use of infliximab for gastrointestinal involvement showed rapid healing of ulcers, resolution of bloody diarrhea and healing of esophageal perforation and fistulae. The response in gastrointestinal involvement seems to be more sustained compared to other organs. The limited experience with vascular involvement shows that infliximab was beneficial in 2 patients with pulmonary artery aneurysms, but in another case series 2 of the 3 patients with hepatic vein thrombosis had died. Tuberculosis, cryptococcal meningitis, pyomyositis, cytomegalovirus colitis, simple infections, infusion reactions, angioedema, acute heart failure, psoriasiform skin lesions and formation of autoantibodies were the adverse events.

Conclusion: TNF-alpha antagonists seem to be promising agents especially for resistant eye, GI and CNS involvement of BS. Controlled studies are needed since current evidence which relies mostly on open studies and case reports might have caused a false impression of efficacy due to publication bias. Side effects are similar to those reported for TNF-alpha antagonist use in other diseases.

Disclosure: G. Hatemi, None; **V. Hamuryudan**, None; **S. Yurdakul**, None; **H. Yazici**, None.

1846

Association of Behçet's Disease with Familial Mediterranean Fever. Fulya Cosan[1], Neslihan Abaci[2], Bahar Artim Esen[1], Aris Cakiris[2], Duran Ustek[2], Orhan Aral[1] and Ahmet Gul[1], [1]Istanbul University, Istanbul, Turkey, [2]Istanbul University, Turkey

Purpose: Behçet's Disease (BD) is a systemic inflammatory disorder, and it has a strong genetic contribution in its pathogenesis. Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disorder caused by mutations in the MEFV gene. There are patients presented with the clinical features of both BD and FMF. However, it is still controversial that whether there is an association between BD and FMF. We herein aimed to analyse the genetic and clinical features of a group of patients with BD+FMF in a cohort of 1235 BD patients.

Method: The main study group consisted with BD+FMF, and we used the findings of 288 patients with BD (170 male, 118 female) and 289 patients with FMF (134 male,155 female). All BD patients fulfilled the ISG criteria, and all FMF patients fulfilled the Tel-Hashomer criteria. We isolated genomic DNA from all subjects, and genotyping for the MEFV gene M694V, V726A, M680I, E148Q mutations was done by PCR-RFLP. Clinical features of patients were recorded using a standard form. Study protocol was approved by local ethics committee, and all subjects provided written informed consent prior to blood collection.

Results: We identified increased frequency of FMF patients (n=21, 8 male, 13 female; 1.7%) in the BD cohort amongst to other accompanying disorders. Genetic analysis of 21 patients with BD+FMF for 4 common MEFV mutations showed that 42.8% of them had two mutations, 28.6% had one mutation, and 28,6 % had no mutation. The frequency of four MEFV mutations was not significantly different from FMF patients (71.4% vs 85.5%), however the frequency of E148Q was significantly higher in BD+FMF group compared to the frequency in FMF patients (31.3% vs 6.2%, P = 0.003). We compared BD-related clinical finding of BD+FMF patients with the findings of BD patients. We found that arthritis was significantly higher (85.7% vs 55.2%, P = 0.006, OR = 4.9, 95% CI 1,4-16,9), and eye involvement was significantly lower (33.3% vs 57.9%, P = 0.028, OR = 0.36, 95% CI 0,14-0,9) in BD+FMF group compared to BD patients. There was no BD+FMF patient with neurological or intestinal involvement. When we grouped the patients according to disease severity, patients with mild disease were significantly higher in BD+FMF group (52.4% vs 22%, P = 0,006, OR = 3.9, 95% CI 1.6-9.7). We did not observe any association between MEFV mutations and BD-related clinical findings including vascular involvement. Also, in the BD patient group with no FMF findings (n=288), BD patients carrying MEFV mutations was found to be significantly higher (27%) compared to the frequency in healthy controls (10%) (P<0.001, OR = 3,35, %95 CI 1,7-6, 8). We observed no association between the MEFV mutations and any of the BD manifestations, nor the disease severity in this BD group.

Conclusion: This study shows that patients presenting with the clinical features of both BD+FMF run less severe disease course with more frequent articular features and less frequent uveitis. We also observed that the frequency of E148Q mutation was higher in BD+FMF patients compared to FMF patients. Further analysis of BD+FMF patients may provide clues to understand the association of BD with FMF and the role of inflammasome in BD pathogenesis.

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1847

Renal Transplantation in Wegener's Granulomatosis and Microscopic Polyangiitis. Duvuru Geetha, Mark Haas, Edward S. Kraus, Hamid Rabb and Philip Seo, Johns Hopkins University, Baltimore, MD

Purpose: ANCA-associated vasculitis (AAV) is an important cause of end-stage renal disease. How modern immunosuppressive regimens influence outcomes among patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) after renal transplant is unclear.

Methods: We conducted a retrospective cohort study of patients who underwent renal transplant at The Johns Hopkins Hospital between 1999 and 2008. Analysis was performed using STATA 9.0 (College Park, TX).

Results: A total of 24 patients with end stage renal disease due to AAV received a kidney transplant at the Johns Hopkins Hospital between 1999 and 2008. Follow-up data are available for 11 patients with WG and 6 patients with MPA who were followed for 799 patients-months of observation. The majority of these patients were Caucasian (82.4%) with an approximately equal numbers of men and women (8:10). 9/11 of the patients with WG were PR3-ANCA positive, while 5/6 of the patients with MPA were MPO-ANCA positive. Two of the patients with MPA also had anti-GBM antibodies.

All but one patient (94.1%) had renal involvement at the time of their vasculitis diagnosis; 5 WG patients (45.5%) and 2 MPA patients (33.3%) presented with end-stage renal disease. Most patients in this cohort received first renal transplants (72.2%) from a living-related donor (70.6%).

At the time of transplant, patients with WG were older (median age 51.5 versus 39 years) and carried a diagnosis of vasculitis for longer (51 months versus 18.5 months) than patients with MPA, although the difference was not statistically significant (P=0.2 for each comparison).

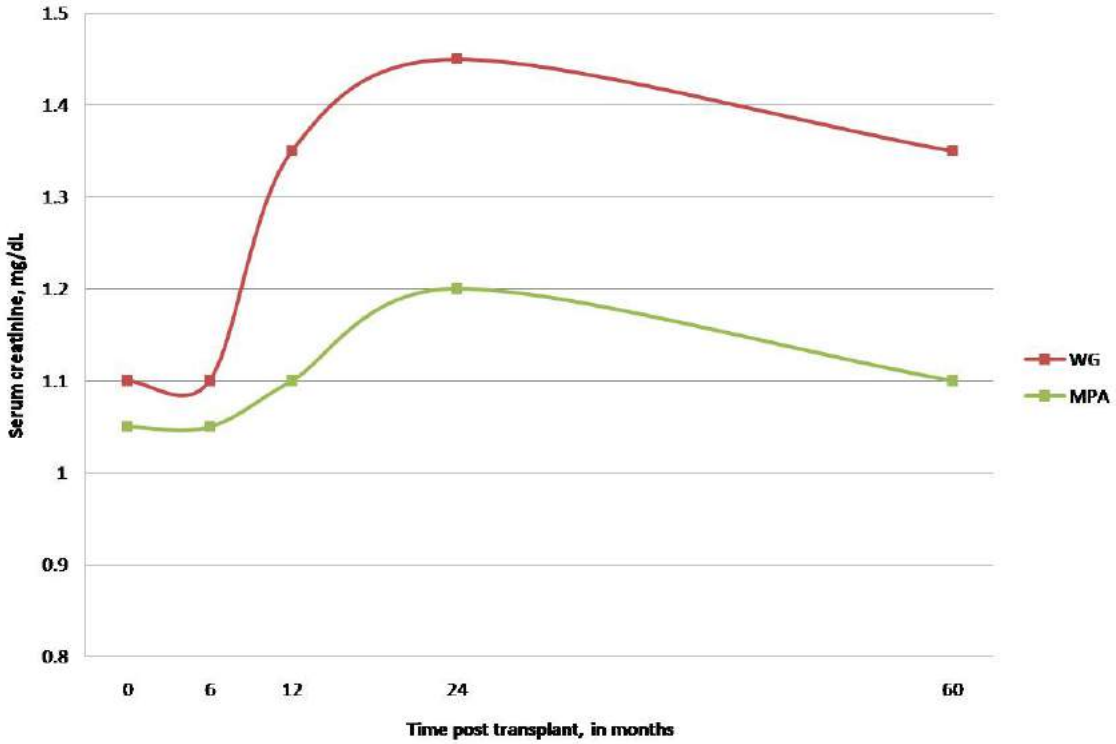
Most patients (10/16) were ANCA-negative at the time of transplant; none of these patients have experienced a vasculitis flare during the observation period. There was one flare per 22 patient-years of observation; all flares occurred in patients who were ANCA-positive: one

patient with WG and one with MPA had recurrent glomerulonephritis affecting the transplanted kidney; one additional WG patient experienced a non-renal vasculitis flare.

All patients received maintenance immunosuppression with a mycophenolate mofetil/tacrolimus-based regimen. There were no episodes of rejection among patients with MPA. Two patients with WG had an episode of rejection; both occurred in patients who were highly sensitized and had received treatment with rituximab, plasmapheresis, and IVIG prior to transplant.

The median serum creatinine following transplant was 1.1 mg/dL. The median serum creatinine at the time of last follow-up was 1.3 mg/dL among patients with WG and 1.0 mg/dL among patients with MPA (P=0.1)

Conclusion: Renal transplantation is effective in patients with WG and MPA. The combination of mycophenolate mofetil and tacrolimus is effective at preventing both disease relapse and rejection for most patients with AAV. Patients who are ANCA-negative have particularly good outcomes; patients who are ANCA-positive may benefit from more aggressive maintenance immunosuppression. Whether patients with MPA may have better outcomes after transplant than patients with WG merits further study.



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1848

Cardiac Involvement in Churg-Strauss Syndrome: Impact of Endomyocarditis. Thomas Neumann[1], Bernhard Manger[2], Michael Schmid[2], Claus Kroegel[1], Andreas Hansch[1], Werner A. Kaiser[1], Dirk Reinhardt[3], Gunter Wolf[1], Gert Hein[1], Gerhard Mall[4], Georg Schett[2] and J. Zwerina[5], [1]University-Hospital, Jena, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Evangelisches Krankenhaus, Hamm, Germany, [4]Klinikum Darmstadt, Darmstadt, Germany, [5]Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

Purpose: Cardiac disease is a major contributor to disease-related death in Churg-Strauss Syndrome. This study aimed to determine the prevalence and clinical impact of cardiac involvement in CSS patients.

Method: A multi-centre, cross-sectional analysis of patients diagnosed with CSS was performed. Cardiac work-up included electrocardiography, echocardiography, cardiac magnetic resonance imaging (MRI) and endomyocardial biopsy.

Results: We analyzed 49 CSS patients: 22 patients had clinical evidence of cardiac involvement. A negative ANCA test and much higher eosinophil counts (9947 vs. 3657/µl, $p<0.001$) distinguished patients with and without cardiac involvement. Impaired left ventricular function (50%), mild to severe valvular insufficiencies (73%) and pericardial effusions (41%) were common findings in these patients. Endomyocarditis was found in 13 patients (59%) as detected by cardiac MRI, cardiac thrombus formation and endomyocardial biopsy and was associated with impaired cardiac function. After a mean follow-up of 47 months, most patients had regained or maintained a good cardiac function. However, patients with endomyocarditis had a more severe outcome. 2 patients died (61 and 99 months after diagnosis) both due to severe cardiomyopathy and heart failure.

Conclusion: Cardiac involvement is common in CSS and is associated with the absence of ANCA and high eosinophil counts. Endomyocarditis may represent the most severe manifestation eventually causing fatal outcome. A structured clinical assessment incorporating cardiac imaging with echocardigraphy and MRI can identify impaired cardiac function and endomyocardial abnormalities.

Disclosure: T. Neumann, None; **B. Manger**, None; **M. Schmid**, None; **C. Kroegel**, None; **A. Hansch**, None; **W. A. Kaiser**, None; **D. Reinhardt**, None; **G. Wolf**, None; **G. Hein**, None; **G. Mall**, None; **G. Schett**, Celgene Corporation, 2 ; **J. Zwerina**, None.

1849

Investigation of Target Organ Associations in Patients with Familial Behçet's Syndrome Using Factor Analysis. Mehmet Karaca, Gulen Hatemi and Hasan Yazici, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

Purpose: We have previously shown that Behçet's syndrome (BS) patients with arthritis are more likely to have acne-like skin lesions and there are distinct symptom clusters such as “papulopustular lesions and joint involvement” or “superficial vein thrombosis and deep vein thrombosis” in our patient population (1, 2). Presence of these clusters suggests that pathogenesis of BS may involve different mechanisms. Increases in frequency of such clusters in familial BS cases would back up the notion that some pathogenetic mechanisms may have a heritable component. To test this hypothesis we aimed to compare the frequency of symptom clusters between familial and non-familial cases of BS.

Methods: We identified 380 patients with BS who reported a first and/or second degree relative among the 6031 patient charts reviewed. Of these 380 patients, 186 had attended the clinic within the previous 3 months (Group F). Eighteen first-degree relative pairs (14 siblings and 4 offspring-parents) were identified in group F. None of these patients reported a second degree or more distant relative with BS. From the same initial pool of 6031 patients 500 were randomly selected using a random number generator (RNG). Of those, only patients who did not report a family history of BS and who also had attended the clinic within the previous 3 months made up the non familial (NF) group (n=221). Using the same RNG, we constructed 110 unrelated pairs among the NF group. Data were analyzed using factor analysis and symptom clusters were extracted from each group. Cluster frequencies and shared cluster ratios were compared using chi-square tests.

Results: Frequency of a first and/or second degree family history of BS for our patient population was 6.8% in the total pool and 7.4% among the 500 patients randomly selected. Clusters we identified in groups F and NF were similar to those previously reported from our clinic (2). Of these clusters only the frequency of the “papulopustular lesions and joint involvement” symptom cluster was significantly higher in Group F as compared to Group NF (39.2% vs. 21.5%, $p<0.000$). Furthermore, the “papulopustular lesions and joint involvement” cluster was shared in 5 of the 17 pairs from Group F and only in 5 of the 110 pairs from Group NF (29% vs. 4.5%, $p=0.004$; OR=8.75, 95% CI 2.2-34.6).

Conclusion: The “papulopustular lesions and arthritis” cluster in BS appears to cluster in familial BS as well. This further supports the notion that the pathogenesis of BS may entail several distinct mechanisms producing separate phenotype clusters.

References:

1. Diri E et al. Papulopustular skin lesions are seen more frequently in patients with Behçet’s syndrome who have arthritis. Ann Rheum Dis 2001;60:1074-6.

2. Tunc R et al. Target organ associations in Turkish patients with Behçet's disease. The Journal of Rheumatology 2002;29:2393-6.

Disclosure: M. Karaca, None; **G. Hatemi**, None; **H. Yazici**, None.

1850

Early Death in Wegener's Granulomatosis: Disease and Treatment Factors. Fernando H.C. Souza, Ari S. Halpern and Samuel K. Shinjo, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil

Purpose: Few studies have focused in early death in Wegener´s granulomatosis (WG) and the only systematic study was restricted to patients with severe organ involvement. We therefore have evaluated disease and treatment factors for death in all patients followed during 20 years in a single tertiary center.

Method: A retrospective chart review of all 114 WG patients (at least two ACR criteria), 87.7% diffuse, followed from 1989 to 2009, was performed evaluating clinical and treatment parameters associated to death exclusively in the first three years of diagnosis.

Results: There were 23 (20.2%) deaths, all in the diffuse subgroup, in the first 3 years of follow-up. This early death group had higher mean age at WG´s diagnosis (54.3±14.7 *vs.* 42.3±13.7 years; p=0.001) with a similar female gender (34.8 *vs.* 55.0%; p=0.084) and white ethnicity (95.7 *vs.* 85.7% whites; p=0.195) distribution compared to 91 who remained alive. The frequency of variables describing kidney function such as dialytic renal insufficiency (47.8 *vs*. 9.9%, p<0.001) and initial creatinine levels (4.8±3.5 *vs*. 2.4±2.9mg/dL, p=0.006) were significantly higher in the early death group, in spite of a similar frequency of glomerulonephritis (87.0 *vs*. 72.5%, p=0.151). No other distinct features were identified comparing the two groups regarding disease extend index (8.3±3.1 *vs*. 8.7±3.0, p=0.568), constitutional symptoms (65.2 *vs*. 64.9%, p=0.973), ear/nose/throat involvement (56.5 *vs*. 67.0%, p=0.345), pulmonary involvement (93.4 *vs*. 83.5%, p=0.170), neuropathy (21.7 *vs*. 19.8%, p=0.834) or the frequency of cytoplasmatic ANCA reactivity (69.6 *vs*. 67.0%, p=0.817). The early death group had a significantly lower frequency of cyclophosphamide use (56.5 *vs*. 82.4%, p=0.008) with an almost universal use of any immunosuppressor (82.6 *vs*. 92.3%, p=0.159) and glucocorticoid therapy (91.3 *vs*. 97.8%, p=0.130) in both groups. In multivariate analysis, renal insufficiency requiring dialysis (HR 7.59; CI 95% 2.24-25.79) was an important risk to mortality and cyclophosphamide use had a protective effect (HR 0.25; CI 95% 0.08-0,77). The three causes of mortality were infection (65,2%), alveolar hemorrhages (17,4%) and myocardial infarction (17,4%).

Conclusion: Severe renal impairment was identified as the major risk factor for early WG mortality whereas cyclophosphamide use had a protective effect.

Disclosure: F. H. C. Souza, None; **A. S. Halpern**, None; **S. K. Shinjo**, None.

1851

Identification of Target Antigens of Anti-Endothelial Cell Antibodies in Patients with ANCA-Associated Systemic Vasculitis: a Proteomic Approach. Hanadi Dib[1], Luc Camoin[2], Cédric Broussard[2], Véronique Witko-Sarsat[3], Loïc Guillevin[4] and Luc Mouthon[5], [1]Paris Descartes University, UPRES-EA 4058, Paris, France, [2]Inserm U 567, CNRS UMR 8104, Cochin Institute, Paris, France, [3]Inserm U 845, Paris, France, [4]Université Paris Descartes, Paris, France, [5]Paris Descartes University, UPRES-EA 4058, Department of Internal Medicine, Cochin Hospital, Paris, France

Purpose: Anti-endothelial cell antibodies (AECA) are frequently detected in anti-neutrophil cytoplasm antibodies (ANCA)-associated systemic vasculitis and are considered to play pathological roles but their antigenic specificities are still unknown. We used a proteomic approach combining two-dimensional electrophoresis and immunoblotting to identify the target antigens of AECA in patients with ANCA-associated vasculitis.

Method: Sera from 36 ANCA-associated vasculitis patients (15 with Wegener's granulomatosis (WG), 12 with microscopic polyangiitis (MPA), 9 with Churg Strauss syndrome (CSS)), tested in pools of 3 sera, were compared to a sera pool from 12 healthy controls (HC). Serum IgG reactivity was analyzed by use of a 2-D electrophoresis and immunoblotting technique with normal human umbilical vein endothelial cell (HUVEC) antigens.

Results: Serum IgG antibodies in the pools of patients with WG with anti-proteinase 3 (PR3) ANCA (n=5), MPA with anti-myeloperoxydase (MPO) ANCA (n=2), MPA without anti-MPO (n=2), CSS with anti-myeloperoxydase (MPO) ANCA (n=1) and CSS without anti-MPO (n=2), recognized 107±17, 148, 211, 128, and 101 protein spots respectively, whereas serum IgG antibodies from HC recognized 79 protein spots. Serum IgG antibodies from patients with WG with anti-PR3, MPA with anti-MPO, MPA without anti-MPO, CSS with anti-MPO and CSS without anti-MPO specifically recognized 37, 12, 22, 15 and 23 protein spots, respectively. Target antigens were identified by mass spectrometry (MALDI-TOF-TOF) including Proteasome subunit alpha type-5, Adenine phosphoribosyltransferase, Growth factor receptor-bound protein 2 and GMP synthase [glutamine-hydrolyzing]. These antigens are involved in cell energy metabolism, and other key cellular pathways.

Conclusion: AECA detected in patients with ANCA-associated vasculitis recognize cellular targets playing key roles in cell biology and maintenance of homeostasis.

Disclosure: H. Dib, None; **L. Camoin**, None; **C. Broussard**, None; **V. Witko-Sarsat**, None; **L. Guillevin**, None; **L. Mouthon**, None.

ACR/ARHP Poster Session C

ARHP Abstracts - C

Tuesday, October 20, 2009, 9:00 AM - 6:00 PM

1852

Moderate to Severe Rheumatoid Arthritis (RA) Is Associated with Significant Work and Activity Impairment in Brazil: Findings From An Observational Study. R. Khandker[1], GRC Pinheiro[2], S. Kay[3], J. Cristino[3] and M. Tedeschi[4], [1]Wyeth Pharmaceutcials, Collegeville, PA, [2]Rio De Janeiro State University, Brazil, [3]Adelphi Real World, [4]Wyeth Pharmaceutcials

Purpose: The impact of RA on work and non-work productivity is not well documented in Brazil. This analysis evaluates the humanistic and economic burden of RA and its severity on productivity as well as health care resource use.

Method: Adelphi's RA Disease Specific Programme (DSP) is an observational cross-sectional study involving 55 rheumatologists in Brazil. Data elements included - physician global rating of severity (mild, moderate, and severe); the Work Productivity and Activity Impairment (WPAI) questionnaire; frequency of hospitalization and rheumatologist visits; and percent of patients needing help with daily activities. WPAI is a validated instrument that measures work time missed and work and activity impairment due to a specified health problem during the past 7 days. This study compared productivity and resource use across physician-rated RA severity groups using ANOVA and t-tests for continuous variables and Chi-square test for proportions.

Results: The primary findings are summarized below:

Variable	Mild (n=219)	Moderate (n=227)	Severe (n=55)
Age (yrs)	51	52	50
Disease Duration (yrs)	5.7	6.3	9.3 [a,b]
WPAI - Currently employed (%)	33	39	16 [a,b]
WPAI - Impairment while at work (%)	16	33 [b]	67 [a,b]
WPAI - Overall work impairment (%)	20	38 [b]	65[b]
WPAI - Activity impairment (%)	26	44 [b]	65 [a,b]

Any hospitalization in 6 months (%)	5	10	20 [b]
# of rheumatologist visits in 6 months	2.65	2.94	3.98 [a,b]
Needed help with daily activities (%)	11	26 [b]	57 [a,b]

a P<0.05 vs. Moderate

b P<0.05 vs. Mild

In this analysis, severe RA patients experienced more impairment in work and daily activities compared to mild patients. Likelihood of hospitalization and visits to rheumatologists were also significantly higher for patients with severe RA. The overall low employment rates may be partially attributable to lower work force participation among women in Brazil.

Conclusion: This study demonstrates that moderate to severe RA is associated with significant work and activity impairment. Healthcare resource utilization also increases directly with the RA severity. Effective medical management and improved treatment strategies may mitigate the burden of RA in Brazil.

Disclosure: R. Khandker, Wyeth Pharmaceuticals, 3 ; **G. Pinheiro**, Wyeth Pharmaceuticals, 5 ; **S. Kay**, Wyeth Pharmaceuticals, 5 ; **J. Cristino**, Wyeth Pharmaceuticals, 5 ; **M. Tedeschi**, Wyeth Pharma, 3 .

1853

"Is Working with Arthritis Bad for Your Health?" Outcomes Associated with Arthritis-Work Role Overload. M. Gignac[1], X. Cao[2], D. Beaton[1], Diane V. Lacaille[3], C. Bombardier[1], A. Anis[4] and Elizabeth M. Badley[1], [1]Univ of Toronto, Toronto, ON, [2]Univ Health Network, Toronto, ON, [3]University of British Columbia, Vancouver, BC, [4]Univ of British Columbia, Vancouver, BC

Purpose: Employment research finds that perceptions of role overload are a critical mediator in whether individuals remain working and in their health and well-being. Yet, perceived role overload or “spillover” has not been well examined in individuals working with arthritis. This study uses longitudinal data from two samples to examine: 1) role spillover from arthritis to work and work to arthritis; and 2) health-related outcomes of spillover at 3, 9, and 18 months.

Method: Participants with osteoarthritis (OA) or inflammatory arthritis (IA) were drawn from 2 separate studies. Sample 1 (S1) was recruited largely from rheumatology clinics (n = 250) and used baseline, 3 month, and 9 month data. Sample 2 (S2) was recruited largely using community advertising (n = 490) with data collected at 4 time points, 18 months apart. Both samples assessed age, gender, illness (diagnosis, pain, fatigue), and work context variables (job sector, work hrs, activity limitations). S2 also collected data on self-rated health, health care utilization, depression, disease duration, joints affected, job control and physical demands of work. Spillover was measured using the Arthritis-Work Spillover (AWS) scale (6 items: 3 items assess arthritis impact on work; 3 items assess work impact on arthritis; strongly disagree-strongly agree). Greater agreement reflects greater spillover. Longitudinal analyses using generalized estimation equations examined the relationship of AWS to subsequent reports of fatigue and pain severity and frequency (S1) and fatigue, pain, self-reported health, depression, and health utilization (S2), controlling for demographic, illness, and work variables.

Results: Half of participants had OA (S1 = 52%; S2 = 56.7%), most were female (S1 = 82.7%; S2 = 77.8%) and were on average 51 yrs old. Participants in both samples reported employment in a range of job sectors. At baseline, 32.6% (S1) and 47.1% (S2) of participants agreed or strongly agreed with half or more AWS items. Greater AWS was associated with later reports of greater fatigue severity and frequency at 3 and 9 months (S1) ($p < .05$). AWS was also associated with fatigue in S2. S2 analyses found those perceiving that arthritis affected their work reported greater fatigue and depression, and lower self-rated health 18 months later. Perceptions of work affecting arthritis were associated with greater health care utilization (all $p < .05$). AWS was not associated with pain in either sample.

Conclusion: Many respondents reported spillover, with arthritis interfering with work and work interfering with caring for arthritis. This may lead to role overload and suggests greater attention needs to be paid to helping people with arthritis balance work and health demands. Spillover may have particularly negative consequences for fatigue and mood in the short- and long-term, even after controlling for disease and job factors. Future research needs to examine whether increased health care utilization related to AWS may ameliorate role overload.

Disclosure: M. Gignac, None; **X. Cao**, None; **D. Beaton**, None; **D. V. Lacaille**, None; **C. Bombardier**, None; **A. Anis**, None; **E. M. Badley**, None.

1854

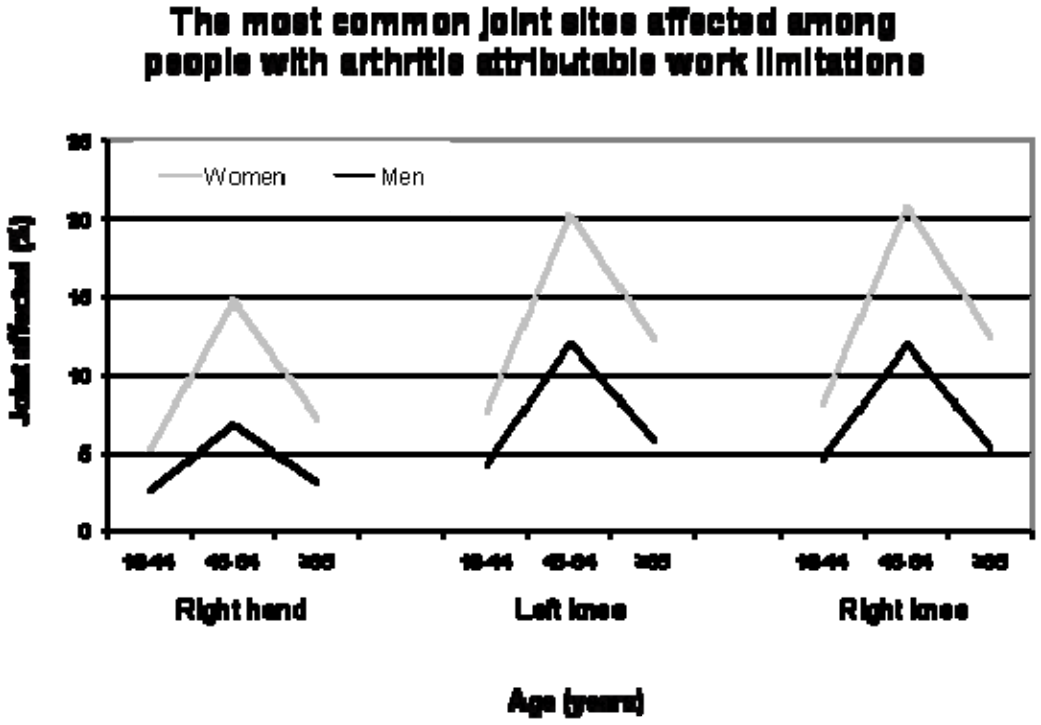
Pain On the Job: Prevalence and Site of Recent Joint Pain Among U.S. Adults with Arthritis-Attributable Work Limitations (AAWL). Kristina A. Theis and Louise Murphy, Centers for Disease Control and Prevention, Atlanta, GA

Purpose: To estimate the prevalence and site of recent joint pain in U.S. adults with AAWL overall and stratified by age and sex.

Method: We analyzed data (2002, 2003 and 2006 combined) from the National Health Interview Survey, an annual interview-administered survey representative of the U.S. civilian, non-institutionalized population. Our sample was restricted to 19,213 adults ≥ 18 years with arthritis ("yes" to: "Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?") We estimated, among adults with arthritis, 1) the prevalence of AAWL (limited in: *whether you work, the type of work you do, or the amount of work you do)* and 2) the prevalence of recent (within the past 30 days) joint pain among people with and without AAWL, overall and stratified by age group (18-44; 45-64; 65+) and sex. Data were analyzed in SAS v9.1 survey procedures to account for the complex sampling design.

Results: Approximately 28% of US adults ≥ 18 years old (12.5 million people) with arthritis reported AAWL. Across all joint sites, recent joint pain was significantly more common among those with AAWL compared with those without. For those with and without AAWL, the top five sites of joint pain were right and left knees, right and left shoulder, and right hand. Among people with AAWL, women reported recent pain in left and right hips and left and right hands significantly more often than men (e.g., right hip pain 38.0% [95% confidence interval (CI)=35.6-40.4] vs. 29.0% [95% CI=26.2-31.9], right hand 42.9% [95% CI=40.7-45.2] vs. 34.0% [95% CI=31.0-36.9]). For all sites, the prevalence of recent joint pain across all age groups was higher among women than men. For both men and women, the prevalence of joint pain, regardless of site, was among highest among adults ages 45-64 years and lowest among those age 18-44 years.

Conclusion: We found a high prevalence of recent knee and shoulder joint pain among adults with AAWL, suggesting that joint pain in these sites may be a useful clinical indicator for job interference due to arthritis. The increased prevalence of joint pain among adults 44-64 years indicates the importance of interventions that enable middle aged adults with arthritis to stay in the workforce and avoid economic insecurity (e.g., premature retirement). People with AAWL may benefit from a combined strategy: public health interventions like self-management education that may be effective in countering pain, worksite accommodations, and increasing availability of ergonomic equipment designs.



Disclosure: K. A. Theis, None; **L. Murphy**, None.

1855

The Association Between Hand Impairment and Hand Function in Rheumatoid Arthritis. Nancy A. Baker and Joan C. Rogers, University of Pittsburgh, Pittsburgh, PA

Purpose: Healthcare professionals frequently measure impairments in range of motion (ROM), grip, or dexterity to help quantify hand function limitations in people with rheumatoid arthritis (RA). This study examines the association between impairments and functional hand use.

Method: 45 people with RA were recruited from the University of Pittsburgh Medical Center Arthritis Network Disease Registry. Hand function was measured with the 4 bilateral applied dexterity tasks (number of seconds to: lace a shoe, button 5 buttons, cut simulated meat with a knife, and manipulate coins) and 1 bilateral strength task (lifting up to 12 cans on a tray) of the Arthritis Hand Function Test (AHFT). Impairments were measured with the Keitel Hand Function Index (KHFI) (ROM), the grip and dexterity from the AHFT, and the number of hand problems as determined by observation of structural deformities by a hand therapist.

AHFT applied task scores were transformed into one of 4 categorical scores and summed to develop a total AHFT score, in which a higher score indicated greater hand function. Total strength and dexterity impairment scores were developed by summing the right and left hand scores for grip and dexterity. Each KHFI item score was summed to develop a total KHFI score in which a higher score indicated greater impairment.

Backward stepwise multiple regression models were developed with applied hand tasks as each outcome, and grip, dexterity, total KHFI, hand problems, and age as the predictors.

Results: Subjects were 56.2 (±8.5) yrs. RA duration was a mean of 16.7 (±10.3) years.

All models were significant except for manipulating coins. Models explained from .30 to .79 of the variance in hand function for each task. Grip and dexterity were most often associated with hand function (*partial* r^2 grip: lacing shoe -.45, cutting meat -.59, lifting .55, total AHFT -.41; dexterity: lacing shoe .60, buttons .41, total AHFT .64). Age and number of hand problems were each significant in only one model (*partial* r^2 age: lacing shoe .38; hand problems: buttons .45).

The total KHFI was not significant in any model.

Conclusion: For tasks requiring strength, such as cutting meat, grip had the strongest association, while dexterity had the strongest association for tasks requiring manipulation. Overall hand function (AHFT) was more strongly associated with dexterity, suggesting that the ability to manipulate items is a better predictor of function than strength. This study suggests that although measuring impairments provides some indication of hand function, practitioners should measure both impairment and function to fully understand performance.

Acknowledgements: Funding was provided by the American College of Rheumatology Research and Education Health Professional Investigator Award. The UPMC Arthritis Network Disease Registry was funded by the St. Margaret Memorial Hospital Foundation.

Disclosure: N. A. Baker, None; **J. C. Rogers**, None.

1856

Problems and Coping Strategies Reported by Computer Users with RA. Nancy A. Baker, Joan C. Rogers, C. Kent Kwoh and Thomas Songer, University of Pittsburgh, Pittsburgh, PA

Purpose: Rheumatoid arthritis (RA) is associated with significant work disability. Computer use can be an important option for preventing work disability. This cross-sectional study describes the type and frequency of problems and coping strategies reported by computer users with RA when using two input devices, the keyboard and mouse.

Method: The Computer Problems Surveys (ComPS) requires each respondent to select from a list the problems they encounter and the coping strategies they use during keyboard and mouse use. The ComPS was mailed to registrants with RA in the Arthritis Institute Network Disease Registry. This registry does not give investigators access to registrants' names, so all mailings are one time and anonymous. Of the 502 mailed, 201 were returned, yielding a response rate of 40%. Differences between the number of problems and coping strategies reported for the keyboard and mouse were assessed using Wilcoxon Signed Ranks Test.

Results: The sample was 83% female and 89% were over the age of 45. They had been diagnosed with the disease for 16 years. Of the 178 respondents who reported using a computer (88%), 119 (67%) reported at least one problem with either the keyboard or mouse. Respondents reported significantly more coping strategies with the keyboard than the mouse ($p < .001$), but not having significantly more problems ($p = .12$). The most common types of problems for both devices were positioning the hand, fatigue, and manipulation (Figures 1A, 2A). The most common coping strategies were those that changed the user's performance: using the device for a shorter time and moving more slowly (Figures 1B, 2B). Respondents rarely reported using alternative input devices.

Conclusion: Although computer users with RA have a similar number of problems using the mouse and keyboard, they use significantly fewer coping strategies for the mouse. Although many of the most common problems reported by computer users with RA could be addressed by using alternative input devices, such as angled keyboards or voice recognition software, study respondents tended to use performance altering coping strategies. Further research is needed to determine why particular coping strategies are adopted and to identify which alternative input devices would best reduce computer use problems.

Acknowledgements: This research was supported by a Chapter Grant from the Arthritis Foundation of Western Pennsylvania

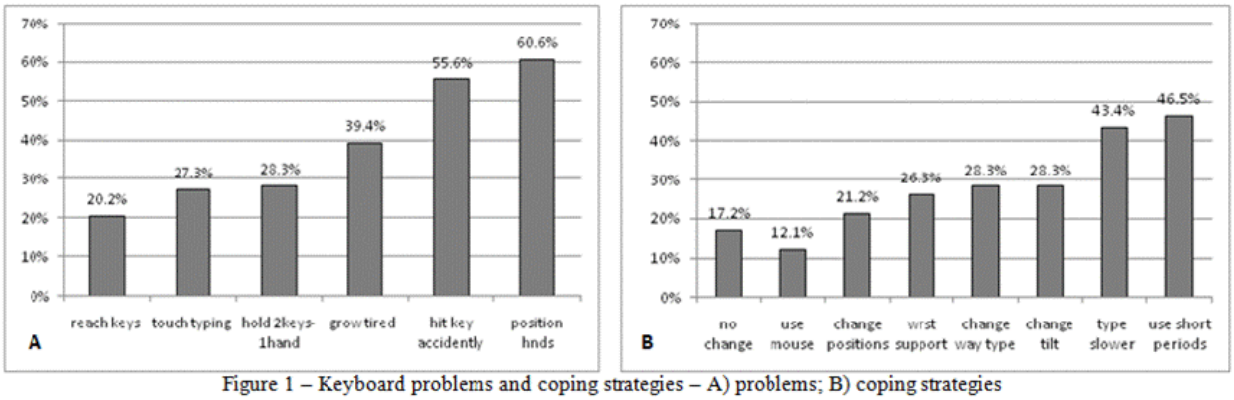


Figure 1 – Keyboard problems and coping strategies – A) problems; B) coping strategies

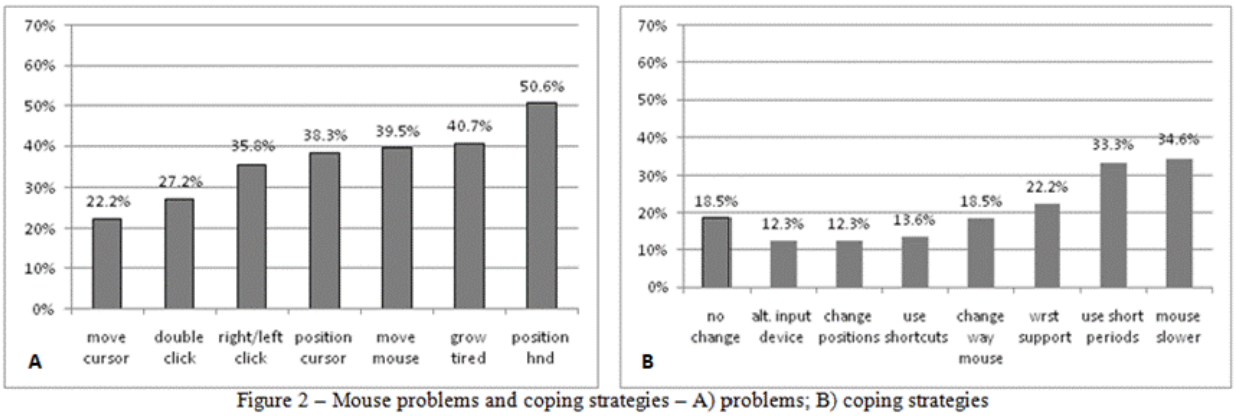


Figure 2 – Mouse problems and coping strategies – A) problems; B) coping strategies

Disclosure: N. A. Baker, None; **J. C. Rogers**, None; **C. K. Kwoh**, None; **T. Songer**, None.

1857

Beliefs and Practices of Occupational Therapists (OTs) and Physical Therapists (PTs) about Their Role in Addressing the Health-Related Work Problems of Patients with Chronic Health Conditions. S. Allaire[1], N. Baker[2] and Julie J. Keysor[3], [1]BUSM, Boston, MA, [2]UPMC, Pittsburgh, PA, [3]Boston UniversityHRS, Boston, MA

Purpose: Solving health-related work problems can help patients with rheumatic conditions stay employed, but little assistance with this is available. Occupational therapists (OTs) and physical therapists (PTs) could provide this help, but it's not clear to what extent therapists perceive they should, or do, address patients' work problems. We assessed therapist beliefs and practices in addressing patients' health-related work problems.

Method: We surveyed OTs and PTs by mail about their beliefs and practices concerning the health-related work problems of patients with chronic health conditions. A random selection of names of professional therapists in U.S. hospital or private practice settings were obtained from the American Physical Therapy Association and American Occupational Therapy Association. 300 each of OTs and PTs were contacted; recruitment is ongoing. A 12 item questionnaire was developed for this study. Besides beliefs and practices, questions assessed confidence in addressing patients' work problems, time available, and the frequency of seeing relevant patients. Questions had ordinal or 10 point scale response measures.

Results: 34% response rate; 12% did not treat employment aged adults and so were ineligible. 46 OT and 63 PT respondents provided consent and data. Both professionals strongly believed they should address patients' health-related work problems. 95.4% believed this was

in their professional scope of practice. Importance of determining patients' employment status was a mean of 9.5 on a 1-10 scale, and the mean score for importance of determining wheher patients' health affects their work was 9.6. PTs and OTs did not differ in their beliefs: in their scope of practice, 95.2 vs. 95.6%; importance of determining employment status, mean 9.3 vs. 9.6; and importance of determining if health affects work, mean 9.5 vs. 9.7. In their practices, 92.7% of therapists always (83.5%) or usually (9.2%) determine patients' employment status, and 94.5% always (76.2%) or usually (18.3%) ask about possible effects of health on work. Proportions of PTs engaging in these practices were slightly lower than OTs, 88.9 vs. 97.8% determine employment status, and 90.5 vs. 100% ask about health effects. 80.7% of all therapists agreed or strongly agreed they were confident in addressing health-related work problems, and PTs and OTs differed little on this. 24.8% of therapists did not have enough time for patients' work problems, with PTs more likely to state this than OTs. Only 7.3% of the sample had not treated patients with a rheumatic condition in the past month.

Conclusion: Therapists in this sample strongly believed they had a role in addressing the health-related work problems of patients with chronic health conditions, and their reported practices closely followed their beliefs. Generalizability of findings is limited given the response rate and subject self-selection from professional organization members.

Disclosure: S. Allaire, None; **N. Baker**, None; **J. J. Keysor**, None.

1858

Work Barriers Encountered by Employed Persons with Scleroderma. Janet L. Poole[1], Sahar Anwar[1], Cindy F. Mendelson[2] and Saralynn J. Allaire[3], [1]1 University of New Mexico, Albuquerque, NM, [2]Univ of New Mexico, Albuquerque, NM, [3]Boston Univ School of Medicine, Boston, MA

Purpose: Systemic sclerosis, or scleroderma (SSc), is an autoimmune connective tissue disease that affects thousands of Americans. Pain, finger ulcers, contractures, Raynaud's phenomenon, esophageal reflux, and internal organ involvement, particularly decreased pulmonary function, make it difficult to perform daily tasks, including work. The economic cost of not working is high in persons with SSc. However, there is no information about the work barriers they experience. The purpose of this study was to identify work barriers faced by persons with SSc.

Method: Persons with SSc who are employed 8 hours or more per week and reported difficulty working due to self-perceived symptoms from SSc were included in this study. Participants completed the Work Experience Survey, a survey that contains lists of potential work barriers including the ability to get to and from work, get around at work, perform essential job functions including physical, cognitive and task related activities. work with others, and handle work conditions.

Results: Results from the first 15 participants are presented (14 females, 1 male; mean age 47.6 years, mean disease duration 7.23 years; 50% working 20 hours or more per week). Temperature (54%) and using stairs (32%) were cited as the most common barriers in regard to work site accessibility. The most common job functions barriers that required physical activity were using hands (54%), lifting (32%), kneeling (32%), prolonged sitting (31%), working 8 hours (27%), prolonged standing (27%), pulling (27%), and pushing (27%). The task related barriers posing the most difficulties were writing (40%) and performing under stress (36%). The only work condition barrier was too cold (63%), but this was the most commonly cited of all barriers. Participants did not cite any barriers in regard to cognitive activities, social activities or company policies. Data from the remaining 15 participants will be included in presentation of the final results.

Conclusion: The most common cited work barriers were cold temperature and hand use (including writing, endurance (working 8 hours), and performing under stress. The barriers identified are similar to those identified by Allaire and colleagues in a study of adults with a variety of rheumatic diseases. The barriers are amenable to job accommodations.

Disclosure: J. L. Poole, American College or rheumatology Research and Education Foundation, 0, National Institute of Nursing Research, 0 ; **S. Anwar**, None; **C. F. Mendelson**, American College of Rheumatology Research and Education Grant, 2, National Institute of Nursing Research, 2 ; **S. J. Allaire**, None.

1859

The Effectiveness of a Scleroderma Self Management Program Delivered Via Booklet and DVD. Janet L. Poole[1], Cindy F. Mendelson[2] and Betty Skipper[3], [1]1 University of New Mexico, Albuquerque, NM, [2]Univ of New Mexico, Albuquerque, NM, [3]Albuquerque

Purpose: To determine the effectiveness of a self management program for persons with scleroderma delivered via booklet and DVD.

Method: Persons with scleroderma were recruited from the Scleroderma Foundation website. This study was a pre-test post-test design where participants were evaluated before and after participating in the program. Participants completed questionnaires regarding self-efficacy (Arthritis Self-Efficacy Scale), performance of daily activities, (Health Assessment Questionnaire), hand function (UK Scleroderma Functional Score), fatigue (Multi-dimensional Assessment of Fatigue Scale), depression (Center for Epidemiologic Studies Depression Scale) and pain (Visual Analogue Scale). Participants were also interviewed about their satisfaction with the program. The intervention program consisted of a booklet with modules on scleroderma, coping, self-advocacy, fatigue and energy conservation, activities of daily living, mouth and teeth care, dysphagia, Raynaud's phenomenon, exercise and a DVD showing face, hand, arm and leg exercises.

Results: Sixty one people with scleroderma competed baseline questionnaires while 49 (80%) completed the program and post intervention questionnaires. Of the participants who completed the program, the mean age was 53.9 years with a mean duration of 6.9 years and mean education level of 15.2 years. Ninety two percent were female, 82% Caucasian, and 73% were married. Depression, fatigue, and pain decreased while hand function, self efficacy to control other symptoms, and self efficacy for controlling pain improved; however, the only significant change was in self efficacy for pain. Participants were enthusiastic about the program and felt the program was needed especially for persons who were newly diagnosed. The most informative topics were the self advocacy module and the exercise DVD.

Conclusion: The findings suggest that self management program delivered via the booklet and DVD may not be as effective as a small group format. However, given the rarity of scleroderma, a small group format may not be available for those who live outside larger metropolitan areas. Thus, research is needed to determine the most effective method to deliver self management programs for this population.

Disclosure: J. L. Poole, National Institutes of Health, 2 ; **C. F. Mendelson**, American College of Rheumatology Research and Education Grant, 2, National Institute of Nursing Research, 2 ; **B. Skipper**, None.

1860

LANtern (Lupus Asian Network): Evaluation of An Innovative National Program. M. Tran, R. Horton, A. Yee and S. Paget, Hospital for Special Surgery, New York, NY

Purpose: Launched in 2003 with a mission to support, empower, and enhance quality of life for Asian-Americans with SLE and their loved ones, Hospital for Special Surgery's LANtern (Lupus Asian Network) is a national resource for its peer based telephone SupportLine and bilingual Chinese educational publications. This complex illness affects Asian-Americans 2-3x as often as whites.

Method: We developed a telephone evaluation for the 101 SupportLine users with lupus or family members who used the program from 2003 – 2006. The 31-item survey consisted of Likert scale and open-ended questions to assess user demographics, program satisfaction, SLE impact, and service recommendations. Interviews were conducted in users' preferred language, English or Chinese (Mandarin/Cantonese), by 2 volunteers not otherwise linked with the program.

Results: We completed 24 interviews. Attrition was due to address change, lack of return calls, or refusal. Of our sample, 22 were female; 18 with SLE; 5 were parents and 1 adult child; 21 were born in other countries, with the majority from China (50%) and Hong Kong (21%). Most callers (42%) were between ages 46-55, followed by 26-35 (25%). More than half (54%) were monolingual in their native language/dialects, in contrast with a few (13%) in English only.

Fifty percent had SLE < 5 yrs and 33% had SLE >10 yrs. Almost half (46%) stated that SLE interfered with their everyday life or the lives of their loved ones with SLE *most* of the time, employment (63%), relationship with spouse/partner (42%), and social activities (42%). Considerable anxiety about the future was expressed (63% sometimes/very often). A majority of those with lupus (59%) reported being a burden to their family sometimes/very often, while 50% reported sometimes feeling down, depressed or hopeless.

Most users (55%) learned of LANtern via Chinese media, health fairs and word of mouth; an additional 37% were referred by social service/health care agencies. Initial contact was prompted very much by a desire to learn more about the illness (54%) and to relieve psycho-social concerns (34%). A significant number (71%) indicated a better understanding about lupus and the receipt of emotional support, and 55% felt less alone, despite the contacts being brief, with 63% reporting 1-2 contacts and 25% 3-5. 67% reported "very important" that the person they spoke with has a similar cultural or language background. Program satisfaction was high, with 92%

reporting being extremely/satisfied, and 96% would recommend the program to others. Additional service needs were also assessed, with recommendations consistent, culturally and linguistically, with their reported desire of peer connections, and family/group oriented activities.

Conclusion: Our results, though limited by a small sample size, underscore that a culturally relevant service need is being met through our telephone peer counseling model for a community reporting significant impact of SLE on their lives. Additional program modalities have since been explored and enhanced for service expansion.

Disclosure: M. Tran, None; **R. Horton**, None; **A. Yee**, None; **S. Paget**, None.

1861

An Innovative Support and Education Program for Early and Newly Diagnosed RA Patients: Emerging Themes. D. Kurtz, A. Batterman, R. Horton, L. Leff, J. Reyes-Canu, T. Fields and Stephen Paget, Hospital for Special Surgery, New York, NY

Purpose: Present treatment models in RA emphasize early medical intervention. Similarly, research indicates that early psychosocial interventions may positively affect long-term functional status and adaptive coping (Evers et al, 2003, Dobkin et al, 2008). Previously we reported on a needs assessment of newly diagnosed (<1year) RA patients which indicated the need for an education and support program to meet their specific psychosocial needs. Based on these results, we designed a unique program within a hospital based early arthritis center. We report now on salient themes that have emerged two years after the program's implementation.

Method: The program was developed using data from a multi-level needs assessment and modeled after a successful program for patients with chronic RA. 16 monthly workshops were convened as a forum for newly diagnosed patients to gain essential RA-related information and to have access to peer support. 4 series consisting of 4 sessions each have met to date. Each featured a lecture by an RA expert and a support group co-facilitated by an MSW and RN. Topics included: Drugs in early treatment, coping skills, joint protection and nutrition. After each session, structured written evaluations with Likert-type and open-ended questions were given to assess program impact. Focus groups were also held to elicit participant feedback and inform future planning.

Results: 114 evaluations were completed from an average of 10 participants per session. Demographics. Gender: 75% f, 25% m. Ethnicity: African American 25%, Asian American 6%, Caucasian 63%, Latino 6%. Mean age: 49.6 yrs. Education: 94% college or higher. 89% agreed (“completely” or “a great deal”) they were satisfied with group discussions. 92% agreed (“completely” or “a great deal”) that the “group is relevant to daily coping with RA.” Salient themes were: new awareness of the importance of early, aggressive treatment; need to address the psychosocial impact of RA; need for social support and improved MD/patient communication. The following patient statements are illustrative of these themes: “I will consider biologics sooner rather than later,” “I recognize that depression needs to be addressed and not ignored,” “Others deal with the same issues,” “This group is helpful in bringing out emotions I had been repressing,” “I will talk to my doctor about how to best evaluate [treatment] progress.”

Conclusion: Current research and our 2 year program experience lead us to believe that discussion of these themes in a structured setting soon after diagnosis offers a window of opportunity for cognitive reframing, which can enhance adaptive coping. This type of intervention is an integral part of a comprehensive treatment plan for the newly diagnosed patient and may serve to inform others in implementing similar programs.

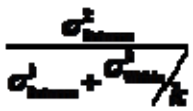
Disclosure: D. Kurtz, None; **A. Batterman**, None; **R. Horton**, None; **L. Leff**, Centorcor, Genetech, 5 ; **J. Reyes-Canu**, None; **T. Fields**, Takeda Pharmaceuticals, 8 ; **S. Paget**, None.

1862

Number of Days Necessary to Wear Portable Activity Monitors in Patients with Rheumatoid Arthritis. Gustavo J. M. Almeida[1], M. C. Wasko[2], KwonHo Jeong[1], Charity G. Moore[1] and Sara R. Piva[1], [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Purpose: Sedentary lifestyle characterizes patients with rheumatoid arthritis (RA) and is associated with morbidity and mortality. Objective measures of physical activity (PA) are needed to measure real-time activities performed by patients with RA**.** Individuals typically vary their level of PA throughout the week. Therefore, it is difficult to establish what days of the week are preferable to monitor PA and also the amount of days necessary to have a consistent estimation of PA. The information about the number of days necessary to obtain reliable estimates of energy expenditure (EE) is conflicting due to different statistical approaches and devices used. Studies of this nature have not been done in patients with RA. Thus, the purpose was to determine the minimal number of days needed to wear a portable activity monitor to obtain consistent measures of PA in patients with RA.

Method: Forty seven women with RA participated in this cross-sectional study. Subjects were asked to wear an activity monitor (Sensewear Armband Pro3, BodyMedia INC, Pittsburgh, PA) on the right upper arm, over the triceps muscle, for 7 days. In addition, they were instructed to take it off during shower and/or water activities, and to report activities they performed on a log-sheet. Variables of interest were daily total EE (TEE), EE during PA (EEPA), and daily number of steps. Analysis: First, an ANOVA was performed to determine if daily values of TEE, EEPA and #of steps were different among weekdays. Then, multiple linear regressions were used to determine the minimal number of days were needed to predict 80% of variability in 7-day of activity monitor use. The criterion was 7-day average and all combinations of continuous days were the predictors. Finally, intra-class correlation (ICC) coefficients were calculated using a one-way model taking repeatability into account. Total error was split in 2 error components: $y_{ij} = \square + \mu_i + \square_{ij}$; where μ_i is a random intercept with zero mean and var $(\mu_i) = \sigma^2_{Between} = \psi$, and $\square_{ij}$ is the random deviation of y_{ij} from subject i's mean with zero mean and var $(\square_{ij}) = \sigma^2_{Within} = \theta$. ICC (k) was then calculated using 7 days of single measurement with the following formula: _, where k is the number of days. ICCs above .80 were considered adequate.



Results: Mean age and BMI were 58±6 years and 28±7 respectively. The magnitude of daily values of TEE, PAEE, and number of steps were not different among the 7 weekdays (p = 0.93). To have a reliable estimation of TEE, it is necessary for the patients to wear the activity monitor for 2 days (ICC=0.83, Adjusted $R^2 \geq 0.86$), 4 days to have reliable estimation of EEPA (ICC=0.82, Adjusted $R^2 \geq 0.84$), and 3 days for number of steps (ICC=0.83, Adjusted $R^2 \geq 0.87$). These results were consistent across all days of the week.

Conclusion: The combination of any 4-day wearing the portable activity monitor predicted more than 80% of the variance across 7 days of data collection, and allowed for consistent measures with ICCs above .80. By minimizing the number of days necessary for data collection will reduce patients' burden and probably improve adherence.

Disclosure: G. J. M. Almeida, None; **M. C. Wasko**, None; **K. Jeong**, None; **C. G. Moore**, None; **S. R. Piva**, None.

1863

Lessons Learned From Community-Based Arthritis Physical Activity and Behavior Change Interventions: Reaching "Hard-to-Reach" Populations. Laura O. Houenou, Britta Schoster, Mary Altpeter, Jean Goeppinger and Leigh F. Callahan, University of North Carolina at Chapel Hill, Chapel Hill, NC

Purpose: To provide researchers and practitioners with recommendations for overcoming recruitment challenges for hard-to-reach populations for physical activity and behavior change interventions.

Method: We conducted evaluations of four community-based interventions among more than 1,600 individuals with self-reported arthritis in over 40 urban and rural counties in a Southeastern state. We reviewed our intervention protocols for overarching themes, common challenges, and successful adaptations and solutions for overcoming barriers to recruiting hard-to-reach populations in community-based research.

Results: For all four interventions, our hard-to-reach populations included **rural residents (62%), African Americans (AA) (45%), males (14%),** and **those without a high school degree (18%)**. One of these studies purposefully recruited **employed (30%)** participants, who are typically underrepresented in arthritis interventions. We found that multipronged approaches were necessary to recruit a diversity of research participants. We partnered with local community leaders who shared similar characteristics as the target populations, which allowed us to access these groups. For **rural** representation, we aligned with statewide agencies, such as the Area Agencies on Aging, as well as Parish

nurses and health departments serving rural areas. Word-of-mouth was the most productive recruitment strategy for rural-dwelling persons. **AA** participation in our interventions was higher in sites where the leader was also AA. Recruitment efforts focused on social and cultural organizations primarily comprised of AAs (e.g. churches and sorority chapters). Men were more likely to participate in the interventions when their female partners enrolled; thus, recruiting men through their partners was an effective recruitment method. Those without a high school degree were recruited by word-of-mouth and by working with local community leaders who could seek out those individuals and refer them to the research team. Because younger (<65 years old), employed individuals are not well represented in similar studies, we recruited from worksites and scheduled assessment activities during lunch and before and after typical work hours.

Conclusion: Increased representation of understudied populations in community-based interventions requires the use of multiple recruitment strategies. Based on our experience, we compiled a set of recommendations that may direct researchers and practitioners in addressing these recruitment challenges. It is imperative that researchers include understudied populations in community-based research so that their perceptions and social norms can be incorporated into interventions. Our lessons learned in community-based arthritis research may be applicable to other disease management intervention frameworks.

Disclosure: L. O. Houenou, None; **B. Schoster**, None; **M. Altpeter**, None; **J. Goeppinger**, None; **L. F. Callahan**, None.

1864

Fit and Strong!: Dissemination of An Evidence-Based Intervention for Older Adults with Osteoarthritis. Susan L. Hughes[1], Rachel B. Seymour[2] and Pankaja Desai[1], [1]Center for Research on Health and Aging, Chicago, IL, [2]University of Illinois Chicago, Chicago, IL

Purpose: Osteoarthritis (OA) is the most common condition affecting older people today. Lower extremity joint impairment caused by osteoarthritis (OA) is a link through which disability has been shown to develop. Fit and Strong! is an award winning evidence-based, multi-component exercise/behavior change program for older adults with osteoarthritis that is being diffused throughout the United States. The translation of evidence-based programs for older adults is a major public health priority.

Methods: Currently, two collaborative efforts are underway to translate and diffuse Fit and Strong!. The first effort is funded by the Centers for Disease Control and Prevention (CDC) and supports dissemination of the program in two states (1R18DP001140). Fit and Strong! is being diffused in two areas on aging in Illinois and two areas on aging in North Carolina with a minimum of 30 providers, involving the enrollment of 1,200 new participants. The Fit and Strong! team is also partnering with the National Arthritis Foundation (NAF) to translate and diffuse the program within four chapters: Northern and Southern New England, Northern California, Michigan, and Western Missouri/ Kansas. The goal of this partnership is to have 24 new providers (6 per state) adopt the program, train and evaluate the implementation of the program by 24 new instructors (6 per state) and enroll an additional 480 persons in the program.

Results: As a result of these efforts, we now offer the program in 7 states at 26 sites with 54 trained instructors and 292 participants. Pre-post outcomes and program evaluations are currently being collected. Preliminary analyses on outcome and mediator variables indicate a significant improvement on exercise participation ($p=0.025$), energy/fatigue ($p=0.035$) and self-efficacy for exercise ($p=0.020$). Factors which facilitate and impede program adoption, fidelity and adaptation and sustainability will be discussed. Practical issues involved in providing Fit and Strong! in the community will be discussed, including space, equipment, recruiting, training and monitoring exercise instructors, and methods for monitoring fidelity of Fit and Strong!.

Conclusion: As a result we now have a Website and a cadre of Master trainers available that make it possible for us to more broadly disseminate the program to other communities that seek to adopt the program.

Disclosure: S. L. Hughes, None; **R. B. Seymour**, None; **P. Desai**, None.

1865

Knowledge of Best Practice Guidelines for Management of Rheumatoid Arthritis Among Physiotherapy Students in a Problem-Based Curriculum. Christina Hallett[1], Jake Tumber[1], Nalin Fernando[1], Magdalena Hul[1], Sydney C. Lineker[2] and Norma J. MacIntyre[1], [1]McMaster University, Hamilton, ON, [2]The Arthritis Society, Toronto, ON

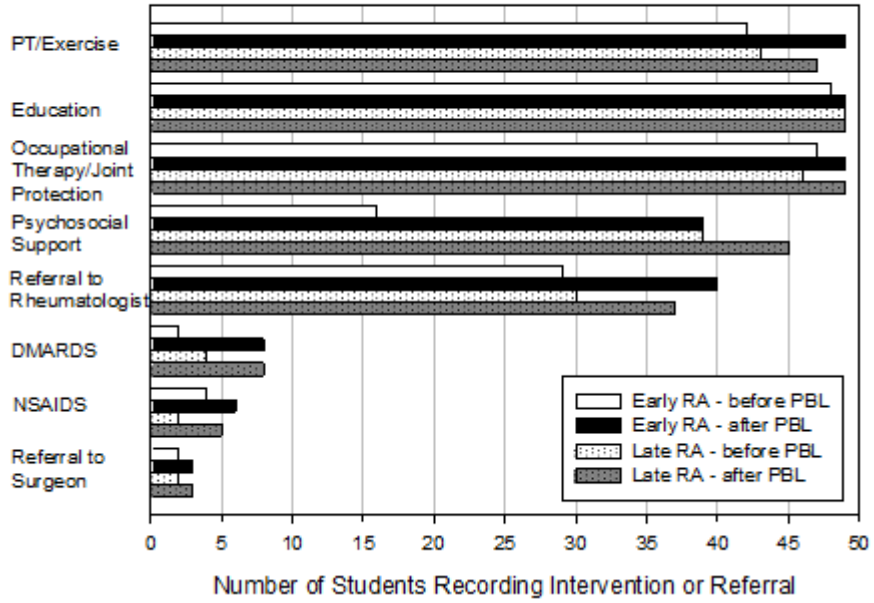
Purpose: A national partners group developed best practice guidelines (BPG) for health professionals in primary care who treat clients with early or late stage rheumatoid arthritis (RA). This study determined whether Physiotherapy (PT) students learned these BPG within their problem-based learning curriculum (PBL). A secondary objective was to pilot a supplemental learning module developed to address knowledge gaps.

Method: Of the 65 eligible senior PT students invited to participate, 49 consented and attended two testing sessions. Knowledge regarding BPG was evaluated using the ACREU Primary Care Survey administered before and after completing the usual PBL content related to physiotherapeutic management of clients with RA. Students were asked to indicate what interventions and referrals they would recommend in response to two case scenarios on early and late stage RA. Changes from baseline were assessed using McNemar's test for dependent proportions. To address identified gaps in learning, a video was developed to educate students regarding BPG. Three months later, a subgroup of participants (n=11) completed the same survey before and 1 week after viewing the video. Changes in scores were evaluated descriptively.

Results: Most students correctly recorded best practices relating to PT/exercise, education, and Occupational Therapy/joint protection before and after PBL (>83% and >95%, respectively). Knowledge related to referral to rheumatology and need to provide psychosocial support improved following PBL ($p<0.05$, Figure 1). Few students considered use of disease-modifying drugs (DMARDS) and non-steroidal anti-inflammatory drugs (NSAIDS) (Figure 1). Most students knew that referral to a surgeon is not best practice for early RA; however, the same number did not recognize this as best practice for late RA (Figure 1). After 11 students watched the educational video, at least 10 retained knowledge of best practice regarding PT/exercise, education, and Occupational Therapy/joint protection. An increased number reported the need for psychosocial support (from 5 to 10 for early RA; from 8 to 11 for late RA), referral to a rheumatologist (from 7 to 10 for both stages), use of DMARDS (from 0 to 8 for early RA; from 1 to 8 for late RA), use of NSAIDS (from 0 to 4 for both stages) and referral to a surgeon for late RA (from 1 to 4).

Conclusion: PT students about to become primary care practitioners have gaps in knowledge regarding best practices for managing clients with RA. Pilot data suggest that an educational video discussing BPG facilitates learning. Future research will assess the effect of incorporating the video into PBL as a supplemental learning module. Other strategies for improving knowledge regarding effective drug regimes and timely surgical consult for people with RA may be needed.

Figure 1. Best Practice for Clients with RA Reported by 49 PT Students Before and After Studying RA in a Problem-Based Learning Curriculum



Disclosure: C. Hallett, None; **J. Tumber**, None; **N. Fernando**, None; **M. Hul**, None; **S. C. Lineker**, None; **N. J. MacIntyre**, None.

1866

The Arthritis Educational Needs Assessment Tool: Will It Work in the Community? Mwidimi Ndosi[1], Jackie Hill[1], Jo Cumming[2] and Claire Hale[1], [1]University of Leeds, Leeds, United Kingdom, [2]Arthritis Care, London, United Kingdom

Purpose: Educational Needs Assessment Tool (the ENAT) was developed in the UK to help clinicians identify individual patients' educational needs in order to plan relevant and timely patient education. The ENAT is an easy to complete questionnaire with 39 items grouped into 7 domains: managing pain, movement, feelings, arthritis process, treatments, self-help measures and support. It has been validated for use across rheumatic diseases in the clinical settings but it has not been tested in the community. The purpose of this analysis was to assess how well the ENAT could capture the educational needs of people with arthritis in the community.

Methods: The ENAT was used to collect data from patients with ankylosing spondylitis (AS), psoriatic arthritis (PsA), scleroderma (Ssc), Lupus (SLE), osteoarthritis (OA), rheumatoid arthritis (RA) and fibromyalgia (FM) attending 4 hospitals in the UK (ENAT data). The educational needs were summarised into their respective ENAT domains namely: Pain, Movement, Feelings, Arthritis process, Treatments, Self-help and Support.

Arthritis Care is a UK patient organisation which offers free confidential service to people affected by arthritis using their helplines. Telephone helpline enquiries were collected from January to June 2008 and were summarised and categorised by type of arthritis and what their enquiry was about (Community data).

The community data were matched with the ENAT domains and were transformed and expressed in terms of x/y; where x = frequency of enquiries for each domain and y = sum of enquiries for all domains. The transformed community data were modelled against the ENAT data and correlational statistics were applied to explore their domain-domain correlation.

Results: The ENAT cohort comprised 911 with male/female ratio 1:2.5 while the community cohort comprised 5443 people with male/female ratio of 1:3. The ENAT cohort had roughly equal number of patients with AS, PsA, Ssc, SLE, OA, RA and FM. The community cohort had varying proportions of all the above diagnoses in addition to polymyalgia, juvenile idiopathic arthritis and people with no diagnosis.

Out of 16187 telephone inquiries 15475 (95.7%) could be matched with all the ENAT domains. The remaining 4.3% of the unmatched data included: self-management training, employment, sex/relationship and education.

The priority order of needs from the ENAT data was: arthritis process (0.122), treatments (0.114), pain (0.111), feelings (0.109), movement (0.109), self-help (0.110) and support (0.095). For the community data, the priority order was: self-help (0.217), arthritis process (0.192), treatments (0.185), pain (0.174), feelings (0.116) support (0.059) and movement (0.056).

When modelled against the ENAT data, the community data displayed a strong domain-domain correlation ($r = 0.678$) with the ENAT data ($p = 0.047$).

Conclusion: The results suggest that the ENAT could capture well the educational needs of people with arthritis in the community. This opens the possibility of the ENAT use in the community settings such as patient organisations or the web. Despite this potential, further validation of the ENAT for such uses will be necessary before its application.

Disclosure: M. Ndosi, None; **J. Hill**, None; **J. Cumming**, None; **C. Hale**, None.

1867

Improving Quality of Referrals From Primary to Specialty Care in An Underserved Community. Heather M. Greysen and Mark F. Gourley, NIH, Bethesda, MD

Purpose: Communication between the primary care provider (PCP) and specialist is important in the management of chronic rheumatic conditions and leads to improved patient care. Rapid referral to a rheumatologist and early treatment improves patient outcomes; however, inappropriate or excessive referrals to the specialist can strain clinic resources. Evidence suggests that distributing standardized guidelines for referral and providing education to primary care providers improves the referral process.

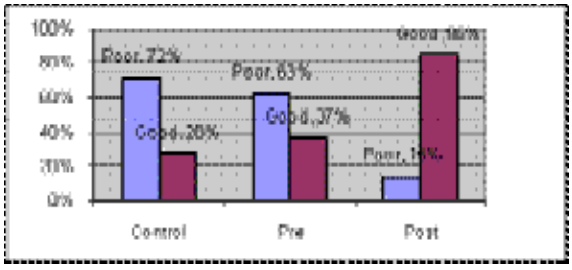
Method: Thirty-six PCPs in 5 clinics in the Washington DC area who refer patients to an NIH community clinic received a standardized referral sheet and a 40 minute educational intervention about common rheumatic diseases, taught by a rheumatology physician and nurse practitioner. The standardized referral sheet included guidelines for when to refer a patient and what information should be included in the referral. Referral quality was assessed pre- and post-intervention and compared to a control group that did not receive the guidelines sheet or the intervention. Quality was assessed by means of a scoring system, ranging from 0 to 3, developed for this study.

0 = PCP did not provide clinical data nor direction; 1 = PCP provided direction and no clinical data or provided clinical data without direction; 2 = PCP provided direction and one piece of clinical data. 3 = PCP provided direction and more than one piece of clinical data. Scores of 0-1 are considered poor, and 2 to 3 are considered good. Direction is awarded for formulating a specific clinical question. Clinical data includes recent progress note, lab results, and x-rays. The scoring system was validated by 4 other rheumatologists in the practice. Statistical significance was calculated using a paired t-Test.

Results: From June 2008 – June 2009, we analyzed referrals from each intervention clinic 3 months pre- and post-intervention. Control group referrals were gathered from September 2008 – February 2009. More than half (63%) of pre-intervention referrals were scored 0-1 (poor) compared with only 15% post-intervention. Most (85%) of post-intervention were scored 2-3 (good) compared with 37% of pre-intervention referrals. Referrals received after the intervention improved significantly ($p < 0.05$). The control group, without any intervention, sent primarily poor quality referrals; 72% were poor and 28% were good.

Conclusion: Our results show that this standardized tool and intervention improved referral quality, which helps the specialist deliver better quality care. Poor referrals lead to long wait lists and delay in initiation of therapy. Others authors have found that a guidelines tool was inadequate without a personal interaction between the PCPs and the specialist. Our intervention sessions increased communication by opening up a dialog between primary and specialty care providers.

Number of Referrals	0 or 1 = Poor	2 or 3 = Good
Control, n=58	42 (72%)	16 (28%)
Pre, n=30	19 (63%)	11 (37%)
Post, n=34	5 (15%)	29 (85%)



Disclosure: H. M. Greysen, National Institutes of Health, 3 ; **M. F. Gourley**, None.

1868

Organization and Provider Factors That Influence Utilization of Arthritis Best Practices in Primary Care. Sydney C. Lineker[1], Janice A. Husted[2], K. Stephen Brown[2] and Steve R. Manske[2], [1]The Arthritis Society, Toronto, ON, [2]University of Waterloo, Waterloo, ON

Purpose: The dissemination of clinical practice guidelines (CPGs) has been suggested as one method for improving primary care delivery. An inter-professional educational program was developed to disseminate best practices based on CPGs for the management of osteoarthritis (OA) and rheumatoid arthritis (RA). Primary care organizations were invited to enroll providers in 1 of 27 workshops on arthritis best practices (ABP) followed by 6 months of reinforcement activities. This study developed and tested 2 models of knowledge utilization (KU) to determine which organizational and individual level factors contributed to improved provider use of ABP following the workshops.

Method: To evaluate their use of ABP, workshop participants were surveyed at baseline and six months following the workshops using the ACREU Primary Care Survey. The survey assessed providers' responses on how they would manage patients described in 3 hypothetical case scenarios on early RA, late RA, and moderate knee OA. One point was given for each recorded best practice and totaled for each case with the highest possible score being 8 for the late RA and moderate knee OA cases and 7 for the early RA case. The survey also assessed provider satisfaction with their ability to deliver arthritis care and confidence with their ability to manage arthritis. Each participating organization also completed a practice profile. For Model 1, two-level hierarchical linear modeling was used to determine the direct effects of organization and provider level variables on intended use of ABP six months following the workshops. In Model 2, logistic regression was used to determine the influence of organization level factors on one specific ABP, dissemination of educational materials.

Results: Two hundread and seventy-five providers from 131 organizations completed baseline and 6 month follow-up surveys. For all 3 case scenarios, total ABP scores were predicted by the discipline of the providers, the model of care in which they worked, and baseline ABP scores (P<.05). Baseline confidence also predicted the 6 month scores for moderate knee OA (P=.05) and baseline satisfaction predicted the total score for late RA (P=.04). The estimated probability of disseminating educational materials was >82% for providers working in community health centres, physician networks and regionally funded organizations compared to 30% for federally funded organizations (P<.01) and was 88% for organizations that sent interdisciplinary team members to the workshops compared to 70% for those that did not (P=.07).

Conclusion: Use of ABP may be influenced by provider (discipline, satisfaction, confidence) and organization characteristics (model of care, team learning experience). These results have implications for the training and education of health professionals and the design and staffing of models of primary care to enhance arthritis care delivery.

Disclosure: S. C. Lineker, The Arthritis Society, 3 ; **J. A. Husted**, None; **K. S. Brown**, None; **S. R. Manske**, None.

1869

Racial and Ethnic Differences in the Prevalence, Impact and Management of Doctor-Diagnosed Arthritis—United States, 2002, 2003 & 2006. Julie Bolen, Charles G. Helmick, Jennifer M. Hootman, Louise Murphy and Gary Langmaid, Centers for Disease Control and Prevention, Atlanta, GA

Purpose: : By 2010 about one in three US residents will belong to a minority group (one in two by 2050). Previous studies have shown racial and ethnic differences in arthritis prevalence and impact (e.g., prevalence is similar between whites and blacks, but impact is more severe for blacks). We describe the prevalence, impact and management of arthritis among six racial groups (White, Black, Hispanic, American Indian, Asian and other) and 8 Hispanic subgroups.

Methods: We combined data from the 2002, 2003 and 2006 National Health Interview Survey (NHIS), an in-person national sample of the U.S. civilian, non-institutionalized population aged >18 years (N=85,897). Respondents were asked about health conditions, including doctor-diagnosed arthritis, arthritis-attributable activity and work limitations, arthritis-related pain, and health care provider counseling to lose weight, be more physically active or to take a class to manage arthritis symptoms. Non-Hispanic blacks, Hispanics and Asians were oversampled.

Results: Overall about 21.2% of US adults have doctor-diagnosed arthritis; of these 37.8% report an arthritis attributable activity limitation and 25.6% report severe joint pain. Of adults of working age (18-64) who had arthritis 31% reported arthritis-attributable work limitations. White non-Hispanics have less arthritis-attributable limitation (36.3%, 95% C.I. 35.3-37.3) than Black non-Hispanics 44.7, CI 42.6-46.7), or Hispanics (43.2%, CI 40.2-46.3). Similar patterns were observed for work limitation and severe joint pain. Differences remained when estimates were age-adjusted. Health care provider counseling to lose weight to help arthritis symptoms was 30.7% overall and was highest for black non-Hispanics (39.6%, CI 37.5-41.8) and Hispanics (38.6%, CI 35.9-41.2). Counseling to increase physical activity was 53.6% overall but lower among American Indians (38.8%, CI 30.6-47.6). Counseling to take a class to manage arthritis symptoms was only 10.5% overall and differences between racial groups were not significant.. Estimates varied among the 8 Hispanic subgroups but, due to small sample sizes, no differences were significant.

Conclusion: There is considerable racial and ethnic variation in arthritis prevalence, impact, and management. Possible reasons include 1) lack of health care access and/or utilization leading to delays in seeking medical attention for joint problems, 2) the presence of co-morbid conditions such as obesity, diabetes, heart disease and cancer, 3) cultural differences in perception of pain or willingness to report pain, and

4) employment in jobs that are physically demanding. Arthritis interventions may need to target minority populations in different ways to help reduce arthritis related impact.

Disclosure: J. Bolen, None; **C. G. Helmick**, None; **J. M. Hootman**, None; **L. Murphy**, None; **G. Langmaid**, None.

1870

To Measure Patients' Adherence and Factors Influencing Adherence with Prescribed Medications for Rheumatoid Arthritis.
Christina Doyle[1] and Georgina Gethin[2], [1]Our Lady's Hospice Ltd, Harolds Cross, Dublin, Ireland, [2]Royal College Surgeons Ireland, Dublin, Ireland

Purpose: Rheumatoid Arthritis (RA) affects 1% of the population, with increasing numbers of individuals being diagnosed every year. It is a treatable illness, which includes adherence with prescribed medication. The World Health Organisation identified between one third to a half of medications prescribed for long-term medical conditions are not taken as directed. There is a lack of studies in an Irish context which profiles patients level of adherence and understanding which prescribed medication in the management of RA. The aim is to measure patients' adherence and factors influencing adherence with prescribed medications for Rheumatoid Arthritis.

Method: A Self-report questionnaire was administered to 200 randomly selected patients attending a Rheumatology Rehabilitation Unit. Data collection included demographic details, disease profile, medication usage, MARS score, MTQ score, and health beliefs.

Results: Response rate of 40% (n=80) achieved. 82% were over 50 years of age and a ration of female to male of 3:1 was recorded. 55% (n=44) had disease duration > 10 years. 64% (n=51) self-reported that they were adherent to their medications as prescribed. 80% (n=57) frequently seek information about their RA while 97% (n=72) believe they themselves were responsible for their own health. 34% reported having been seen by the Rheumatology Nurse Specialist.

Conclusion: This is the first designated Irish study exploring patients' adherence with prescribed medications for RA. It has revealed there was no relationship found between gender, disease duration, education or visits to the Rheumatology Nurse Specialist and adherence. Patients are requesting more education into their disease and disease management. More structured education needs to be developed by healthcare professionals and disseminated to the patients. Further research that is more extensive is required into this phenomenon.

Disclosure: C. Doyle, None; **G. Gethin**, None.

1871

Decision Aid Formats to Communicate the Effect of DMARDs On Structural Joint Damage in Rheumatoid Arthritis.
Matthew E. Brower[1], Donald J. Tellinghuisen[1], Patience J. Gallagher[1] and Richard W. Martin[2], [1]Calvin College, Grand Rapids, MI, [2]Michigan State University College of Human Medicine, Grand Rapids, MI

Purpose: A discussion regarding changing disease modifying anti-rheumatic drugs (DMARD) takes place in about 25% of rheumatology office visits.[1] The power to slow progression of structural joint damage (SJD) is a distinguishing DMARD attribute considered in this discussion. Rheumatoid arthritis (RA) patients, like most people, have difficulty accurately interpreting numeric statements of risk.[2] This study explored how potential presentation formats used in a patient decision aid effected comprehension of a DMARD's ability to slow RA SJD.

Method: Ninety-one healthy volunteers were presented with one of four written scenarios. Each contained a brief introduction to RA, description of SJD, and a statement of the % reduction in SJD progression rate associated with a hypothetical drug. Participants were randomly assigned to narrative only (N), or one of three alternative formats: N + graphic representation of SJD over time, N + natural frequency pictograph, and N + speedometer metaphor. Each of these formats combined N with a visual depiction of SJD progression and provided identical risk information. All four experimental groups' participants then answered 5-point Likert scale questions derived from the COMRADE[3], rating the quality and participant satisfaction with the information. In addition, verbatim recall of the rate SJD would progress (0-100) and rate SJD would be reduced (0-100) was evaluated. Average responses to COMRADE questions were evaluated with one-sample T-test to compare mean response to 3 (neutral value) for each group. Between group differences recalling SJD progression rates were evaluated with one-way ANOVAs.

Results: One-sample t-tests indicate that responses did not significantly differ from the neutral value (3) to the statement, "materials gave enough explanation about how the medicine slows joint damage" in the N + graphic, N + natural frequency and N + speedometer conditions. In the N condition, however, participants significantly disagreed with that statement ($M = 2.40$, $p = .004$). A similar, although non-significant, pattern was shown regarding whether materials left participants "adequately informed" about decision issues. One-way ANOVAs indicated that across all conditions, participants underestimated the slowing in rate of progression associated with use of the hypothetical drug. Participants tended to more accurately rate the progression in the N + natural frequency pictograph and N + speedometer metaphor compared to N and N + graphic representation of SJD over time. These differences, however, were not significant ($p < .05$).

Conclusion: Patient decision aid risk presentation format can enhance patient acceptance of numeric statements of risk and may potentially affect accuracy of subject recall of the benefits of anti-rheumatic drugs to slow structural joint damage in RA.

References: [1]McKown KM Arthritis Rheum 2008;56:S731. [2]Martin RW Arthritis Rheum 2006;54:S369. [3]Edwards A. Patient Educ Couns 2003;50:311-22.

Disclosure: M. E. Brower, None; **D. J. Tellinghuisen**, None; **P. J. Gallagher**, None; **R. W. Martin**, None.

1872

Exploring the Ways People with Early Rheumatoid Arthritis (RA) Medically Self-Manage. Paul M. Adam[1], Anne F. Townsend[2], Susan M. Cox[2], Catherine L. Backman[2], Zubin Amarsi[3], Linda C. Li[2] and ERAHSE team, [1]Mary Pack Arthritis Centre, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Purpose: The Chronic Care Model (Wagner, 2001) aims to provide patients with timely and effective health care. Successful self-management is a key element of this approach. In this study we focus on the various ways study participants medically self-managed their rheumatoid arthritis (RA) early post-diagnosis.

Method: 46 (8 pilot study, 38 ERAHSE study) adults with early RA defined as ≤ 12 months post-diagnosis were recruited from rheumatologists, family physicians, and patient advocacy newsletters. In-depth face-to-face interviews were organized around three overlapping sections: onset of symptoms and initial illness actions; seeking help from health professionals leading to diagnosis; and post-diagnosis experiences. Follow-up phone calls were made to check and elaborate on data gained at interview. Two researchers read the initial transcripts independently. Emergent themes were identified through discussion and negotiation, constant comparisons made between and within transcripts, and both diverse and common experiences sought. Subsequent transcripts were read with initial findings and the literature in mind. To aid conceptual clarity, we used Koch and colleagues (2004) three models of self-management (the medical, collaborative, self-agency models), as a heuristic device.

Results: The data revealed several emerging and cross-cutting themes showing that post-diagnosis medical self-management is complex and dynamic. Personal beliefs and values, past medical experiences, knowledge of others with RA, media sources, and relationships with practitioners impacted how people interpreted and understood their symptoms, disease, and treatment options; gained information; and made treatment decisions. Against the backdrop of Koch's self-management models, our results revealed that (1) people move between models over time, (2) people use a combination of models depending on the type and nature of the treatment intervention, and (3) there are inherent difficulties in practicing each model of self-management, such as knowing what questions to ask practitioners, where and how to seek reliable information, and how to attribute cause and effect when assessing treatment benefits. An improved sense of body awareness, recording of treatments and outcomes, and trial & error are all techniques that were found to support medical self-management.

Conclusion: People medically self-manage in a range of ways, and move between models. Practitioners need to be aware of these variations in order to provide support and care that is consistent with patient needs and priorities as they self-manage.

[1]Wagner et al. Health Affairs. 2001;20(6):64-78.
[2]Koch et al. Journal of Advanced Nursing. 2004;48(5):484-92.

Disclosure: P. M. Adam, None; **A. F. Townsend**, None; **S. M. Cox**, None; **C. L. Backman**, None; **Z. Amarsi**, None; **L. C. Li**, None.

1873

Clinical Correlates of Sexual Impairment in Women with Systemic Sclerosis. Ruby Knafo[1], Brett D. Thombs[2], Fredrick M. Wigley[3] and Jennifer A. Haythornthwaite[4], [1]McGill University, Montreal, QC, [2]McGill University and Jewish General Hospital, Montreal, QC, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD

Purpose: The objective of this study was to assess the correlates of sexual impairment in a sample of women with systemic sclerosis (SSc).

Method: Female SSc patients completed measures of sexual function (Sexual Relationships subscale of the Psychosocial Adjustment to Illness Scale – Self-Report; PAIS-SR), body image (Satisfaction With Appearance Scale; SWAP), and pain (Visual Analog Scale; VAS). Sociodemographic and disease specific variables were recorded. Pearson correlations and multiple regression analyses were run to assess the associations between body image, pain, and sociodemographic and disease variables, with sexual function.

Results: 117 female SSc patients were sampled (33 [28.2%] diffuse; mean age 51.4±11.9 years; mean time since diagnosis 9.1±8.5 years). Unadjusted analyses revealed a moderate positive correlation between sexual function and pain ($r = 0.439$, $p < 0.001$), satisfaction with appearance ($r = 0.350$, $p < 0.001$), and a moderate negative correlation with being married ($r = -0.338$, $p = 0.000$). Adjusted analyses revealed that being married ($\beta = -0.228$, $p = 0.006$), disease duration ($\beta = 0.171$, $p = 0.046$), and pain ($\beta = 0.290$, $p = 0.001$) are independent predictors of sexual function. Satisfaction with appearance was not independently associated with sexual function ($\beta = 0.158$, $p < 0.067$).

Conclusion: This is the first empirical study to investigate the clinical correlates of sexual impairment in women with SSc, and the first to document the association between sexual impairment and pain in women with SSc. Pain, longer disease duration, and not being married are associated with increased sexual impairment in women with SSc.

Disclosure: R. Knafo, None; **B. D. Thombs**, None; **F. M. Wigley**, None; **J. A. Haythornthwaite**, None.

1874

Sexual Relationships in Rheumatoid Arthritis: The Development and Use of the ASBLA Model. Gill Grundy[1], Robert J. Moots[1], John A. Goodacre[2], Alan Riley[3] and Lynne Goodacre[2], [1]University Hospital Aintree, Liverpool, United Kingdom, [2]Univ of Central Lancashire, Preston, United Kingdom, [3]UCLAN, Lancashire, United Kingdom

Purpose: Rheumatoid arthritis [RA], a chronic inflammatory joint disease, impacts on all aspects of peoples' lives, including their sexual relationship. This study aimed to explore the impact of RA on the sexual relationships and sexual function of patients and partners of people with RA, and to investigate communication between couples and healthcare professionals on this issue.

Method: A mixed method approach, within a phenomenological paradigm was adopted, comprising semi-structured interviews and validated questionnaires. Interviews were used to collect detailed insights of participants' experiences and questionnaires to provide demographic, clinical and relationship data. Purposive sampling ensured a heterogeneous population in terms relationship status, disease duration and disease activity. Interpretative phenomenological analysis facilitated by ATLAS-ti guided analysis of the qualitative data. Questionnaire data was analysed using descriptive statistics. Ethics approval was obtained and participants were recruited from 2 out-patient rheumatology departments.

Results: Fifty-one participants, 16 male and 15 female patients 10 male and 10 female partners were recruited. Age range 27–70 years, disease duration 1-30 years. Data analysis identified 5 super-ordinate themes: Adjustment, Self-image, Balance, Limitation Acceptance [ASBLA] which informed the ASBLA model. This model highlights the importance of locating sexual activity within the wider relationship context. It represents the major challenges RA posed to sexual relationships: the need to adjust to the impact of the impairment: challenges to self image: limitations placed on sexual activity: acceptance of the changing status of RA. Informed by individual participant approaches to these challenges it also identifies mediators to the impact of RA: knowledge, understanding, communication and commitment. Communication between patients, partners and healthcare professionals [HPCs] was found to be limited.

Conclusion: Whilst highlighting the relationship challenges participants faced, this study provided insights into their positive experiences providing a reminder that positive sexual relationships are possible and that, given the right support, challenges can be overcome. The ASBLA model has the potential to be used as a tool to facilitate dialogue between patients/partners and HCPs and could be used to help HCPs develop an understanding of the relationship challenges patients with RA and their partners face.

Disclosure: G. Grundy, None; **R. J. Moots**, None; **J. A. Goodacre**, None; **A. Riley**, None; **L. Goodacre**, None.

1875

Depression and Couple Mutuality in Prospective Data From Rheumatoid Arthritis Patients. Shelley Kasle[1], Patrick E. McKnight[2] and Mari S. Wilhelm[1], [1]Univ of Arizona, Tucson, AZ, [2]George Mason University, Fairfax, VA

Purpose: Social support, including couple relationship quality, has important implications for the health of Rheumatoid Arthritis (RA) patients. Depression is prevalent in RA and predicts increased inflammation. Mutuality, measured as the frequency of engaged, empathic, authentic responses during important couple communications, has been inversely linked with depression in RA patients in cross-sectional data. The purpose of this study was to test the hypothesis that higher levels of mutuality are consistently linked with lower levels of depression in prospective data from RA patients.

Method:

Married/partnered RA patients (N=156; 76% female, mean age = 56 yrs, mean RA duration = 8 yrs) completed 4 questionnaires at 0, 6, 12, and 18 months. Packets included valid, reliable measures of couple mutuality (Mutual Psychological Development Questionnaire),depression (CES-D), and control variables: daily hassles (Daily Stressors Checklist), affect (Positive and Negative Affect Scales), and counts of chronic health conditions. Hierarchical regression was used to estimate additive effects on depression of the variables (in order): intercept, timepoint, health conditions, daily hassles, positive affect, negative affect, mutuality, and a mutuality X timepoint interaction.

Results: All predictors in the model had significant effects on depression (Table 1). Timepoint had an inverse effect, equal to a 6.084-point decrease in the depression score for each wave (P <.001). After accounting for prior predictors in the model, mutuality exerted a significant inverse effect, with each point increase in the mutuality score associated with a 3.74-point decrease in the depression score (P < .001). A positive interaction of mutuality with timepoint reflected a floor effect in depression scores at later timepoints.

Conclusion: Consistent with hypothesis, RA patients who reported more couple mutuality reported less depression at each timepoint. This consistent inverse effect of mutuality on depression emerged after accounting for other effects, including a large effect of timepoint. These results suggest a potentially protective effect of mutuality on depression. As depression is a risk for worse RA outcomes, mutuality may be a useful prognostic indicator. With more research, mutuality may emerge as a therapeutic target for psychosocial interventions.

Table 1. Hierarchical Regression of Depression (N=156)

Predictors	Estimates*	(SE)	P
Intercept	29.363	3.816	<0.001
Timepoint	-6.084	1.287	<0.001
Health Conditions	0.385	0.157	0.014
Daily Hassles	0.562	0.114	<0.001
Positive Affect	-3.570	0.277	<0.001
Negative Affect	5.583	0.405	<0.001
Mutuality	-3.742	0.776	<0.001
Mutuality X Timepoint	1.044	0.285	<0.001

*Unstandardized regression coefficients

Disclosure: S. Kasle, ACR-REF, 2, Arthritis Foundation, 2 ; **P. E. McKnight**, None; **M. S. Wilhelm**, None.

1876

Younger Subjects with Chronic Musculoskeletal Pain and High Depression Scores Benefit the Most From a Cognitive Rehabilitation Programme. Ann B. I. Bremander and Stefan Bergman, R&D Center Spenshult, Oskarstrom, Sweden

Purpose: Chronic musculoskeletal pain is a major health care problem. The recommended treatment is multimodal with a cognitive approach to maintain the effects over time. However, it is not clear as to who will benefit the most from a specific form of treatment. The aim of this study was to explore who a multimodal treatment with a cognitive approach will benefit the most concerning health related quality of life outcome (HRQoL).

Method: 131 subjects who participated in a rehabilitation programme with a non pharmacological cognitive approach were followed by patient reported outcome measures. The Hospital Anxiety and Depression Scale (HADS), the Short Form 36 question health survey (SF-36), pain and global health measured with a visual analogue scale (VAS) and a pain mannequin were administered at admission and 6 months later at the end of the treatment period. For analysis of change due to intervention t-test was used and categorical values were analyzed using chi-square tests. Multivariate analysis was performed to study associations between explanatory personal characteristics and an improved outcome in HRQoL measured by the SF-36 subscales physical function, bodily pain, vitality and mental health.

Results: Complete data were available for 97 patients (85 women, mean age (SD) 44.6 (9.7)). VAS pain improved significantly ($p<0.05$) during the rehabilitation period, so did HADS and SF-36 subscales physical function, general health, vitality, social functioning and mental health.

In the multivariate analysis scores suggesting a probable depression (≥ 11) were associated with a favourable outcome of the SF-36 subscale physical function (OR 4.6, p 0.04), bodily pain (OR 2.5, p 0.12), vitality (OR 4.7, p 0.03) and mental health (OR 2.8, p 0.11). Sex, age, anxiety, pain and pain distribution were not associated with improved outcome of HRQoL. However, there was a stronger association for younger subjects (20-45 years) with probable depression scores and a favourable HRQoL outcome in the subscales physical function (OR 21.6, p 0.01), bodily pain (OR 5.9, p 0.04) and vitality (OR 8.1, p 0.04).

Conclusion: This multidisciplinary rehabilitation programme with a non pharmacological cognitive approach seemed to yield a better outcome concerning HRQoL measures in younger patients with higher depression scores at baseline. This is important information to the clinics when tailoring a multidisciplinary rehabilitation programme for patients with musculoskeletal chronic pain.

Disclosure: A. B. I. Bremander, None; **S. Bergman**, None.

1877

Body Composition and Disability Among Women with RA and Lupus. Patricia Katz, Holly Wing, Sandi Kaplan, Rachel Diskin, L. J. Julian, Laura Trupin, J. Yazdany, L.A. Criswell and E.H. Yelin, UCSF, SF, CA

Purpose: Body composition has been linked to disability in the general population. Less research has focused on the role of obesity or body composition in rheumatic conditions, but there is preliminary evidence that body composition may be related to functioning. We examine the relationship between body composition and valued life activity (VLA) disability among women with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Method: Women (RA: n=81, mean age 56; SLE: n=128, mean age 46) underwent dual-energy x-ray absorptiometry (DXA) for measurement of body composition (fat and lean mass). Height-adjusted fat mass (FM) and lean mass (LM) were calculated. Sarcopenia (low muscle mass) was also determined from DXA[1]. Height and weight to calculate body mass index (BMI) were collected at the same visit. VLA disability because of RA/SLE was defined in 3 ways: the mean difficulty rating of 33 activities (range 0 [no difficulty] – 3 [unable to perform]; proportion of activities affected to any degree; and proportion of activities individuals were unable. Associations between body composition and disability were assessed separately for each disease cohort with linear regression, controlling for age.

Results: For RA, mean VLA difficulty was 0.54, VLAs affected 44.7%, and VLAs unable to perform 1.6%. For SLE, mean VLA difficulty was 0.77, VLAs affected 57.8%, and VLAs unable to perfor m 3.6%. In both cohorts, greater FM from DXA and BMI obesity were each associated with greater difficulty and a higher proportion of VLAs affected (Tables 1, 2). Lower LM was associated with greater difficulty and a higher proportion of VLAs affected only in the RA cohort. Sarcopenia was present in 11 women with SLE and 12 with RA, and was associated with both greater difficulty performing and a higher proportion of VLAs unable to perform (Table 3).

Table 1. Association of Disability and Height-Adjusted Fat and Lean Mass

		VLA difficulty	% VLAs affected	% VLAs unable
RA	FM	0.01 (.05)*	1.4 (.01)	-0.02 (.75)
	LM	-0.02 (.03)	-1.5 (.006)	0.03 (.97)
SLE	FM	0.03 (.03)	1.8 (.05)	.22 (.21)
	LM	-0.02 (.68)	0.1 (.97)	-.32 (.51)

Cells are coefficients (p-values) from regression analysis

Table 2. Disability by BMI categories

	BMI category	n	VLA difficulty	% VLAs affected	% VLAs unable
RA	Underweight	0			
	Normal	43	0.50	41.0	2.0
	Overweight	20	0.47	36.8	1.7
	Obese	16	0.75*	67.4*	0.6
SLE	Underweight	3	1.01*	57.5	15.0*
	Normal	48	0.66	51.7	2.0
	Overweight	21	0.67	53.0	2.7
	Obese	36	1.02*	73.8*	5.8

* p<.05 compared to normal BMI

Table 3. Disability by Sarcopenia

	Sarcopenia	n	VLA difficulty	% VLAs affected	% VLAs unable
RA	No	67	0.50	42.1	0.9
	Yes	12	0.82	63.0	5.7*
SLE	No	107	0.74	57.5	2.7
	Yes	11	1.13*	69.5	10.9*

*p<.05 compared to no sarcopenia

Conclusion: Body composition is significantly associated with disability in both RA and SLE. Greater fat mass is associated with increased difficulty performing activities, but low muscle mass appears to be associated with greater activity disruption.

[1]Cesari M. Am J Clin Nutr 2005;82:428.

Disclosure: P. Katz, None; **H. Wing**, None; **S. Kaplan**, None; **R. Diskin**, None; **L. J. Julian**, None; **L. Trupin**, None; **J. Yazdany**, None; **L. A. Criswell**, None; **E. H. Yelin**, None.

1878

Decreased Physical Activity in RA Women Is Associated with Cardiovascular Risk Factors but Not with Body Fat Mass. Ann-Charlotte Elkan[1], Niclas Håkansson[2] and Ingiäld Hafström[3], [1]Karolinska Institute, Stockholm, Sweden, [2]The National Institute of Environmental Medicine at Karolinska Institute, Stockholm, Sweden, [3]Karolinska Institute, Stockholm, Stockholm, Sweden

Purpose: Many patients with RA have increased fat mass (FM) often associated with decreased fat free mass (FFM), i. e. rheumatoid cachexia (ref). We evaluated if total physical activity (MET-hours) was associated with body composition and cardiovascular risk factors in women with RA.

Methods: Sixty-one out-ward RA women answered a short self-administered physical activity questionnaire, to measure mean long-term (1 year period) total daily physical activity. The physical activity level was measured as metabolic equivalents (MET) x h/day. Mean values (SD) for healthy Swedish women are 40.8 (3.9). Body composition, FM% and FFM, was estimated by whole-body dual-energy X-ray absorptiometry (DXA). Blood lipids, oxidized low-density lipoprotein (oxLDL) and antibodies against phosphorylcholine (anti-PC) were determined. The diet content was assessed by a food frequency questionnaire.

Results: The RA women were 60.8 (57.3-64.4) years, mean (CI), and had a median disease duration of 6 years (range 1-52). DAS28 was mean (CI) 3.3(3.0-3.6), HAQ 0.7(0.5-0.8), BMI 25.0 (23.6-26.3) and total FM% 37.8 (35.7-39.9). Forty-one percent of the women had BMI >25. The median (IQR) total physical activity was 40.0 (37.4-47.7), and 48% of the RA women were less active than healthy Swedish women in the same age. Total physical activity did not significantly correlate with DAS28, HAQ-score, BMI, FM% or FFM at this level of activity. Patients in the lowest quartile of total physical activity did not differ in BMI, FM% or FFM from those in the highest quartile. The women in the lowest quartile had significantly lower values of HDL ($p=0.05$), Apo A1 ($p=0.028$), the atheroprotective natural anti-PC ($p=0.011$) and higher levels of insulin ($p=0.039$) than those in the highest quartile. Insulin resistance was present in 30% of the patients in the lowest quartile and in 13% in the highest. Patients in the lower quartile consumed significantly higher quantities of saturated fatty acids, than those in the highest quartile ($p=0.042$).

Conclusion: This cross sectional study demonstrated that about half of RA women with fairly low disease activity and a good functional capacity were less physically active than healthy Swedish women in the same age. The amount of physical activity was not associated with disease activity, functional capacity or body composition. However, low physical activity was associated with dyslipidemia and insulin resistance, which is of interest in the context of CVD in RA.

Reference: Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: a cross sectional study. Arthritis Res Ther 2009 Mar 10;11(2):R37

Disclosure: A. C. Elkan, None; **N. Håkansson**, None; **I. Hafström**, None.

1879

Association of Cardiovascular Disease Risk Factors with Ischaemic Manifestations of Giant Cell Arteritis. Esther F. Vicente, Amparo Casado, María J. García-Arias, Juan P. Lopez-Bote, Alicia Humbria, Jesús A. Garcia-Vadillo and Santos Castañeda, Rheumatology. Hospital de la Princesa, Madrid, Spain

Purpose: To describe the prevalence of classical cardiovascular disease risk factors (CVDRF) and the clinical characteristics of a population of giant cell arteritis (GCA) at diagnosis, and to analyse the association of the CVDRF with the ischaemic manifestations of the disease.

Method: Cross-sectional study including 58 patients with biopsy-proven GCA (age at diagnosis: 74.2±7.2 yrs; 86.2% women). Demographic, clinical, analytical (hemoglobin, ESR and biochemistry), arterial ischaemic manifestations, CVDRF [smoking, hypercholesterolemia, diabetes mellitus (DM) and hypertension (HT)] and therapy with immunosupressants (IS) and corticosteroids (CS) were collected. Anemia was defined as Hb<11 g/dl and elevated ESR if >40 mm/h. Arterial ischaemic manifestations were classified as moderate (jaw claudication, “amaurosis fugax”, transient visual loss [TVL] and diplopia) and severe (blindness, stroke, ischaemic heart disease [IHD] and peripheral arteriopathy). Statistical analysis: continuous variables are expressed as mean±SD and categorical as number of cases and percentage (%). The factors associated with the ischaemic manifestations of GCA were evaluated using the Student’s t test, the Fischer exact test or the Pearson’s $\chi 2$ test. Statistical significance was assumed for $p< 0.05$ two-tail tests (Stata, v 10.0).

Results: Follow-up time from diagnosis was 5.5±4.7 yrs. Clinical characteristics: 33 patients (58.9%) headache, 29 (50.8%) polymyalgia rheumatica (PMR) and 20 (37%) pathologic temporal artery examination. Anemia was detected in 25 patients (43%) and elevated ESR in 56

(98.2%). CVDRF were found in 44 patients (75.8%): HT (62.5%), hypercholesterolemia (55.2%), DM (14%) and smoking (5 active [9.6%] & 28 previous [53.8%]). Ischaemic manifestations occurred in 29 patients (50%): 20 jaw claudication (35.1%), 5 “amaurosis fugax” (8.6%), 6 TVL (10.3%), 6 blindness (10.3%), 1 stroke, 1 peripheral arteriopathy and 1 IHD. None had diplopia. Seven patients were classified as severe (12.1%) and 22 as moderate (37.9%). Among severe cases, 4 associated jaw claudication. Bivariate analysis by gender showed an older age at diagnosis in women (p=0.004). HT was associated with higher initial dose of CS (p=0.017) and active smoking with TVL (p=0.044). Multivariate analysis identified HT (p=0.016) and hypercholesterolemia (p=0.018) as the factors associated with moderate ischaemic manifestations. Age at diagnosis and initial CS dose were the only factors associated with blindness (p=0.018 & p=0.028, respectively).

Conclusion: Clinical characteristics of our series are close to previous descriptions by other authors. Jaw claudication and visual impairment are the most frequent ischaemic manifestations in our patients. Our study suggests that classical CVDRF could be associated with some ischaemic manifestations in GCA.

Disclosure: E. F. Vicente, None; **A. Casado**, None; **M. J. García-Arias**, None; **J. P. Lopez-Bote**, None; **A. Humbria**, None; **J. A. Garcia-Vadillo**, None; **S. Castañeda**, None.

ARHP Concurrent Abstract Session

Exercise: Focus on Impairment or Activity?

Tuesday, October 20, 2009, 7:45 AM - 8:45 AM

1880

Chronic Foot Symptoms in Relation to Self-Reported and Performance-Based Physical Function. Y.M. Golightly[1], M.T. Hannan[2], X. Shi[1], C.G. Helmick[3], Jordan B. Renner[4] and Joanne M. Jordan[4], [1]Thurston Arthritis Research Center, Chapel Hill, NC, [2]BUSPH, IFAR HSL, Boston, MA, [3]Centers for Disease Control an, Atlanta, GA, [4]The University of North Carolina, Chapel Hill, NC

Purpose: This cross-sectional analysis examines associations of chronic foot symptoms with self-reported and performance-based measures of functional status in a large, community-based sample, controlling for confounders, including presence of radiographic osteoarthritis (rOA) and symptoms in the knee and hip.

Method: Of the 2,705 Johnston County Osteoarthritis Project participants clinically evaluated in 1999-2004, 2,700 had data available for analyses (mean age 63.6 years). Presence of chronic foot symptoms was defined as pain, aching, or stiffness of at least one foot on most days. Physical function was assessed by the Stanford Health Assessment Questionnaire (HAQ) and by two performance-based measures: timed 5 repeated chair stands and 8-foot walk time. Total HAQ score was categorized into 3 levels (0; greater than 0 but less than 1; and ≥1). Timed chair stands was coded into 3-levels (< median completion time of 12 seconds (s), ≥ 12 s, and unable). Timed 8-foot walk was dichotomized at the median completion time (< 3.35s and ≥ 3.35 s). Separate multivariable logistic regression models examined associations between foot symptoms and the three functional status measures, controlling for age, race, gender, measured body mass index (BMI), knee and hip rOA, knee and hip symptoms, and depressive symptoms (CES-D Scale). Interaction terms between each of the self-reported and performance-based measures with each demographic and clinical characteristic were examined.

Results: Participants with chronic foot symptoms were more likely than those without foot symptoms to report greater difficulty with function, as indicated by higher HAQ scores (adjusted odds ratio [aOR]=1.79, 95% confidence interval [CI] 1.50-2.12), and to require more time to complete the 8 foot walk (aOR=1.32, 95% CI 1.08-1.61). Among obese (BMI >30 kg/m2) participants, those with foot symptoms required more time to complete the chair stands (aOR=1.38, 95% CI 1.03-1.86) than those without symptoms, a difference not seen among non-obese (aOR=0.88, 95% CI 0.66-1.18).

Conclusion: Chronic foot symptoms were independently and significantly associated with self-report of greater functional difficulty and longer completion times for performance-based measures. Interventions for chronic foot symptoms may be important for helping patients prevent or cope with an existing decline in perceived and performance-based functional abilities.

Disclosure: Y. M. Golightly, None; **M. T. Hannan**, None; **X. Shi**, None; **C. G. Helmick**, None; **J. B. Renner**, None; **J. M. Jordan**, None.

1881

Exercise Effects On Self-Reported Functional Tasks in Knee Osteoarthritis. Paulo E.P Teixeira, Sara R. Piva and G. Kelley Fitzgerald, University of Pittsburgh, Pittsburgh, PA

Purpose: Exercise therapy is commonly recommended for people with knee osteoarthritis (KOA). Although this intervention has been beneficial to KOA patients, in general it has yielded only modest improvements on measures of self-reported function[1]. A potential explanation for these modest effects may be that exercise therapy is typically impairment-based and may only improve some functional tasks while not having much effect on other tasks included in self-reported function measures. Understanding whether or not exercise therapy can influence self-reported ratings of various functional tasks may lead to refinement of rehabilitation programs to improve physical function in people with KOA. Therefore the purpose of this study was to determine the effect of exercise on the specific functional tasks assessed in self-reported function measures.

Method: Sample:159 KOA patients (65%female, mean BMI: 30.1 ± 6.3) aged between 40 - 85 years old who completed a standard KOA rehabilitation program consisting of lower extremity stretching and strengthening, aerobic activities, and balance and agility activities. Using baseline and post-treatment (2 months) data from 3 questionnaires of self-reported function (Western Ontario and McMaster Universities – WOMAC; Lower Extremity Functional Scale – LEFS; Activities of Daily Living Scale - ADLS), the level of change in the specific functional tasks (e.g. "climbing stairs", "walking" or "rising from a chair") assessed in each questionnaire was calculated. Using statistical methods for paired ordinal categorical data, the probability of an improvement in specific functional task performance after treatment was determined using relative position (RP) analysis[2]. The RP value is an estimation of the probability that subjects will rate their ability to perform a specific functional task as changed following the intervention period. RP values range from -1 to 1. Positive RP values reflect the probability of an improvement in function. Negative values reflect the probability of worse function.

Results: RPs for all functional tasks reported on the WOMAC, LEFS and ADLS items were low and ranged from 0.14 – 0.23, 0.05 – 0.28, 0.08 – 0.15 respectively. The probability of an improvement in specific functional task performance after treatment was never greater than 23% for the WOMAC, 28% for the LEFS and 15% for the ADLS. **Conclusion:** Impairment-based exercise therapy does not seem to have more than small effects on subject perception of ability to perform task-specific functional activities. Our findings may indicate the need for current KOA rehabilitation programs to incorporate task-specific training to better improve functional outcomes.

Disclosure: P. E. P. Teixeira, None; **S. R. Piva**, None; **G. K. Fitzgerald**, None.

1882

Exercise Program Elements Deemed Important by Physiotherapists in Exercise Prescription Following Osteoporotic Fracture. Lynne M. Feehan[1], Linda C. Li[1], Donna MacIntyre[1], Susan Harris[1], Amy Kirkham[1] and Osteo-fx review team[2], [1]University of British Columbia, Vancouver, BC, [2]Vancouver, BC

Purpose: Exercise is a complex intervention. A major challenge to exercise prescription is identification of the optimal exercise program elements for favorable treatment outcomes. The purpose of this study was to identify those components that physiotherapists (PTs) deem most effective for people recovering from osteoporotic fracture.

Method: We conducted an online survey of members of a national physiotherapy association. The survey was targeted at those members who participated in a teleconference on exercise prescription following osteoporotic fracture. The survey evaluated 15 exercise program components, which were identified through a review of post-fracture exercise intervention themes from a scoping review of over 9,500 articles exploring exercise prescription following osteoporotic fracture. The PTs were asked to identify the importance of each program element to clinical practice in their facility and the element most effective for optimizing health outcomes in four domains: *fracture healing, functional recovery, secondary fall and fracture prevention and health care costs*. Findings were used to specify key exercise program elements as a focus for data extraction, and will inform a Bayesian multivariable meta-regression analysis of a systematic review of exercise after osteoporotic fracture.

Results: 188 PTs responded to this survey. The majority (56%) of PTs had over 15 years of clinical experience. Over 90% of PTs ranked the following elements as somewhat or very important in their clinical practice: 1) timing of exercise initiation after fracture, 2) a regional exercise focus (e.g. ROM or strengthening exercises), 3) a physical performance exercise focus (e.g. balance training or walking) and 4)

dosage (e.g. number of exercise sessions). Whereas, less than 70% of PTs identified location of exercise facility, monitoring of exercise adherence, specialized training and a physical activity exercise focus (e.g. yoga or aquatic) as somewhat or very important in thier clinical practice. 53% of participants ranked timing of exercise initiation as the most effective factor contributing to favorable post-fracture healing outcomes. A physical performance exercise program was ranked most effective by 39% and 24%, respectively, for post-fracture functional recovery and for secondary fall or fracture prevention outcomes. 34% ranked the design of the program, such as an individualized, standardized or multidisciplinary exercise program, as the most effective factor for influencing post-fracture health care cost.

Conclusion: Identifying exercise characteristics deemed important by PTs provided valuable clinician input regarding the effect of specific elements of an exercise program on post-osteoporotic fracture recovery. Incorporating the perspective of practicing clinicians is an informative and important strategy to guide the analysis of systematic reviews of complex interventions like exercise.

Disclosure: L. M. Feehan, None; **L. C. Li**, None; **D. MacIntyre**, None; **S. Harris**, None; **A. Kirkham**, None.

1883

Falls Prevention in Persons with Osteoporosis: A Randomized Clinical Trial. Ellen Smulders[1], Vivian Weerdesteyn[2], Jacques Duysens[3], Roland Laan[2] and Wim Lankveld[1], [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]K.U.Leuven, Leuven, Belgium

Purpose: Persons with osteoporosis are particularly at risk for fall-related fractures, because of decreased bone strength. It has been shown that exercise programs can prevent falls and fall-related injuries in the elderly. [1] For instance, the 'Nijmegen Falls Prevention Program' ('NFPP') has shown to be successful with a 46% reduction in the number of falls in community-dwelling elderly. [2] However, patients with osteoporosis were excluded from this program, because of safety reasons. The benefits of a falls prevention program for patients with osteoporosis, however, are expected to be large. Therefore, the NFPP was adjusted for patients with osteoporosis and evaluated for its efficacy in a randomized clinical trial.

Method: A total of 92 persons with osteoporosis (mean age (SD): 71.0 (4.7), 86 female, 6 male; T-score $\leq$ -2.5) participated. After a baseline measurement (M1), participants were randomly allocated to an exercise (n=47) and control group (n=45). Subsequently, the exercise group participated in the NFPP for persons with osteoporosis (5.5 weeks) whereas the control group received usual care. After the program had ended the second measurement took place (M2) followed by the third (M3) after one year. Primary outcome measure was fall incidence, measured for one year with monthly fall registration cards. At M1, M2 and M3 balance confidence (ABC-scale), quality of life (qualeffo-41) and activity level (pedometer) were assessed.

Results: Fall incidence rates decreased by 39% in the exercise group compared to the control group (0.72 vs. 1.18 falls/year, IRR= 0.61 (95% CI 0.40-0.94)). There was a significant GroupxTime interaction (p=0.038) for balance confidence. Quality of life and activity levels remained the same in both groups for all three measurements.

Conclusion: Since the results show that the program was effective in reducing the number of fall incidents and increasing the balance confidence of the participants, it is concluded that it is a valuable new alternative tool for the prevention of falls and fractures in elderly subjects with osteoporosis.

References:
[1] Robertson et al. J Am Geriatr Soc 2002;50:905-911.
[2] Weerdesteyn et al. Gerontology, 2006;52:131-141

Disclosure: E. Smulders, None; **V. Weerdesteyn**, None; **J. Duysens**, None; **R. Laan**, None; **W. Lankveld**, None.

ARHP Concurrent Abstract Session

Health Disparities in Rheumatic Disease

Tuesday, October 20, 2009, 9:15 AM - 10:15 AM

1884

Severity of Rheumatoid Arthritis in Oklahoma Native Americans. Angela D. Genovese[1], Joe C. Rawdon[2], Sheryl Delancy[2], Sanober Malik[2], Nicholas Knowlton[3], Stephen Apel[2], Debbie Gladd[2], Joan T. Merrill[3] and Ewa Olech[3], [1]Oklahoma Med Rsrch Foundation, Oklahoma City, OK, [2]Oklahoma Med Resrch Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Rheumatoid arthritis (RA) is prevalent in Native American populations, and severe disease is often described. Few publications have systematically compared disease activity between Southwestern Native Americans and other groups.

Methods: A cross-sectional analysis of 160 patients referred from Indian Health Services (IHS) and Primary Care Offices to the Oklahoma Rheumatoid Arthritis Cohort was performed. Medical history, medications, and serologies were reviewed. Disease activity was assessed with 28 Tender and Swollen Joint Counts, duration of AM Stiffness, pain scale, and Physician Global Assessment. Patients were selected for this study by self-reported ethnicity in three categories: Native Americans (NA) (n=62), Caucasian (CAUC) (n=81) and African descent (AA) (n=17).

Results: There were no differences in gender, age, disease duration, or the likelihood of taking prednisone or methotrexate between the groups. The dose of methotrexate was lower in NA than other patients: 15 vs 17.5 mg/wk ($p < 0.05$) . Exposure to biologics was significantly different, only 3 NA were prescribed anti-TNF and none received Rituximab or Orencia ($p <0.005$ vs all others, $p=0.002$ vs CAUC). There were modest trends towards increases in most inflammatory markers, serology titers, and DAS 28 vs other pts (p=ns). NA had higher ANA titers ($p =0.045$ vs AA and 0.07 vs CAUC) and higher anti-CCP titers than AA ($p=0.01$). NA were similar to CAUC in median length of AM stiffness (60 vs 60 min), median tender jts (11 vs 13) and swollen jts (12 vs 12), but had higher values than AA ($P < 0.03$ in each case). Numbers of tender and swollen joints do not necessarily reveal severity of inflammation. NA reported more pain with VAS = 64.1 vs 54.3 for CAUC ($p=0.055$) and 42.4 for AA ($p=0.012$) and median physicians global assessments were significantly higher for NA: 64.1 vs 53 for CAUC ($p=0.05$) and 50 for AA ($p=0.014$).

Conclusion: These data suggest consistent, but modest trends towards worse disease activity in NA pts compared to CAUC and increased severity compared to AA. A significant discrepancy in access to biologic treatments at a similar stage of disease, and increased patient-reported pain as well as physician assessment of global disease severity confirms that NA may be a particularly vulnerable population with RA.

Disclosure: A. D. Genovese, None; **J. C. Rawdon**, None; **S. Delancy**, None; **S. Malik**, None; **N. Knowlton**, None; **S. Apel**, None; **D. Gladd**, None; **J. T. Merrill**, None; **E. Olech**, None.

1885

Associations of Education, Occupation and Community Poverty with Knee Osteoarthritis (OA). Leigh F. Callahan, Jack Shreffler, Todd Schwartz, Britta Schoster, Jordan B. Renner and Joanne M. Jordan, University of North Carolina at Chapel Hill, Chapel Hill, NC

Purpose: Education and occupation, individual level measures of socioeconomic status (SES), have been demonstrated to be associated with OA outcomes in numerous studies, but to date community SES measures have not been evaluated in OA. In other chronic diseases and in self-report arthritis of any type, the poverty rate of one's community was found to be associated with disease prevalence and health status outcomes independent of a person's education level. This study examined associations between education, occupation, and community poverty with radiographic knee OA (rOA), knee symptoms, and symptomatic knee OA (sympOA) in the Johnston County OA Project.

Method: A cross-sectional analysis was conducted on 4098 individuals (65% White and 35% African American [AA]) who resided in 67 of the 68 census block groups of Johnston County NC. Education (<high school (HS) degree or ³HS) and occupation (physically demanding or not) were used as individual measures of SES. Census block group household poverty rate (<12%, 12-25%, >25%) was used as a measure of community SES. Covariates included age, gender, race, current smoking, and BMI. Three outcomes were assigned as a finding in one or both knee joints: rOA defined as Kellgren-Lawrence grade ³2, knee symptoms (pain, aching or stiffness on most days), and sympOA (symptoms and rOA in the same joint). Race was evaluated for effect modification and not found so multiple logistic regression models of the whole sample were used to determine associations of outcomes with each of the main SES effects, adjusting for covariates. Multivariate analyses were also conducted with all 3 SES variables in the model simultaneously, adjusting for the covariates and allowing for random intercepts based on block groups.

Results: In bivariate analyses with education and the covariates, <HS was significantly associated with rOA (OR=1.4, CI 1.2, 1.6), symptoms (OR=1.7, CI 1.5,2.0), and sympOA (OR=1.6, CI 1.3,2.0). In bivariate analyses, occupation was significantly associated with symptoms (OR=1.5, CI, 1.3,1.8) and sympOA (OR=1.3, CI 1.03,1.6). Residing in a block group with >25% poverty (with referent <12% poverty) was significantly associated with rOA (OR=1.8, CI 1.3,2.5) and sympOA (OR=1.5 CI 1.1, 2.1) in bivariate analyses. In the multivariate regression models including all 3 SES variables simultaneously, adjusting for the covariates, <HS (OR=1.4, CI 1.1,1.6) and poverty >25% (OR=1.8 CI 1.3,2.4) were significantly associated with rOA. <HS (OR=1.6, CI 1.3, 1.9) and a physically demanding occupation (OR=1.3, CI 1.1, 1.5) were associated with symptoms, but poverty rate was not. And, <HS (OR=1.6, CI 1.3, 1.9) and poverty >25% (OR=1.5, CI 1.1, 2.0) were associated with sympOA.

Conclusion: Both individual and community SES measures were independently associated with knee OA in a population-based study of individuals from a rural community, after adjusting for some of the primary risk factors for knee OA including age, BMI, gender and smoking.

Disclosure: L. F. Callahan, None; **J. Shreffler**, None; **T. Schwartz**, None; **B. Schoster**, None; **J. B. Renner**, None; **J. M. Jordan**, None.

1886

Associations Between Individual and Community Socioeconomic Status (SES) Measures with Psychosocial Outcomes in Individuals with Arthritis. Leigh F. Callahan[1], Jack Shreffler[1], Britta Schoster[1], Jay Kaufman[2] and Todd Schwartz[1], [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]McGill University, Montreal, QC

Purpose: To examine associations between individual level (education, income, occupation and home ownership) and census-based community-level (% poverty rate) SES measures with psychosocial outcomes in individuals with self-reported arthritis.

Method: In 2004-2005, 1307 arthritis participants from urban and rural areas in the southeast completed a telephone survey assessing health status, chronic conditions, health attitudes and beliefs, and socio-demographic variables. Education [< high school (HS), HS degree, and > HS], income [<15, 15-45, >$45K] , occupation [professional, or not], and home ownership were individual level SES measures. The 2000 U.S. Census block-group-level variable "% of individuals living below the poverty line" (trichotomized into low, medium, high) was used as the community SES measure. Outcomes included the SF-12v2 Mental Component Summary (MCS), the CDC Health Related Quality of Life (HRQOL) Healthy Days mental health component, and the CES-D depression measure. Regression analyses with clustering on study sites were performed with STATAv9 and included adjustment for race, gender, BMI, and age in all cases.

Results: When entered separately, lower education, lower income, non-professional occupation, and no home ownership were significantly (all p<.05) associated with poorer MCS, mental health days, and CES-D scores. Income, however, was more strongly associated with the outcomes than the other individual SES variables. For example, the MCS score is 7.2 higher for people in the high income group and 3.4 higher for people with >HS (both compared to <0.05). The highest block group poverty is significant (p<0.05) for high CES-D score when education, homeownership, or occupation are in the model, but becomes non-significant when income is in the model. Finally, a complete model with all 4 individual SES measures and block group poverty shows income significant for each of the 3 outcomes of mental health, with the MCS score 6.05 higher for the high income group. There was no significance for homeownership, and marginal significance only for occupation associated with MCS and block group poverty associated with mental health days.

Conclusion: When 4 individual SES measures are examined for associations with psychosocial outcomes in people with arthritis, poorer status on all outcomes is associated with lower SES levels. Income, however, is the strongest predictor of poorer psychosocial status. Community SES measured by block group poverty rate is mainly associated with CES-D when individual income is not included as a modeling variable.

Disclosure: L. F. Callahan, None; **J. Shreffler**, None; **B. Schoster**, None; **J. Kaufman**, None; **T. Schwartz**, None.

1887

Socioeconomic Burden of Psoriatic Arthritis in Hong Kong: Direct and Indirect Costs and the Influence of Disease Pattern. Tracy Zhu[1], Lai-Shan Tam[1], Ying-Ying Leung[2], Lai Wa Kwok[3], Kong-Chiu Wong[3], Emily W. Kun[4] and Edmund K. Li[1], [1]The Chinese University of Hong Kong, Hong Kong, China, [2]North District Hospital, Hong Kong, China, [3]Prince of Wales Hospital, shatin,NT, Hong Kong, [4]Tai Po Hospital, Hong Kong, China

Purpose: There is less information about the economic burden of illness in psoriatic arthritis (PsA). We performed a cost-of-illness analysis on patients with PsA in Hong Kong to estimate the direct costs and indirect costs of PsA. We also attempt to identify the independent costs predictors for the whole cohort, as well as patients with peripheral and axial disease respectively.

Methods: A retrospective cost-of-illness study was performed on 125 PsA patients, diagnosed according to ClASsification critera for Psoriatic ARthritis. Participants completed questionnaires on sociodemographics, employment status and out-of-pocket expenses. Health resources consumption was recorded by chart review and patient self-reported questionnaire. Details relating to direct costs of the disease were collected for the preceding 12 months, consisting of use of all types of hospital or clinic services. Human capital approach was used to calculate indirect costs Patients were grouped according to disease pattern, i.e. peripheral and axial disease. Multiple regression was used to determine the predictors of the costs.

Results: The mean (SD) age of the cohort was 47 (12) years old. The average annual direct costs were $4,275 (2006 USD) per patient. Costs of inpatient care accounted for 26% of direct, followed by costs of visits to healthcare providers (24%). The estimated average indirect costs were $3,127 per patient-year. Forty-eight (42%) patients incurred no indirect costs. One hundred and one patients were defined as having peripheral disease, whereas 24 with axial disease. No difference in demographics, clinical characteristics and annual direct costs was found between the two groups. Sixty percents of patients with peripheral disease were still employed, compared to 39% of patients with axial disease. Patients with axial disease incurred almost twice indirect costs than those with peripheral disease (p=0.005). Increased pain and poor function were independently associated with increases direct costs. Worse physical health status, determined whether indirect costs were incurred. Once they were incurred, poor function and old age predicted high costs.

Conclusion: Both direct and indirect costs of PsA are substantial. Patients with axial disease had lower employment rate and generated higher indirect costs compared to those with peripheral disease. There was no difference in peripheral joint involvement between the two groups. The higher indirect costs in patients with axial disease are probably due to the burden incurred by spondyloarthritis, which may further impair patients' capability of being employed. Increased pain and poor function predict high direct costs, and poor physical health and function, and old age predict high indirect costs. Our results justify appropriate monetary expenditure for research and therapy in PsA.

Disclosure: T. Zhu, None; **L. S. Tam**, None; **Y. Y. Leung**, None; **L. W. Kwok**, None; **K. C. Wong**, None; **E. W. Kun**, None; **E. K. Li**, None.

ARHP Concurrent Abstract Session

Pediatrics and Parenting

Tuesday, October 20, 2009, 10:45 AM - 11:45 AM

1888

Pediatric Rheumatology Improvement Network for Clinical Excellence and Safety - PRINCES. E. Morgan DeWitt[1], M. Passo[2], Y. Kimura[3], T. Beukelman[4], Beth S. Gottlieb[5] and P. Margolis[6], [1]Duke University Medical Center, Durham, NC, [2]MUSC, Charleston, SC, [3]Hackensack Univ Medical Ctr, Hackensack, NJ, [4]Univ of Alabama, Birmingham, AL, [5]Schneider Childrens Hospital, New Hyde Park, NY, [6]Cincinnati Children's Hospital, Cincinnati, OH

Purpose: Currently, there is tremendous variability in care of patients with juvenile idiopathic arthritis (JIA). Determinants of patient outcomes, or key drivers, are not systematically collected, measured or tracked in most pediatric rheumatology centers. PRINCES will use a population registry and population management report to plan delivery of care and improve care for JIA patients.

Method: The PRINCES Collaborative will engage clinical improvement teams to work together over two 18-month periods to achieve measurable improvements in the care provided to patients with JIA. Participating sites will develop local improvement teams, with a physician champion. Teams will receive quality improvement training and support from the Cincinnati Children's Center for Health Care

Quality. Teams will receive expert coaching on applying well established, evidence based strategies for chronic disease management to JIA, including self-management support, delivery system design, decision support and clinical information systems. Teams will meet at periodic intensive Learning Sessions. In between, they will submit performance data monthly along with summaries of changes being tested; this information will be posted on a project "extranet" for shared learning across the Collaborative. Benchmarking can be identified by analysis of the data from participating practices and shared information can improve the processes of care in collaborating centers. Teams will be supported and connected via a listserv and monthly conference calls. Teams will use a Collaborative population registry and a population management report to plan and deliver care.

Results: Quality measures derive from the ACR supported Quality Measures Workgroup study through nominal group techniques. The Collaborative will focus on the following domains over the two project phases: Measurement and evaluation of the proportion of patients meeting criteria for "inactive disease", safe use of therapeutics, consistent best practice care, satisfactory optimization of health status and functional outcomes, patient/family satisfaction with care.

Conclusion: Quality improvement methods can reduce variation in care by identifying and testing approaches to care delivery. This reduction in variation leads to practice efficiency by improving processes of care, increased patient safety, and improved outcomes for patients. Reduction in variation also facilitates research by increasing statistical power. PRINCES will apply the science of quality improvement to the treatment of JIA. Participation in this improvement collaborative will fulfill Maintenance of Certification requirements for QI work needed for recertification by the American Board of Pediatrics.

Disclosure: E. Morgan DeWitt, None; **M. Passo**, Pfizer Inc, 5, American Board of Pediatrics, 6 ; **Y. Kimura**, None; **T. Beukelman**, None; **B. S. Gottlieb**, None; **P. Margolis**, None.

1889

Pain and Mood as Predictors of Sleep Quality in Children with Polyarticular Arthritis. Maggie Hood Bromberg[1], Karen M. Gil[1], Kelly K. Anthony[2] and Laura E. Schanberg[3], [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Duke Unvi Medical Ctr, Durham, NC, [3]Duke University Medical Center, Durham, NC

Purpose: Since pain and depressed mood are associated with sleep problems in children with chronic illness, we examined the role of mood and pain in predicting sleep quality in children with polyarticular arthritis.

Method: The sample consisted of 51 children with polyarticular arthritis (31 girls; 84% Caucasian; mean age 12.4 years). All children were participating in a larger study that included a baseline assessment and daily reports of pain, mood, stress, coping and disease symptoms completed over a two month period, from which the present data were gathered. An active joint count and a physician global assessment (PGA) were completed by a pediatric rheumatologist at baseline. Children rated their current pain and sleep quality during the previous night on 100mm visual analogue scales. Daily mood was assessed via the *Facial Affective Scale* (FAS). Descriptive statistics were performed and daily reports were aggregated to produce an average score on each daily variable for each child. Following Pearson-product moment correlations, a hierarchical regression using the aggregate data was conducted to examine predictors of sleep quality.

Results: Children had mild to moderate disease severity (mean PGA = 31.5mm) with active arthritis in 9 joints on average. Across the diary reporting period, children endorsed moderate to high sleep quality (mean = 75.3mm) and positive mood (mean FAS = 2.8). Correlations revealed no significant relationships between disease-related variables and sleep quality. Both aggregated pain (r = -.61, p < .0001) and mood (r = -.58, p < .0001) were highly correlated with sleep quality. Hierarchical regression revealed that both pain (ΔR^2 = .34, p < .0001) and mood (ΔR^2 = .14, p < .001) predicted a significant proportion of variance in children's sleep quality ratings after controlling for disease severity and active joint count Indicating that increased pain and less positive mood are associated with poor sleep. The interaction between pain and mood did not significantly predict variance in sleep quality. The final model uniquely accounted for 49% of the variance in sleep quality.

Conclusion: These results provide further support for the relationship between pain and sleep in children with arthritis. Furthermore, mood plays a significant role in predicting sleep quality. Health care professionals should assess for sleep difficulties as part of clinical care and future research should investigate longitudinal relationships between pain, sleep, and mood, as well as the impact of sleep difficulties on daily function in children with arthritis.

Disclosure: M. H. Bromberg, None; **K. M. Gil**, None; **K. K. Anthony**, None; **L. E. Schanberg**, None.

1890

Parenting Experience of Mothers with and without Inflammatory Arthritis. Catherine Backman[1], Andrew Chalmers[1], Pam Montie[2] and Diane V. Lacaille[1], [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Vancouver

Purpose: Arthritis may limit participation in life roles such as parenting. This study compared self-reported performance of parenting tasks, parenting satisfaction and parenting efficacy in mothers with and without inflammatory arthritis (IA), and explored factors associated with parenting outcomes.

Method: This is the second part of a mixed methods study where the initial qualitative phase informed the content of a cross sectional mailed survey. Invitation letters were sent to women with IA who attended an out-patient arthritis clinic or rheumatology practices in the past 3 years. Community advertising and word-of-mouth was used to recruit women without chronic illness. All women had at least one child ≤18 yrs living at home. Reminders sent at 2 and 4 weeks maximized returns. The Parenting Disability Index (PDI) and Parenting Sense of Competency Scale (PSOC) were used to measure parenting outcomes. Surveys also inquired about employment, household work, social support, family quality of life, health status and demographics. Descriptive, t-tests and chi squared statistics were used for between group comparisons. Multiple regression analyses (with variables entered stepwise in blocks) identified predictors of parenting outcomes (PDI and PSOC scores).

Results: 342 women participated: 190 with IA and 152 in the comparison group (CG), aged 21 to 60 yrs. Of those with IA, 58% had RA, 15% psoriatic arthritis, 13% ankylosing spondylitis, 4% juvenile arthritis, and 3% lupus. Disease duration ranged from 6 mos to 45 yrs, (mean=12 yrs ± 10). Participants' children were ages 4 months to adults; typically, mothers were caring for 2 children (range 1 to 6). Regardless of the age of the children (≤5, 6-12, or >12 years), mothers with IA reported greater difficulty with parenting tasks on the PDI ($p<.02$). Average parenting satisfaction (PSOC subscale) scores did not differ ($p=0.74$); a very small difference in parenting sense of efficacy (PSOC subscale) was statistically significant at $p=0.05$, with the IA group reporting lower scores (IA=4.4, CG=4.6 on a 5-point scale). Women with IA were less likely to be employed outside the home, reported fewer hours of paid and unpaid work, and had lower household income than the CG. There were no significant differences in family quality of life. Mothers reporting better physical function and family quality of life and less fatigue had lower PDI scores (adj. $R^2 = .59$). Those reporting greater resilience, sense of accomplishment and positive affect, and lower mental health scores had higher PSOC parenting satisfaction (adj. $R^2 = .35$) and efficacy (adj. $R^2 = .29$), although the relative contribution of each variable differed in the two models.

Conclusion: Despite greater limitations experienced in performing parenting tasks, mothers with arthritis report as much satisfaction with their parenting role as do mothers without arthritis. A better understanding of factors associated with participation in life roles, like parenting, is necessary to select outcomes that are meaningful to people living with arthritis.

Disclosure: C. Backman, None; **A. Chalmers**, None; **P. Montie**, None; **D. V. Lacaille**, None.

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Children of Parent's with Chronic Inflammatory Musculoskeletal Diseases (CIMD): Experiences, Needs and Resources. Elizabeth Hale[1], Gareth Treharne[2], Yvonne Norton[3] and George D. Kitas[4], [1]Dudley Group of Hospitals NHS Trust, Dudley, England, [2]University of Otago, Dunedin 9054, New Zealand, [3]Lupus UK, [4]Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom

Purpose: CIMD such as systemic lupus erythematosus are chronic multisystem rheumatic disorders characterised by periods of exacerbation and remission. The children or grandchildren of people with SLE may find the disease and its impact within the family unit confusing and frightening. People with SLE may themselves have their own fears about disease progression, heritability and the subsequent consequences for the family unit. Whilst there are information leaflets available for SLE patients, there are no educational resources available for the children of patients with the condition.

Method: Pilot study: In-depth semi-structured interviews were carried out with 10 women with SLE whose age ranged from 32 to 68 years. All women had children whose ages ranged from 14 months to 18+ and some of the women had grandchildren. The participants were recruited from routine care and an open-access lupus clinic in secondary care. Time since diagnosis with SLE ranged from 1 to 12 years. The

interviews were audio-recorded and transcribed verbatim. Data were analysed using interpretative phenomenological analysis (IPA) to investigate what potential problems existed for the children of parents and grandparents with SLE.

Results: Five themes emerged from the data regarding lupus and parenting. These concerned children taking the role of carer for the participant; children taking self-care roles; participant worries about loss of social roles; heredity issues and the impact of SLE on the family unit and relationships. Children fetched shopping, kept the house tidy and helped themselves to convenience food. Participants were worried about losing their own social role as mother when friends and relatives had to take over tasks they usually performed, such as brushing their children s hair. They were worried about heritability, particularly in the case of daughters. There were also fears for the impact of the disease on the family unit both now and in the future. Pain, distress and frustration could cause angry outbursts from the participant when their children misbehaved causing guilt and regret later

Conclusion: Although patients said that their children understood they were unwell, it appears that there is no literature available for children and parents to read and discuss together those concerns that they may have about a parent with SLE. In the next stage of our study we will investigate what information would be useful to these children and the format in which they would like this delivered. The children will drive this part of the study and formats are likely to be varied given the developmental age of the child

Disclosure: E. Hale, None; **G. Treharne**, None; **Y. Norton**, None; **G. D. Kitas**, None.

ACR Plenary Sessions

Plenary Session III: Discovery 2009

Tuesday, October 20, 2009, 11:00 AM - 12:30 PM

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Mir-203 Regulates the Expression of IL-6 and Matrix Metalloproteinase(MMP)-1 in RA Synovial Fibroblasts. Joanna Stanczyk Feldges[1], Emmanuel Karouzakis[1], Astrid Jungel[1], Caroline Ospelt[1], Christoph Kolling[2], Beat A. Michel[1], Renate E. Gay[1], Steffen Gay[1] and Diego Kyburz[1], [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland

Purpose: MicroRNA (miRNA) have emerged as a new class of modulators of gene expression and have been shown to be involved in the development of cancer and the proper functioning of the immune system. The goal of our study was to assess the expression of miRNA in synovial fibroblasts derived from patients with rheumatoid arthritis (RA), osteoarthritis (OA) and normal individuals.

Method: Synovial fibroblasts have been obtained from patients with RA (RASF; n=6), osteoarthritis (OASF; n=6) and normal subjects (NSF; n=3). Total RNA was isolated by using the mirVana miRNA isolation kit. The human TaqMan Real-time PCR-based miRNA panel comprising 260 individual miRNA was used to determine the profile of miRNA expression in RASF and OASF. For the functional studies a synthetic precursor pre-miR-203 was used. Further the influence of cytokines and the role of DNA methylation on the expression of miR-203 in RASF was studied.

Results: miRNA screening revealed an up-regulation of miR-203 in RASF. RASF showed a 2.6-fold higher level of miR-203 as compared to OASF ($p=0.01$). The increased level of miR-203 in RASF was even more pronounced when compared to the normal synovial fibroblasts (NSF), demonstrating a 7-fold higher expression of miR-203 in RASF. Interestingly, we did not find any change in the expression of miR-203 in RASF after treatment with IL-1β and TNF-α nor with the TLR-4 ligand LPS. However, we observed a stimulatory effect of the hypomethylating agent 5-Azacytidine on the expression of miR-203 in NSF. Over-expression of miR-203 by transfection with pre-miR-203 resulted in the up-regulation of IL-6 in RASF. The level of IL-6 mRNA was increased by 1.8±0.4 (mean±SEM of fold change), 2.4±0.3 ($p<0.01$) and 2.6±0.3 ($p<0.01$) at 24, 48 and 72 hours after transfection. Moreover, RASF treated with the miR-203 precursor produced at 48 hours 58±13% ($p<0.01$) more IL-6 protein as compared to the cells treated with the control negative pre-miR. We could further show that the stimulatory effect of miR-203 on the production of IL-6 is dependent on the NFκB pathway, as treatment of RASF with SC-514 (IKK-2 inhibitor) abrogated the miR-203-dependent increase in the production of IL-6. Also MMP-1 was found to be up-regulated at the mRNA level by 2.2±0.1-fold in RASF after transfection with pre-miR-203, but neither MMP-3, MMP-9 nor MMP-13.

Conclusion: Our data provide for the first time evidence that miR-203 is over-expressed in RASF and involved in the up-regulation of IL-6 and MMP-1 indicating a role of miR-203 in the development of the activated phenotype of RASF. Furthermore, our data suggest that epigenetic mechanisms are involved in the up-regulation of miR-203 in synovial fibroblasts.

Disclosure: J. Stanczyk Feldges, None; **E. Karouzakis**, None; **A. Jungel**, None; **C. Ospelt**, None; **C. Kolling**, None; **B. A. Michel**, None; **R. E. Gay**, None; **S. Gay**, None; **D. Kyburz**, None.

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Meta-Analysis of Six Genome-Wide Association Studies in >25,000 Case-Control Samples Identifies New Rheumatoid Arthritis Risk Loci. E. Stahl[1], S. Raychaudhuri[1], R. Chen[1], J. Coblyn[1], N. Shadick[1], Michael E. Weinblatt[2], K.A. Siminovitch[3], X. Liu[4], G. Xie[4], L. Klareskog[5], L. Padyukov[5], M. Seielstad[5], AnnetteT Lee[6], P.K. Gregersen[7], J. Worthington[8] and R.M. Plenge[1], [1]Brigham & Women's Hospital, Boston, MA, [2]Brigham & Women's Hosp, Boston, MA, [3]University of Toronto, [4]University of Toronto, Toronto, [5]Karolinska Institutet, Stockholm, Sweden, [6]Feinstein Institute for Medical Research, Manhasset, NY, [7]Feinstein Insititute Med Rsch, Manhasset, NY, [8]arc Epidemiology Unit, Manchester, United Kingdom

Purpose: Approximately one-third of the genetic basis of rheumatoid arthritis (RA) can be explained by validated risk alleles. To identify additional RA risk alleles, we conducted a meta-analysis of six genome-wide association studies (GWAS).

Method: Through an international collaboration, we accessed GWAS genotype data from 5,539 RF or CCP-positive RA cases and 20,169 matched controls, all of self-reported European ancestry: Brigham Rheumatoid Arthritis Sequential Study (BRASS), Mount Sinai Hospital and University Health Network, Toronto, Canada (Canada), Epidemiological Investigation of RA (EIRA), North American RA Consortium (NARAC), and Wellcome Trust Case Control Consortium (WTCCC). We implemented strict quality control filtering of SNPs based on minor allele frequency, Hardy-Weinberg equilibrium and genotype call rate. We filtered individuals based on genotype call rate, identity-by-state, and principal components analysis. We imputed over 2.4 million SNPs from CEU HapMap. To test for association within each of the 6 case-control collections, we used logistic regression at genotyped and imputed SNPs. Association statistics were combined across the 6 collections using inverse-variance weighted beta and standard error values.

Results: Most known RA loci show substantial signal, including $P<5x10-8$ for SNPs within the MHC, PTPN22, TNFAIP3, CTLA4, and CD40 loci. One new locus at 5q11, near the IL6ST and IL31RA genes, was also genome-wide significant (rs10040327, $P=3x10-11$). Ten additional loci had $P<10-6$, whereas only 2 would be expected by chance alone. Fourteen alleles associated with other autoimmune diseases had $P<0.01$ in our RA GWAS meta-analysis, indicating shared etiology with psoriasis, celiac disease, lupus, type 1 diabetes, multiple sclerosis, and Crohn's disease. We found little evidence for association at PADI4 ($P=0.02$ for rs2240340), and no evidence for association at CD244 ($P=0.27$ for rs3753389), both of which have been implicated in RA pathogenesis among patients of Asian ancestry. Independent replication is ongoing in >10,000 additional case-control samples.

Conclusion: Our GWAS meta-analysis has identified new RA risk alleles among patients of European ancestry. These genetic discoveries provide fundamental insight into the pathogenesis of RA.

Disclosure: E. Stahl, None; **S. Raychaudhuri**, None; **R. Chen**, None; **J. Coblyn**, None; **N. Shadick**, biogen idec, 2, crescendo biosciences, 2, Amgen, 2, Bristol-Myers Squibb Foundation, 2 ; **M. E. Weinblatt**, Biogen/Idec, Crescendo, 2, Biogen/Idec, Crescendo, 5 ; **K. A. Siminovitch**, None; **X. Liu**, None; **G. Xie**, None; **L. Klareskog**, None; **L. Padyukov**, None; **M. Seielstad**, None; **A. Lee**, None; **P. K. Gregersen**, None; **J. Worthington**, None; **R. M. Plenge**, UCB Pharma, Amgen, Biogen-Idec, 5 .

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TEAR: Treatment of Early Aggressive RA: A Randomized, Double-Blind, 2-Year Trial Comparing Immediate Triple DMARD Versus MTX Plus Etanercept to Step-up From Initial MTX Monotherapy. Larry W. Moreland[1], James R. O'Dell[2], Harold Paulus[3], Jeffrey R. Curtis[4], S.L. Bridges Jr.[4], Xiao Zhang[4], George Howard[4] and Stacey S. Cofield[4], [1]Univ of Pittsburgh, Pittsburgh, PA, [2]University of Nebraska Med Ctr and Omaha VA, Omaha, NE, [3]UCLA School of Med, Los Angeles, CA, [4]The University of Alabama at Birmingham, Birmingham, AL

Purpose: No direct data compares triple DMARD (methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ]) to MTX + anti-TNF therapy (etanercept) in patients with early RA. The relative benefit of a strategy of either combination vs MTX monotherapy with step-up after 6 months is also uncertain. The TEAR trial evaluates both issues.

Methods: The investigator-initiated, multi-center, randomized TEAR trial began in 2004 and enrolled 755 participants to compare immediate (I) vs step-up (S) strategy with MTX, etanercept (E) and triple DMARD (T) in 4 arms: immediate MTX + E (IE) or triple therapy (IT); step-up from MTX to MTX+E (SE) or to T (ST). In SE/ST, if DAS28 ≥ 3.2 at 6 months of MTX, patients were blindly stepped-up to IE/IT. Inclusion criteria: disease duration ≤ 3yrs, diagnosis by ACR criteria; RF+, CCP+ or ≥ 2 radiographic erosions; ≥ 4 tender and 4 swollen joints; MTX naïve. The primary endpoint was mean DAS28 from weeks 48-102. Other endpoints: ACR 20, 50, 70; discontinuation for lack of efficacy, DAS28 remission, QOL and Radiographic progression.

Results: Subjects were 72% female; 80% Caucasian, 11% African American; with a mean age at entry of 49±13 yrs, with 3.6±6.5 months since diagnosis, 90% RF+. The mean DAS28 at entry 5.8±1.1; 28 joint count: 14.3±6.8 painful and 12.8±6.0 swollen joints. As shown in the Table, during the second year of treatment, patients randomized to S arms had clinical responses that were not statistically different than those who received I combination therapy, regardless of treatment arm (p-values: I vs S: 0.95, E vs T: 0.23). There were significant differences in the outcome of ACR response at 6 months between treatment arms: patients initially receiving IE or IT were significantly more likely to achieve an ACR 20/50/70 response at 6 months than those randomized to step-up arms (all $p < 0.0001$), regardless of treatment (E vs T).

Conclusion: A 2-year double-blinded trial of early RA patients found no differences in the mean levels of DAS28 during weeks 48-102 among patients randomized to etanercept or triple DMARD, regardless of whether they received immediate combination treatment or MTX monotherapy with a step-up. At 6 months immediate combination treatment with either strategy was more effective than MTX monotherapy; however, there were no significant differences in groups at 2 years. Initial use of MTX monotherapy with the addition of SSZ/HCQ or etanercept, if necessary after 6 months, is a reasonable therapeutic strategy for early RA.

	DAS28	**ACR response at 6 months**		
Treatment arm	**at week 102**	**ACR 20, %**	**ACR50, %**	**ACR70, %**
IE	3.0 ± 1.4	63.6	35.5	13.1
IT	2.9 ± 1.5	64.0	38.6	11.4
SE	3.1 ± 1.4	45.2	22.1	3.2
ST	2.8 ± 1.3	47.7	21.5	4.7

Disclosure: L. W. Moreland, Amgen, 2, Barr Pharmaceuticals, 2, Pharmacia, 2, NIAMS-NIH, 2, NIH, 2 ; **J. R. O'Dell**, Amgen, 5 ; **H. Paulus**, Amgen, 5 ; **J. R. Curtis**, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Corrona, 5, Novartis Pharmaceutical Corporation, 2, Amgen, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Corrona, 2, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Eli Lilly and Company, 8, Roche Pharmaceuticals, 8, Merck Pharmaceuticals, 8 ; **S. L. Bridges**, None; **X. Zhang**, None; **G. Howard**, Amgen, 2 ; **S. S. Cofield**, GlaxoSmithKline, 5 .

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All-Trans Retinoic Acid Promotes the Differentiation of Itreg Cells Via Smad and Non-Smad Signaling Pathways. Xiao H. Zhou[1], Ling Lu[1], Julie Wang[1], Hejian Zou[2], David A. Horwitz[1], David Brand[3], Huimin Fan[4], Zhongmin Liu[4] and Song Guo Zheng[1], [1]University of Southern California, Los Angeles, CA, [2]Huashan Hospital, Fudan University, Shanghai, China, [3]VA Medical Center, Memphis, Memphis, TN, [4]East Hospital, Tongji University, Shanghai, China

Purpose: Recent studies have revealed that All-trans Retinoic Acid (ATRA), a vitamin A derivative, promotes the development of CD4+Foxp3+ regulatory T cells induced by TGF-β (iTreg), however, the mechanisms by which ATRA regulates the differentiation of iTreg remain poorly understood.

Method: Naïve CD4+CD25- cells isolated from wild type or Smad3 KO or Smad2 conditional KO in T cells were stimulated with anti-CD3/CD28 beads ± TGF-β± ATRA for 5 days. Phenotype and functional activity was determined by FACS. TGF-βRI and TGF-βRII expression was determined by qRT-PCR. Western blot detected the Smad2/3, ERK1/2, P-38 and JNK activation. CHIP assay detected acetylation of Foxp3 protein. A methyl-sensitive PCR was used to analyze the methylation status of the CpG island of the Foxp3 promoter.

Results: We confirmed ATRA markedly increased the conversion of CD4+Foxp3+ iTreg cells in wild type and Foxp3 GFP transgenic mice. Additionally, we observed ATRA increased the Foxp3 binding ability with chromatin although it did not decrease hypermethylation of Foxp3 promoter and increase acetylation of Foxp3 protein. ATRA increased the Foxp3 binding on IL-2 promoter. Both ATRA and TGF-β treated cells developed mote potent anergy status and suppressive activity *in vitro* and *in vivo*. ATRA markedly increased the expression of CD103, alpha4-beta7, alphaV-beta8, CCR-9 on TGF-β treated CD4+ cells although it did not affect TGF-β receptor I and receptor II expression. CD4+ cells treated with both ATRA/TGF-β produced markedly lower amounts of IL-2 but higher amount of IL-10. ATRA also suppressed the apoptosis and sustained the Foxp3 expression. Although ATRA significantly increased the phosphorylated Smad2/Smad3 expression, ATRA still increased the Foxp3 expression and suppressive activity of TGF-β-treated CD4+ cells in Smad3 KO and Samd2 conditional KO mice. In addition, ATRA markedly increased ERK1/2 activation on TGF-β treated CD4+ cells and blockade of ERK1/2 signal significantly decreased the increased Foxp3 expression.

Conclusion: ATRA mainly activate Erk1/2 to promote the differentiation of iTreg cells. ATAR also enhances its binging ability on its target gene and alterations of the distribution and structure of Foxp3 might account for increased suppressive activity.

Disclosure: X. H. Zhou, None; **L. Lu**, None; **J. Wang**, None; **H. Zou**, None; **D. A. Horwitz**, None; **D. Brand**, None; **H. Fan**, None; **Z. Liu**, None; **S. G. Zheng**, None.

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Toll-Like Receptor 4 Blockade Ameliorates Murine and Humanized Models of Rheumatoid Arthritis; A Comparison with IL-1 and TNF Blockade. Shahla Abdollahi-Roodsaz, Marije I. Koenders, Leo A. Joosten, Fons A. van de Loo and Wim B. van den Berg, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose: Toll-like receptor 4 (TLR4) potently instructs innate and adaptive immune responses. Current evidence including increased expression of TLR4 and its endogenous agonists in rheumatoid joints supports the involvement of TLR4 in RA. The objective of this study was to evaluate the therapeutic efficacy of TLR4 blockade in a murine and a humanized in vivo model of RA in comparison with the well-known interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibitors.

Method: Mice with established collagen-induced arthritis (CIA) were systemically treated with saline or either TNF, IL-1 or TLR4 inhibitors (Enbrel, Anakinra and purified *B. quintana* LPS, respectively) applied in osmotic minipumps. Clinical and histopathologic parameters of arthritis and cytokine responses were compared. Severe combined immunodeficient (SCID) mice were engrafted with active RA synovial tissue, and spontaneous cytokine production and synovial inflammation were evaluated after treatments.

Results: TLR4 blockade was as effective as the clinically applied IL-1 and TNF blockers in suppressing the clinical manifestations of CIA. On histology, TLR4 inhibition prevented synovial inflammation and bone erosion. Importantly, proteoglycan depletion from cartilage and the irreversible cartilage pathology, i.e. chondrocyte death and cartilage destruction, were effectively blocked as well. The protective effects of TLR4 inhibition on histopathology of established CIA were similar to those of the IL-1 inhibitor, while being more substantial than the TNF blocker. Analysis of the proinflammatory cytokine expression revealed a reduction in both local and systemic levels of IL-1β, IL-6 and IL-23. Interestingly, TLR4 blocker was the only inhibitor that suppressed systemic TNFα expression. In contrast to TNF blockade, inhibition of TLR4 and IL-1 reduced synovial expression of IL-17 and the Th17-related transcription factor RORγt as well as the serum concentrations of IL-17.

The humanized RA-SCID model was used to translate the therapeutic value of TLR4 targeting in CIA into RA. Blockade of TNF, but not IL-1, ameliorated synovial inflammation and reduced serum levels of human cytokines in SCID mice. Interestingly, TLR4 inhibition significantly suppressed the spontaneous cytokine production by transplanted RA synovium. In addition, TLR4 blockade markedly suppressed the severity of inflammation in RA synovial transplants to the same extent as TNF blockade, whereas IL-1 blockade was not effective.

Conclusion: Data in murine CIA and the humanized SCID model collectively indicate that TLR4 is positioned upstream to a number of proinflammatory cytokines with an impact on IL-17 production. The latter might favor TLR4 blockade above TNF blockade. Beneficial effects of TLR4 blockade on synovial inflammation and joint destruction emphasize the relevance of TLR4 as a novel therapeutic target for RA.

Disclosure: S. Abdollahi-Roodsaz, None; **M. I. Koenders**, None; **L. A. Joosten**, None; **F. A. van de Loo**, None; **W. B. van den Berg**, None.

ACR/ARHP Combined Abstract Session

Advances in the Care of Children with Rheumatic Disease

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

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Juvenile Dermatomyositis: A Novel Gingival Vessel Alteration Pattern? Cynthia Savioli[1], Clovis A. Silva[2], Gisele M. Fabri[1], Katia Kozu[3], Lucia M.A. Campos[3] and José T. T. Siqueira[4], [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da USP, São Paulo, Brazil, [3]Faculdade de Medicina da USP, Sâo Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo, Sâo Paulo, Brazil

Purpose: To evaluate oral health in juvenile dermatomyositis (JDM) patients and compare to controls.

Methods: 26 JDM patients were studied and compared to 22 age-matched healthy subjects followed at the Dentistry Division. At study entry all patients were examined by a rheumatologist and a dentist in order to evaluate social and demographic data, clinical manifestations, disease activity [using disease activity score (DAS), childhood myositis assessment scale (CMAS) and manual muscle testing (MMT)], muscle enzymes and treatment. The dental and facial examination included questionnaire, tooth decay (DMFT) index, periodontal assessment [plaque and gingival bleeding index, probing pocket depth (PPD), cementoenamel junction (CEJ) and clinical attachment level (CAL)], Helkimo's index, research diagnostic criteria for temporomandibular disease (RDC/TMD) and salivary flow.

Results: The mean current age of JDM patients was comparable to controls (11.88±3.97 vs. 11.66±2.59 years, p=0.469). The two groups were homogeneous regarding age, gender and Brazilian social-economic class (p>0.05). Alteration of mandibular mobility index was significantly higher in JDM patients than controls (0.5 vs. 0, p=0.007) probably due to higher frequency of low interincisal mouth amplitude in JDM versus controls (31% vs. 0%, p=0.005) and a lower median interincisal mouth amplitude in JDM (42 vs. 45mm, p=0.01). The median plaque, gingival bleeding and DMFT indices were similar in JDM patients and controls (89.42% vs. 80.95%, p=0.323; 21.7% vs. 12.7%, p=0.141; 2.0 vs. 1.5, p=0.151; respectively). Remarkably, a peculiar bushy loop formation in gingiva that spread over teeth was only observed in JDM patients (61% vs 0%, p=0.001). These patients had lower values of median cementoenamel junction (-0.26 vs. -0.06mm, p=0.009) and higher gingival bleeding index compared to patients without this manifestation (27.7% vs. 14.15%, p=0.048). No differences were observed between demographic data, DAS, CMAS, MMT, muscle enzymes and treatment in both groups (p>0.05).

Conclusion: The description of a novel gingival vessel alteration pattern associated with hyperplasia and gingival bleeding, distinct from periodontal disease, suggest that gingiva is a possible target tissue for JDM. In addition, these patients also have a compromised mandibular movement.

Disclosure: C. Savioli, None; **C. A. Silva**, Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPQ (Edital MCT/CNPq 472953/2008-7 to CAS and 300248/2008-3 to CAS), 2 ; **G. M. Fabri**, None; **K. Kozu**, None; **L. M. A. Campos**, None; **J. T. T. Siqueira**, None.

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Psychiatric Illness of Systemic Lupus Erythematosus in Childhood. Siok Hoon Lily Lim[1], Arlette Lefebvre[1], Susanne Benseler[1], PN Tyrrell[2], Michelle Peralta[1] and ED. Silverman[3], [1]SickKids, Toronto, ON, [2]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, [3]Hospital for Sick Children and University of Toronto, Toronto, ON

Purpose: 1) To describe characteristic clinical, laboratory and imaging features; 2) To determine distinct entities in the spectrum of psychiatric disease of Juvenile SLE and 3) to report treatment regimens and outcomes.

Method: Single centre cohort study of consecutive JSLE patients followed between 08/1985 and 12/2008 was performed. Patients were evaluated following standardized protocol. All patients were assessed by an experienced psychiatrist. Clinical features of psychiatric disease of Lupus were identified and classified according to ACR nomenclature except cognitive dysfunction. Cognitive dysfunction in this study defined as memory or attention deficits reported by patients/ parents, affecting academic performance. Specific investigations (neuroimaging and lumbar puncture) were extracted. Psychiatric outcomes: 1) response- no psychiatric symptoms, stopped anti-psychotic medications and Prednisone <50% maximal dose for at least 3 months; 2) remission- no psychiatric symptoms, stopped anti-psychotic medications and Prednisone ≤10mg/day for at least 3 months; 3) relapse- recurrence of symptoms (after response) requiring 50% increase in dose of Prednisone, change of 2nd line immunosuppressive not due to adverse effects.

Results: 447 JSLE patients were followed during the study period: 12% (53) developed psychiatric disease of JSLE; 87% (46) females, median follow- up from psychiatric diagnosis 2.0 years (0.5-6.8). Half (27/53) had psychiatric disease at diagnosis of JSLE. Median interval from first psychiatric symptom to diagnosis was 60 days (1- 1460).Clinical features of psychiatric disease of JSLE: Psychosis-like symptoms seen in 75% (40) with hallucinations predominant- 73% visual, 85% auditory and 20% tactile hallucinations. Insight preserved in 70%. Novel symptom of visual distortions seen in 38% of those with Psychosis. Clinically significant cognitive dysfunction present in 25% (13). No patient had isolated depression or anxiety. Specific investigations: 42 had Magnetic Resonance Imaging (MRI): 45% normal, 29% cerebral atrophy and 17% white matter changes. Lumbar puncture performed in 53% (28/53) at diagnosis: 29% had abnormally elevated total protein, 7% had elevated white cells. Treatment: Prednisone was started/ increased following protocol. 60% (24) of patients with Psychosis required antipsychotic therapy. All but 3 were treated with 2nd line agents during their course: 85% (45) Azathioprine, 55% (29) Cyclophosphamide and 28% (14) Mycophenolate. Outcomes: 74%(39) responded by last follow-up, 25 attained remission (but 3 relapsed), 6 relapsed, 8 improved but not attained remission.

Conclusion: Psychiatric illness of JSLE was distinctly different from neuropsychiatric SLE in adults, with mainly psychosis and cognitive dysfunction. All patients with psychosis had hallucinations but insight was intact. Unique symptom of visual distortion was seen. Most patients (74%) responded to standard therapy.

Disclosure: S. H. L. Lim, None; **A. Lefebvre**, None; **S. Benseler**, None; **P. Tyrrell**, None; **M. Peralta**, None; **E. Silverman**, None.

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Targeted Nutritional Intervention for Children On High Dose Corticosteroid Therapy. J. Tekano[1], A. Uribe[1], P. Khattra[1] and LB Tucker[2], [1]BC Children's Hospital, Vancouver, BC, [2]BC Childrens Hospital, Vancouver, BC

Purpose: Corticosteroids (CS) are widely used in the treatment of childhood rheumatic diseases, but are associated with morbidity. One of the most troublesome side effects of CS is excessive weight gain. The study aim is to determine the impact of a standardized dietary intervention on total weight gain over the first year of CS treatment in children with newly diagnosed rheumatic disease requiring high dose CS.

Method: This study is a prospective cohort intervention study (1 yr f/u), with a historical retrospective comparison group from the same clinic (treated with similar dose CS and no dietary intervention). Enrollment was at diagnosis of rheumatic disease, with start of high dose prednisone (≥1 mg/kg/day). Study subjects and parents received dietary counseling at the time of prednisone start, with prescription of an individualized dietary plan (low fat, low calorie, low sodium diet with increased calcium and fiber). Subjects had follow-up nutrition visits at each clinic visit (every 3 months) until 12 months. Measurements included: weight, BMI (BMI index>25=obese), body composition using skin fold thickness and waist circumference, and level of routine physical activity by the patient report Habitual Activity Estimation Scale (HAES; score > 3 hrs activity/wk=active).

Results: 20 patients aged 5-17 yrs (13F/7M; 8 systemic lupus, 5 Wegener's Granulomatosis, 5 juvenile dermatomyositis, 1 Takayasu's arteritis, 1 sarcoidosis)who received the nutritional intervention were compared to 15 patients aged 2-16 yrs who received standard care. Mean prednisone doses ranged from 1.1 m/g/d at diagnosis, to mean 0.19 mg/kg/d at 12 mos. Weight gain peaked at 9 mo with a mean(SD) gain of 7.9 (8.2) kg. One subject was obese at study entry with a baseline BMI of >95% and weight gain of 33 kg over 9 mos. When this subject was removed, the intervention group mean weight gain at 9 mo was significantly (p=0.03) less thank the historical comparison group (6.8 vs. 9 kg). At baseline, 2 subjects had BMI index>25; this increased to 5/20 (25%) at 9 mo, whereas 8/15 (53%) of the comparison group

had a BMI index >25 at 9 mo. At diagnosis, 12/20 subjects were scored as active on the HAES; at 9 mos this increased to 17/20. Inactivity was not associated with higher weight gain.

Conclusion: A personalized dietary intervention program was effective in limiting weight gain in a small group of children requiring high dose CS treatment for newly diagnosed rheumatic disease. Nutritional counseling should be included as a standard part of pediatric rheumatology team care.

Disclosure: J. Tekano, None; **A. Uribe**, None; **P. Khattra**, None; **L. Tucker**, None.

1901

Safety and Immunogenicity of Varicella Vaccine in Patients with Juvenile Rheumatic Diseases Using Methotrexate and Corticosteroids. Gecilmara S. Pileggi, Cleonice B. S. de Souza and Virginia P. L. Ferriani, School of Medicine of Ribeirão Preto, São Paulo University, Brazil., Ribeirao Preto- Sao Paulo, Brazil

Purpose: To evaluate the safety and immunogenicity of varicella vaccine (VV) in patients with juvenile rheumatic diseases (JRD) using disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids.

Methods: Twenty five patients with JRD (2-19 years) and 18 healthy children and adolescents (3-19 years) received one dose of VV BIKEN (*Aventis Pasteur*). All 25 patients were using methotrexate; 13 were also receiving prednisone, and 5 were on other DMARDs too. None of the vaccinated patients or controls had previous history of varicella.

IgG anti varicella zoster virus antibody (VZV-IgG) titers were measured by ELISA immediately before, 4-6 weeks and one year after vaccination.

Patients and controls were monitored prospectively for adverse reactions related to the vaccine, exposure and occurrence of varicella. Disease activity in JRD patients was assessed 3 months before and 3 months after VV.

Results: Twenty two patients had negative pre-immunization titers of VZV-IgG; 3 patients had equivocal levels and were excluded from the analysis of vaccine response, but were kept in the safety evaluation. Protective VZV-IgG titers were detected in 12/22 seronegative patients (54.5%) and 13/18 controls (72.2%) 4-6 weeks after VV (p=0.12). One year after vaccination, 10/12 patients maintained protective VZV-IgG titers.

No overt varicella episodes and no severe adverse reactions were observed.

No worsening of clinical parameters and flares of JRD or changes in doses of medications used were detected after vaccination. In fact, the number of active joints in JIA patients was significantly lower after VV (p=0.009).

Conclusion: Varicella vaccine seems to be safe in patients with JRD using methotrexate, as long as continuous prospective vigilance for side effects is performed. Lower than expected vaccine response rate in patients and controls suggests the need of using two doses of VV.

Disclosure: G. S. Pileggi, None; **C. B. S. de Souza**, None; **V. P. L. Ferriani**, None.

1902

Methotrexate Monitoring in Children: What Is Necessary? Maria Gutierrez[1], Svetlana Lvovich[2], C. Martucci[1] and Donald P. Goldsmith[3], [1]St. Christopher's Hospital for Children, Philadelphia, PA, [2]St Christopher's Hospfor Child, Philadelphia, PA, [3]St Christopher Hosp Children, Philadelphia, PA

Purpose: To assess the safety of monitoring for MTX toxicity in children with various rheumatic disorders at 12 week intervals.

Methods: A retrospective random chart review was completed on 66 (52F, 14M) children who had received MTX for the treatment of various rheumatic disorders (JIA-51; JDM-6; Uveitis-3; SLE-2; UCTD-1; Lin Scl-1;Wegeners-1) between 1996 and 2009 and in whom monitoring had been performed at 12 week intervals. The average age at disease onset was 10.8y, the average treatment duration 2.7y, and the average dose (mg/m2) 10.8 mg. Specific laboratory assessments included a basic metabolic panel (BMP), liver function tests (LFT) and complete blood count (CBC). Anemia was defined as a drop in Hgb of more than 2g compared with the baseline value.

Results: Mild elevation of LFT and transient hematological abnormalities were the most common side effects. 18 children had AST elevations, 4 with more than twice the upper limit of normal. 17 had abnormal ALT levels, 6 with elevations greater than twice the normal value. 2 patients with elevation of LFT required a slight decrease in the MTX dose and only 1 patient required temporary discontinuation. 13 developed leukopenia, 1 neutropenia, and 2 anemia. All of these abnormalities were mild and MTX was not permanently discontinued in any child as a result of these laboratory aberrations.

Conclusion: None of these MTX treated children experienced serious side effects. Laboratory abnormalities were mild and required minimal or no intervention. These findings confirm that the incidence of severe MTX toxicity in children with rheumatic disorders is negligible and are also compatible with a prior study (J Rheumatol 2004;31: 2501) which indicated that less frequent monitoring was safe. The formal recommendation for the monitoring of MTX toxicicity in children should be reformulated to reduce the emotional burden of frequent testing and the economic impact for families and the healthcare system.

Disclosure: M. Gutierrez, None; **S. Lvovich**, None; **C. Martucci**, None; **D. P. Goldsmith**, None.

1903

Ultrasound Abnormalities of Peripheral Joints in Juvenile Idiopathic Arthritis and Correlation with Clinical Examination. Sandrine Jousse-Joulin[1], Sylvain Breton[2], Claire Cangemi[2], Elisabeth Finel[3], Loic De Parscau[3], Alain Saraux[1] and Valerie Devauchelle-Pensec[1], [1]Rheumatology, Brest, France, [2]Radiology, Brest, France, [3]Paediatric, Brest, France

Purpose: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous condition leading to poor prognosis due to joint destruction in long term outcome for 50% of patients. Plain radiographs are commonly used to monitor joint damage but are quite insensitive, revealing narrowing and erosions often with delayed. Ultrasonography (US) with gray scale and power Doppler can allow early detection of synovitis in children. However, in opposite to the adult, there is no standardization of the technique and the correlation with clinical findings is poorly described.

The aim of our study was to define ultrasound abnormalities in the metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints in JIA and to compare US findings with clinical examination.

Method: Patients with recent JIA in according to Durban criteria were included. Ultrasound in B mode and power Doppler was performed with an HDI 5000 ultrasonography system (IU-22 Philipps) using a 12, 5-MHz linear array. 18 peripheral joints were examined for each patient: MCP 2,3,4,5 and MTP 1, 2,3,4,5, both sides. Physical and US examination were performed by two different experimented practitioners (SJJ and VDP). US practitioner was unaware of diagnosis and clinical examination. For clinical examination the tenderness and/or the swelling was noted as present or absent. For US findings, synovitis was considered and scored using the OMERACT criteria validated for adults (grey scale and Power Doppler). Others US findings were also considered as synovial thickness without DE, erosion, cartilage PD vascularity and bursitis.

Results: 25 patients with JIA were included (14 females, median age 12.5 ± 3 years, range 3.6 to 16.9 years). 20% (5/25) had polyarthritis with rheumatoid factors and 36% (9/25) had oligoarthritis. 450 joints were evaluated. 9.3% (42/450) had US synovitis, 50% were (21/42) located at the hand. Overall, US synovitis and physical examination scores were significantly associated ($p<0.001$) for both tenderness and swelling. However, inter-observer agreement between US synovitis and clinical evaluation was poor (kappa 0.18) concerning tenderness and only fair (kappa 0.44) concerning the swelling.60% (25/42) of the US synovitis were undiagnosed by clinical examination. In children the most frequently affected joints were the

MCP 2 (38%) and the MTP 1 (43%). Concerning the others abnormalities described with US, bursitis was not associated with synovitis, but synovial thickness without DE was associated with synovitis. Cartilage PD vascularity was not associated with synovitis, and was also found in a cohort of healthy children.

Conclusion: US of the MCP and MTP joints is a safe procedure in JIA allowing the detection of US synovitis associated with clinical examination. 50% of the US synovitis are not found by clinical examination. The OMERACT definition of active US synovitis can be used for JIA. Cartilage PD vascularity can be found in healthy children

Disclosure: S. Jousse-Joulin, None; **S. Breton**, None; **C. Cangemi**, None; **E. Finel**, None; **L. De Parscau**, None; **A. Saraux**, None; **V. Devauchelle-Pensec**, None.

ACR Concurrent Abstract Sessions

Infection-related Rheumatoic Disease

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

1904

Targeted Delivery of Nanodevices to *Chlamydia Trachomatis* -Infected Tissues in Murine Reactive Arthritis. I. Benchaala[1], I. Sinha[1], S.M. Wykes[1], M. Hali[1], M. Mishra[2], K. Kotta[2], R.M. Kannan[2] and J.A. Whittum-Hudson[1], [1]School of Medicine, Wayne State University, Detroit, MI, [2]College of Engineering, Wayne State University

Purpose: Dendrimers are emerging as a new class of nanoscale drug delivery vehicle because of their well-defined structure, tailored surface properties, and ability to deliver drugs intracellularly. We tested whether dendrimer-folic acid (FA) conjugates could target inflamed tissues in our murine model of chlamydia-associated reactive arthritis (ReA).

Method: Two nanodevices were synthesized for *in vivo* animal imaging experiments: Cy5.5, a near IR imaging agent, was conjugated to PAMAM dendrimer (D-Cy5.5) and compared to FA-D-Cy5.5. Conjugates were injected IV into BALB/c mice genitally infected with *C trachomatis.* Biodistribution of the nanodevices was determined using a Kodak whole animal imager 2h to120h after injection at 7-14 dpi. Paws (major sites of inflammation after dissemination of organism), and various organs were harvested for quantification of dendrimer conjugate uptake. Therapeutic nanodevices based on PAMAM dendrimer-Azithromycin conjugates (D-Z) were evaluated in chlamydia-infected HEp2 cells which were treated with either free Z (control) or D-Z (at equivalent Z concentrations from 2-256ng/ml) at the time of infection.

Results: Image analysis suggested that significantly higher amounts of FA-D-Cy5.5 were taken up into inflamed tissues including paws and genital tracts compared to D-Cy5.5 ($p<0.001$), and supported folate-dendrimer targeting of inflammation. Chlamydial inclusion numbers and size were significantly reduced >50% by D-Z compared to free Z at 16-32ng/ml; dendrimer alone did not reduce infection.

Conclusion: Our *in vivo* results suggest that dendrimers efficiently traffic to inflamed tissues and transport drug into infected cells to reduce infectious loads. To our knowledge this is the first report of folate-dendrimer targeting of infectious arthritic inflammation and in experimental chlamydia-associated ReA. These nanodevices may provide useful new therapeutic and imaging moieties for treatment of reactive arthritis in patients.

Disclosure: I. Benchaala, None; **I. Sinha**, None; **S. M. Wykes**, None; **M. Hali**, None; **M. Mishra**, None; **K. Kotta**, None; **R. M. Kannan**, None; **J. A. Whittum-Hudson**, None.

1905

Transcriptome Analysis of Chlamydia Trachomatis During the Transition From Active to Persistent Infection Identifies Gene Panels Whose Expression Is Required to Support That Transition. Alan Hudson[1], H. C. Gerard[2], Robert J. Belland[3] and Judith A. Whittum-Hudson[2], [1]School of Medicine, Wayne State University, Detroit, MI, [2]Wayne State University School of Medicine, Detroit, MI, [3]University of Tennessee Health Sciences Center, Memphis, TN

Purpose: *C trachomatis* elicits reactive arthritis when it infects synovial tissue in the persistent form, but we do not understand the genetic basis for persistent vs active infection. We performed a complete transcriptome analysis of this organism over time post-infection in the *in vitro* monocyte model of persistence to assess gene expression during the transition from active to persistent infection.

Method: PBMC were prepared from 4 healthy donors, mixed, and infected with serovar K at MOI 3:1. Infected cultures were harvested at d 0, 1, 2, 3, and 4 post-infection (pi), by which time chlamydiae were in the persistent state. RNA was prepared from each sample and following standard manipulation was hybridized to Affymetrix gene chips that included all chlamydial genes and several thousand host genes. Data were analyzed using GeneSpring as in previous studies.

Results: The initial transcript profile of chlamydiae within monocyte inclusions reflected that of the first 24 hr of normal active infection. However with the exception of the *trp* operon, by d 3 pi genes encoding products required for all amino acid biosynthetic pathways were

severely down-regulated, as was expression of *omp1*, *ftsK, ftsW,* and other genes consistent with published results. Expression from *pmpA, pmpB, pmpC, pmpD* was severely down-regulated; other *pmp* genes were less affected. Genes encoding products required for energy transduction, translation, protein transport, *etc* showed transcriptional attenuation by d 3 pi. K-means clustering analysis identified 38 genes in 4 distinct transcriptional groups showing internally consistent transcript patterns during transition from active to persistent infection. Of those 38 genes, 17 encode products of unknown function. Host cells displayed increased expression from many genes encoding products related to immune system function, and increased expression from genes encoding intracellular signaling systems.

Conclusion: Chlamydiae modify a number of enzymatic, transport, and other systems during the transition to persistent infection. Importantly, a distinct set of bacterial genes products of currently unknown function also are required to complete the transition, and it will be critically important to determine how those gene products do so if we are to design new therapeutic approaches to treat *Chlamydia*-induced ReA. We now are assessing additional details of host and chlamydial gene expression to determine which products from each might elicit a transcriptional response from the other.

Disclosure: A. Hudson, None; **H. C. Gerard**, None; **R. J. Belland**, None; **J. A. Whittum-Hudson**, None.

1906

The Chemokine CINC-1 Plays a Key Role in Innate Immunity in Reactive Arthritis. R. D. Inman[1] and B. Chiu[2], [1]U of Toronto, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON

Purpose: Innate immunity represents the first line of host defence against pathogens and functions as a key regulator of the development of reactive arthritis. Influx of neutrophils into the joint in experimental Chlamydia trachomatis-induced arthritis (CtIA) is genetically controlled and can be modified by environmental elements. This study addressed what factor may play a central role in the primary inflammatory response in the joint.

Method: Brown Norway rats are resistant to CtIA but rendered susceptible after prior exposure to mercuric chloride. Arthritis was induced by injection of synoviocyte-packaged Chlamydia, either in the absence (resistant phenotype) or presence (susceptible phenotype) of $HgCl_2$.Cellular infiltration was analyzed on H&E-stained sections of infected joints. ELISA was used to measure the following cytokines in serum (reported as mean values) 7 days after the onset of arthritis: IL-4, IL-6, IL-10, IL-17, IL-22, VEGF, TGF-β, IFN-γ, TNF-α, and CINC-1 (cytokine-induced neutrophil chemoattractant) which is equivalent to human Gro-α.

Results: The hallmark of susceptibility to reactive arthritis is an acute neutrophilic infiltration in the synovium which subsequently leads to erosive cartilage changes. This phenotype was associated with significant elevation in serum CINC: 492.9 pg/ml (+/- 67.6) for susceptible animals *vs* 141.6 pg/ml (+/- 48.16) for resistant animals, $p<0.0001$. The aggressive inflammation in susceptible animals was accompanied by significant elevation in serum levels of IL-6 (276.9 pg/ml +/-127.5 *vs* 7.7 pg/ml +/- 5.9, $p<0.001$) and in VEGF (110.6 pg/ml +/-37.4 *vs* 4.5 pg/ml +/- 2.3, $p<0.001$). The resistant phenotype was associated with a significant increase in IL-17 (4.2 pg/ml +/- 2.8 *vs* 1.2 pg/ml +/-0.56, $p<0.05$), in IL-22 (59.0 pg/ml +/- 50.4 *vs* 3.4 pg/ml (+/- 2.8, $p< 0.01$), and in IFN- γ (63.4 pg/ml +/- 18.9 vs 10.0 pg/ml +/- 7.6, $p< 0.005$).

Conclusion: Susceptibility to reactive arthritis after exposure to an arthritogenic pathogen depends critically innate immune responses, and CINC-1 plays a key role in this process by modulating neutrophil influx into the joint. Th-17 cells may play a hitherto unrecognized role in resistance to Chlamydia-related reactive arthritis

Disclosure: R. D. Inman, None; **B. Chiu**, None.

1907

Comparison of Two Interferon-Gamma Release Assays to Tuberculin Skin Testing for Latent Tuberculosis Screening in Rheumatic Patients Starting Anti-TNF Treatment. Dimitrios Vassilopoulos, Stamatoula Tsikrika, Emilia Hadziyannis, Anna Kandili, Nikolaos Stamoulis and Athanasios Archimandritis, Athens University School of Medicine, Athens, Greece

Purpose: Tuberculosis reactivation is a potential complication of anti-TNF treatment in patients with rheumatic diseases. Thus, the detection of latent tuberculosis infection prior to treatment initiation is of critical importance. Standard screening with the tuberculin skin test (TST) has its limitations mainly due to frequent false positive and negative results. Newer diagnostic assays such as the interferon – γ release assays (IGRAs) are promising alternatives to TST for more accurate Mycobacterium tuberculosis (MTb) infection diagnosis. Head to head studies

comparing the IGRAs to standard TST in high risk rheumatic patient populations are limited. The purpose of this study was to compare the performance of two commercially available IGRAs (T-SPOT.TB, Oxford Immunotec and QuantiFERON Gold in tube, QFT, Cellestis) to standard TST for TB screening in rheumatic patients starting anti-TNFa treatment.

Method: 55 patients (20 men/35 women) with various rheumatic diseases were screened for MTb infection with TST, two IGRAs (T-SPOT.TB and QFT), chest X-ray, standard questionnaire for demographics, history of TB, pevious MTb contact, BCG vaccination and concurrent immunosuppressive therapy. The majority of patients had been previously vaccinated with BCG (82%).

Results: Among the 55 patients tested (mean age= 53 ± 15 years), the rate of positivity was 45% for TST (25/55), 29% (16/55) for QFT and 24% (13/55) for T-SPOT.TB, respectively. In 56% of patients (31/55) there was agreement between the 3 assays (8 were all positive and 23 all negative). The agreement rate between the 2 IGRAs was moderate (84%, Kappa rate=0.58) whereas the agreement rate between TST and QFT and T-SPOT.TB was poor to fair (58%, κ=0.13 and 71%, κ=0.39), respectively. Previous BCG vaccination was statistically associated only with a positive TST result (OR=1.84, p=0.02) and not with a positive IGRA. Discordant results between the two IGRAs were observed in 9 patients (16%): 6 were QFT+/T-SPOT.TB- and 3 were QFT-/T-SPOT.TB+. Comparing the combination of the 2 IGRAs (T-SPOT.TB and/or QFT) to TST, we identified 24 discordant cases (44%): 7 IGRA+/TST- (13%) and 17 IGRA-/TST+ (31%) cases, who could represent "false negative" and "false positive" results of the standard TST, when it is used as the sole screening test.

Conclusion: In a patient population with high rates of latent TB infection and BCG vaccination, the application of both IGRAs and standard TST revealed discordant results in a significant number of cases. The comparison between the 2 IGRAs showed a good agreement rate. These results indicate the usefulness of these diagnostic assays as screening tools for TB screening in high risk rheumatic patient populations.

Disclosure: D. Vassilopoulos, None; **S. Tsikrika**, None; **E. Hadziyannis**, None; **A. Kandili**, None; **N. Stamoulis**, None; **A. Archimandritis**, None.

1908

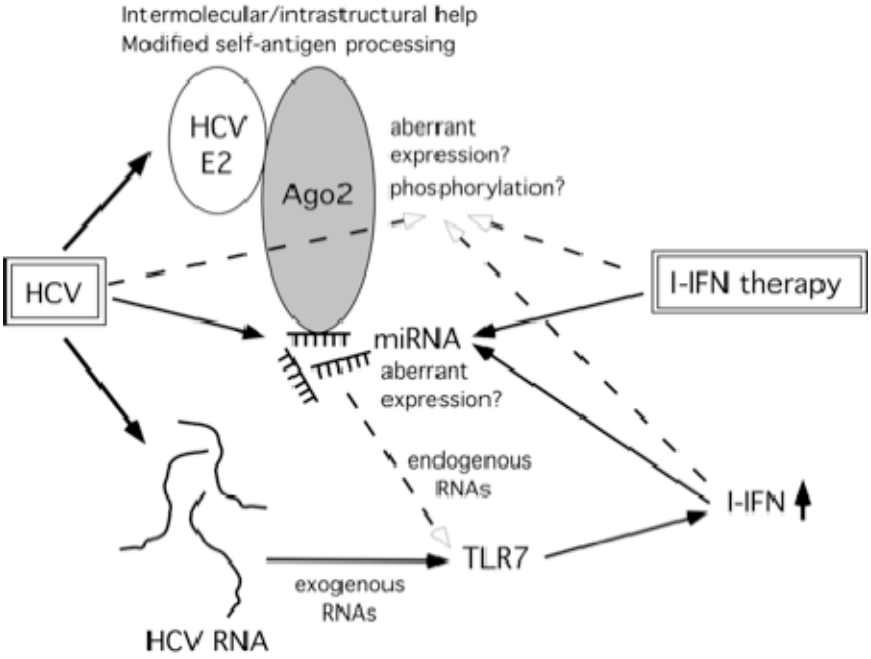
Autoantibodies to miRNA-Binding Protein Argonaute 2 (Su antigen) in Patients with Hepatitis C Virus Infection. Monica Vazquez-Del Mercado[1], Laura V. Sánchez Orozco[2], Brad A. Pauley[3], Jason Y.F. Chan[4], Edward K.L. Chan[4], Montserrat Maldonado González[5], Arturo Panduro[5], Erika A. Martínez García[6], Beatriz T. Martín Márquez[6], Jose F. Muñoz-Valle[6], Laura González Lopez[7], Jorge I. Gámez Nava[8] and Minoru Satoh[9], [1]Instituto de Investigacion en Reumatologia y del Sistema Musculo Esqueletico, U de G, , Hospital Civil JIM., Guadalajara, Mexico, [2]Instituto de Biología Molecular en Medicina, U de G, Mexico, [3]Dept. of Oral Biology, Univ. of Florida, Gainesville, FL, [4]University of Florida, Gainesville, FL, [5]Hospital Civil FAA, Mexico, [6]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, U de G, Guadalajara, Mexico, [7]H R 110, IMSS, Mexico, [8]Unidad de Investigación en Epidemiología Clínica, IMSS, Mexico, [9]Dept. of Medicine, Univ. of Florida, Gainesville, FL

Purpose: Chronic liver diseases caused by hepatitis B (HBV) or C virus (HCV) are common worldwide. In addition to viral infection itself, type I interferon (I-IFN, mainly IFN-alpha), a standard treatment for HCV appears to induce or enhance autoimmunity. Despite reports on autoimmunity in viral hepatitis, studies on lupus-related autoantibodies are limited and inconsistent. Autoantibodies associated with rheumatic diseases were tested in patients with HCV and HBV infection.

Methods: Ninety Mexican patients (36 male, 54 female, 58 HCV, 6 HCV+HBV, 26 HBV) with chronic viral hepatitis, confirmed by nested- or RT-nested-PCR, HBsAg and anti-HCV antibodies, were studied. Autoantibodies were tested by immunofluorescence, immunoprecipitation (IP), and ELISA.

Results: Antinuclear antibodies were found in 38% HBV, 17% HBV+HCV, and 28% in HCV. Antimitochondria antibodies (AMA) were found in 10 cases [8 without type I-IFN (I-IFN) therapy, 9 females)]; 12% in HBV, 17% in HBV+HCV, and 10% in HCV. In HCV (and co-infection), all 7 AMA positives were females (17% vs. 0% in males, $P = 0.04$). Antibodies to a microRNA (miRNA) binding protein Ago2/Su were found in HCV (3/58) or HBV+HCV (1/6) but not in HBV (0/26). Anti-Ago2/Su was in 2/8 HCV treated with I-IFN vs. 2/56 in cases without I-IFN, indicating both anti-Ago2 and AMA can be produced in HCV without I-IFN treatment. HCV did not have other lupus autoantibodies whereas 5/26 of HBV had anti-U1RNP+Ku, Ro+La, RNA polymerase II, or U5snRNPs by IP. AMA is more frequent in anti-Ago2/Su positives (3/4) vs. negatives (4/60) ($P = 0.0032$).

Conclusion: Lupus autoantibodies were uncommon in HCV except anti-Ago2/Su. HCV and I-IFN have many ways to affect TLR signaling, miRNA and miRNA binding protein Ago2/Su. HCV replication is regulated via miRNA. HCV envelope protein E2 is known to bind to Ago2. To understand the mechanism of specific targeting of Ago2 in HCV may provide insights to specific autoantibody production.



Disclosure: M. Vazquez-Del Mercado, None; **L. V. Sánchez Orozco**, None; **B. A. Pauley**, None; **J. Y. F. Chan**, None; **E. K. L. Chan**, None; **M. Maldonado González**, None; **A. Panduro**, None; **E. A. Martínez García**, None; **B. T. Martín Márquez**, None; **J. F. Muñoz-Valle**, None; **L. González Lopez**, None; **J. I. Gámez Nava**, None; **M. Satoh**, None.

1909

Rituximab for Severe Cases of Hepatitis C Virus-Associated Mixed Cryoglobulinemia. Dario Roccatello, Simone Baldovino and Daniela Rossi, CMID - Center of Research of Immunopathology and Rare Diseases, Turin, Italy

Purpose: Type II mixed cryoglobulinemia (MC) is a systemic vasculitis associated in most cases with hepatitis C virus (HCV) infection which is sustained by

proliferation of oligoclonal cells. Systemic B cell depletion and clinical remission can be achieved in non-Hodgkin lymphoma by human/mouse chimeric monoclonal antibody that specifically reacts with the CD20 antigen(rituximab). Similar effects could be expected in type II MC.

Method: Twelve patients, mean age 61.9 years (range 37-76), 11 with HCV infection genotype 2a2c (4 cases) or 1b (6 cases) and 3 (1 case) and symptomatic type II MC with systemic manifestations, including renal involvement with biopsy-proven membranoproliferative glomerulonephritis, marrow clonal restriction, large necrotizing ulcers, and polyneuropathy, were considered eligible for rituximab therapy because of resistance or intolerance to conventional therapy or important bone marrow infiltration. Rituximab was administered intravenously at a dose of 375 mg/sm on days 1, 8, 15, and 22. Two more doses were administered 1 and 2 months later. No other immunosuppressive drugs were added. Response was evaluated by assessing the changes in clinical signs, symptoms, and laboratory parameters.

Results: Levels of proteinuria (1.6 g/24h at T0 vs 0.2 g/24h at 18 mths), erythrocyte sedimentation rate (58 mm/h at T0 vs 37 mm/h at 18 mths), cryocrit (2,2% at T0 vs 0.3% at 18 mths), rheumatoid factor (550 UI/ml at T0 vs 250 UI/ml at 18 mths), and IgM (500 mg/dl at T0 vs

200 mg/dl at 18 mths) significantly decreased while C4 values increased (6 mg/dl at T0 vs 15 mg/dl at 18 mths) and HCV viral load remained stable during short, medium and even long-term (until 48 mnths) observation. Bone marrow abnormalities were found to reverse to normal. Constitutional symptoms disappeared or ameliorated. No acute or delayed side effects were seen, including worsening of HCV infection.

Conclusion: Rituximab appears to be a safe and effective therapeutic option in symptomatic patients with HCV-associated MC with signs of systemic vasculitis.

Disclosure: D. Roccatello, None; **S. Baldovino**, None; **D. Rossi**, None.

ACR Concurrent Abstract Sessions

Molecular Mechanisms in Cartilage and Bone Pathophysiology
Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

1910

Regulation of the IGFBP-5 and MMP-13 Genes by the Micro RNAs Mir-140 and Mir-27a in Human Osteoarthritic Chondrocytes. Ginette Tardif[1], David Hum[1], Jean-Pierre Pelletier[1], Nicolas Duval[2] and Johanne Martel-Pelletier[1], [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]Duval Orthopaedic Clinic, Charmilles Pavillion, Laval, QC

Purpose: MMP-13 and IGFBP-5 are important factors involved in osteoarthritis (OA). We investigated the potential regulation of these two genes by microRNAs (miRNAs) in cultured human OA chondrocytes.

Method: Gene expression was determined by real-time PCR. The effect of each miRNA on IGFBP-5 and MMP-13 expression/production was evaluated by transiently transfecting their precursors (pre-miRNAs) and inhibitors (anti-miRNAs) into human OA chondrocytes. Modulation of IGFBP-5, miR-140 and miR-27a expression was determined upon treatment of OA chondrocytes with cytokines and growth factors.

Results: IGFBP-5 was expressed in cultured human chondrocytes with levels significantly ($p<0.04$) lower in OA. Computational algorithms identified miR-140 and miR-27a as possible regulators of MMP-13 and IGFBP-5 expression. Data showed that both miRNAs were expressed in chondrocytes. There was a significant ($p<0.01$) reduction in miR-140 expression in OA. Transfection with pre-miR-140 significantly ($p<0.005$) decreased IGFBP-5 expression at 24 hours, while pre-miR-27a did not affect either MMP-13 or IGFBP-5. Treatment with anti-miR-27a, but not with anti-miR-140, significantly increased the expression of both MMP-13 ($p<0.05$) and IGFBP-5 ($p<0.01$) but only after 72 hours incubation. These data indicate that IGFBP-5 is a direct target of miR-140, whereas miR-27a indirectly down-regulates both MMP-13 and IGFBP-5. TGF-β down-regulates miR-140 and up-regulates IGFBP-5.

Conclusion: Data revealed that miR-140 acted directly on decreasing IGFBP-5 expression but that miR-27a indirectly decreased both MMP-13 and IGFBP-5. Data from the study could be the first step in generating more comprehensive knowledge of the regulation of other MMPs and IGFBPs involved in OA, which could open up novel avenues in therapeutic strategies targeting this disease.

Disclosure: G. Tardif, None; **D. Hum**, None; **J. P. Pelletier**, None; **N. Duval**, None; **J. Martel-Pelletier**, None.

1911

Reactive Oxygen Species Contribute to IGF-I Resistance in Osteoarthritic Chondrocytes through Inhibition of the IRS-I-PI3 Kinase-Akt Signaling Pathway. Richard F. Loeser and Weihong Yin, Wake Forest University School of Medicine, Winston-Salem, NC

Purpose: IGF-I stimulation of chondrocyte proteoglycan synthesis requires activation of the PI-3 Kinase-Akt signaling pathway. With aging and during the development of osteoarthritis (OA), chondrocytes become hyporesponsive to IGF-I. We tested the hypothesis that an increase in reactive oxygen species (ROS) causes IGF-I resistance by altering the activation of the IGF-I signaling pathway.

Method: Human articular chondrocytes were isolated from normal ankle cartilage obtained from adult tissue donors or from OA knee cartilage removed during joint replacement. High density serum-free monolayer cultures were stimulated with 50ng/ml IGF-I with or without pre-treatment with hydrogen peroxide (exogenous ROS) or the anti-oxidants MnTBAP or NAC. IGF-I signaling proteins were evaluated by immunoblotting with phosphospecific and control antibodies. Proteoglycan synthesis was measured by sulfate incorporation corrected for cell numbers by DNA and aggrecan and type II collagen expression were measured by real-time PCR. Lentiviral constructs were used to overexpress constitutively active (CA) Akt and MEK and dominant (DN) Akt.

Results: In normal human chondrocytes, IGF-I initiated a strong and sustained phosphorylation of IRS-1 (Y612) and Akt (S473 and T308) which are activating sites, and a transient ERK1/2 phosphorylation. In contrast, in osteoarthritic chondrocytes, which possessed elevated basal IRS-1 phosphorylation at S312 (inhibitory site) and ERK phosphorylation, IGF-I failed to stimulate IRS-1 (Y612) or Akt phosphorylation. In normal human chondrocytes, exogenous ROS triggered strong IRS-1 (S312 and S616) and ERK phosphorylation and inhibited IGF-I-induced IRS-1 (Y612) and Akt phosphorylation. Lentivirus-mediated overexpression of constitutively active (CA)-Akt significantly enhanced proteoglycan synthesis, while both dominant negative (DN)-Akt and constitutively active (CA)-MEK inhibited proteoglycan synthesis. ROS treatment and CA-MEK inhibited both aggrecan and collagen II mRNA expression, while CA-Akt dramatically increased collagen II, but not aggrecan mRNA expression. In osteoarthritic chondrocytes, antioxidants MnTBAP and NAC increased the ratio of Akt to ERK phosphorylation, and promoted IGF-I-mediated proteoglycan synthesis and type II collagen expression. Chemical inhibition of ERK significantly enhanced IGF-I phosphorylation of Akt and alleviated ROS inhibition of Akt phosphorylation.

Conclusion: These results demonstrate for the first time opposing roles for PI-3 Kinase-Akt and MEK-ERK in the IGF-I regulation of chondrocyte proteoglycan synthesis and type II collagen expression and suggest that excessive ROS in OA chondrocytes inhibit IGF-I mediated matrix synthesis by altering the balance of Akt to ERK activation.

Disclosure: R. F. Loeser, None; **W. Yin**, None.

1912

Chromatin Protein HMGB2 Regulates Articular Cartilage Surface Maintenance Via Beta-Catenin Pathways. Noboru Taniguchi, Beatriz Caramés and Martin Lotz, The Scripps Research Institute, La Jolla, CA

Purpose: The superficial zone (SZ) of articular cartilage is critical in maintaining tissue function and homeostasis and represents the site of the earliest changes in osteoarthritis. Mechanisms that regulate the unique phenotype of SZ chondrocytes and maintain SZ integrity are unknown. We have recently demonstrated that expression of the chromatin protein HMGB2 is restricted to the SZ of articular cartilage suggesting a transcriptional network involving HMGB2 that regulates SZ cell phenotype. This study addresses potential interactions between HMGB2 and the Wnt/β-catenin pathway in regulating SZ cells.

Method: Activation Wnt/β-catenin signaling in articular cartilage was assessed by immunostaining for β-galactosidase in TOPGAL reporter mice at 3, 6, 12 and 18 months of age, and this was compared with HMGB2 expression. Functional interactions of β-catenin and HMGB2 on cyclin D1 and TOPflash promoters which are responsive to Wnt/β-catenin activation was examined by Luciferase assay, and molecular interactions between β-catenin, Lef-1 and HMGB2 were examined by GST-pull down assays. Gel shift assays were used to determine binding specificity and interactions of HMGB2 and Lef-1. To further test the functional significance of β-catenin signaling, we conditionally inactivated β-catenin in chondrocytes isolated from β-catenin floxed mice (Ctnnb1flox/flox) with adenovirus-GFP-Cre and performed apoptosis assays.

Results: We found that the Wnt/β-catenin pathway is active specifically in the SZ in normal mouse knee joints and co-localizes with HMGB2. Both, Wnt signaling and HMGB2 expression decrease with aging in the SZ of mouse knee cartilage. Our molecular studies show that HMGB2, Lef-1 and β-catenin form a tri-molecular complex on a promoter containing a Lef-1 motif. This complex enhances the binding of Lef-1 to its target sequence and potentiates transcriptional activation of the Lef-1-β-catenin complex. Furthermore, conditional deletion of β-catenin in cultured mouse chondrocytes induced apoptosis.

Conclusion: These findings define a pathway where protein interactions of HMGB2 and Lef-1 enhance Wnt signaling and promote SZ chondrocyte survival. Loss of the HMGB2-Wnt signaling interaction is a new mechanism in aging-related cartilage pathology.

Disclosure: N. Taniguchi, None; **B. Caramés**, None; **M. Lotz**, None.

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Gdf5 Deficient Mice Have Increased Susceptibility to Osteoarthritis. Melina Daans, Frank P. Luyten and Rik J. Lories, KU Leuven, Leuven, Belgium

Purpose: A functional polymorphism leading to reduced levels of growth and differentiation factor-5 (GDF5) was recently identified as a susceptibility factor for osteoarthritis (OA). GDF5, also known as cartilage derived morphogenetic protein (CDMP1) is a member of the bone morphogenetic protein family originally identified from a chondrogenic extract of articular cartilage. During development the gene is expressed in early stages of chondrogenesis and in the prospective joint interzone. Postnatally, GDF5 biology has not only been associated with cartilage but also with ligaments and tendons. Mice with a spontaneous mutation in the *Gdf5* gene (*brachypodism* mouse, $Gdf5^{Bp\text{-}J/Bp\text{-}J}$) develop a severe phenotype with joint fusions and shortening of the skeletal elements. Here, we studied the role and mechanism of *Gdf5* involvement in OA using haploinsufficient $Gdf5^{Bp\text{-}J/+}$ mice.

Method: $Gdf5^{Bp\text{-}J/+}$ mice were kept on a CD1/Swiss genetic background. OA development was studied in the collagenase-induced arthritis model, the medial meniscus destabilization model, the papain-induced arthritis model and a treadmill running model. Bone density and subchondral bone parameters were determined using DEXA and peripheral quantitative computed tomography (pQCT). Additional *in vitro* and *ex vivo* analyses studied cartilage metabolism, gait and collagen characteristics.

Results: $Gdf5^{Bp\text{-}J/+}$ mice appear phenotypically normal but show discrete signs of haploinsufficiency during limb development and in trabecular bone area. $Gdf5^{Bp\text{-}J/+}$ mice developed more severe OA in the meniscal destabilization model, in the treadmill model and on the contralateral side in the collagenase-induced model but not in the papain-induced model. These data suggest that stability of the joint is impaired in $Gdf5^{Bp\text{-}J/+}$ mice. This was confirmed by gait analysis demonstrating that distances between 2 steps are smaller in $Gdf5^{Bp\text{-}J/+}$ mice as compared to wild-type mice. Cartilage breakdown analysis did not show differences between the mice but analysis of the subchondral bone demonstrated that $Gdf5^{Bp\text{-}J/+}$ mice have a decreased subchondral bone density and a distorted arrangement of collagen fibers.

Conclusion: These data support a role for GDF5 in OA development. Of interest, the observed phenotypes pointed to an effect of decreased GDF5 levels on joint stability and subchondral bone rather than on the articular cartilage. This highlights the importance of the joint as an organ in concepts of joint disease.

Disclosure: M. Daans, None; **F. P. Luyten**, None; **R. J. Lories**, None.

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Targeted Disruption of Cartilage-Specific microRNA140 Promotes Osteoarthritis-Like Pathology. Shigeru Miyaki[1], Tempei Sato[2], Atsushi Inoue[2], Yoshiaki Ito[2], Shigetoshi Yokoyama[2], Shuhei Otsuki[1], Yoshio Kato[3], Fuko Takemoto[2], Satoshi Yamashita[2], Tomoyuki Nakasa[2], Martin Lotz[1], Hiroe Kudo[2] and Hiroshi Asahara[1], [1]The Scripps Research Institute, La Jolla, CA, [2]Nationa Research Institute for Child Health and Development, Tokyo, Japan, [3]National Institute of Advanced Industrial Science and Technology

Purpose: Osteoarthritis (OA), the most prevalent age-related joint disease, is characterized by degradation in articular cartilage by several proteinases. Small, non-coding microRNAs (miRNAs) play a critical role in development; however, their role in tissue maintenance is largely uncharacterized. We previously observed that miR-140 has an expression pattern suggestive of a role in chondrocyte differentiation and found that reduced miR-140 expression in human OA cartilage and in response to IL-1ß stimulation may contribute to the abnormal gene expression pattern characteristic of OA. The objective of this study was to define the in vivo function of the chondrocyte specific miR-140 in cartilage homoestasis.

Method: To examine the functions of miR-140, we created a mouse deleted for miR-140 and collected knee joints and chondrocytes from wild-type and miR-140-/- mice. To quantify OA-like pathological changes in articular cartilage, we used a validated histological OA scoring system based on Safranin O staining and evaluated expression of cartilage related genes by qPCR or immunohistochemistry. In vitro proteoglycan catabolism was analyzed in cultured femoral head cartilage explants from miR-140-/- mice.

Results: MiR-140-/- mice were born at normal Mendelian ratios and were fertile. Skeletal development during embryogenesis in miR-140-/- mice appeared normal. Postnatally, miR-140-/- mice manifested a mild skeletal phenotype, with short stature and craniofacial deformities characterized by a short snout, short mandibles and domed skull. miR-140-/- mice showed aging-related, OA-like changes characterized by proteoglycan loss and fibrillation in articular cartilage. Cultured miR-140-/- femoral head cartilage explants also showed significantly

increased proteoglycan release compared to wild-type cartilage. Consistent with these phenotypes, ADAMTS-5 was highly expressed in articular cartilage in miR-140-/- null mice and an in vitro reporter assay identified Adamts-5 as a direct miR-140 target.

Conclusion: MiR-140 disruption in vivo induced early onset OA-type changes in articular cartilage, which was associated with increased Adamts-5 expression. Our results indicate that Adamts-5 is directly regulated by miR-140, suggesting that miR-140 plays an important role in regulating the balance between extracellular matrix formation and degradation. This represents one of the first studies to show that a microRNA is required for tissue homeostasis and that its loss contributes to aging-related pathology.

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1915

Syndecan-4 Is a Key Regulator of Osteoarthritic Cartilage Damage. Jessica Bertrand[1], Frank Echtermeyer[2], Rita Dreier[3], Martin Fürst[4], Gregor Theilmeier[2] and Thomas Pap[5], [1]University hospital Muenster, Münster, Germany, [2]University hospital Hannover, Hannover, Germany, [3]University Hospital Muenster, Muenster, Germany, [4]University Hospital Hamburg, Hamburg, Germany, [5]Univ Hosp, Muenster, Germany

Purpose: The cleavage of aggrecan is an important step in the breakdown of cartilage matrix in OA. ADAMTS-5 has been shown to be involved in the loss of proteoglycans, but the mechanisms of ADAMTS-5 activation during cartilage remodeling are poorly understood. Here, we analyzed the role of syndecan-4 in human OA cartilage degradation and in a murine OA model.

Method: Cartilage specimens were obtained from 120 patients with knee OA at joint replacement surgery, and analyzed for syndecan-4 and collagen X expression. For functional analysis, OA-like changes were induced in syndecan-4 k.o. mice and wt animals by surgically achieved joint instability. To verify the data of the syndecan-4 k.o. mice and exclude developmental effects, wt mice were treated with intraarticular injections of a blocking antibody against syndecan-4 following the induction of OA. The histological severity of OA as well as the MMP-3 expression was assessed in histological sections of all animals. ADAMTS-5 activity was determined by a sensitive aggrecanase assay. The effect of the MMP-3 inhibitor NNGH on aggrecan cleavage was analyzed in murine cartilage explants. Changes in IL-1 induced expression of MMPs, ADAMTSs and TIMPs were measured by RT-PCR. Syndecan-4 dependent changes in ERK phosphorylation after IL-1 treatment were determined by Western-Blot.

Results: During the development of murine OA, syndecan-4 was induced specifically in type X collagen expressing chondrocytes. The loss of syndecan-4 in the k.o. mice or treatment of wt animals with syndecan-4 antibodies nearly completely protected from a loss of proteoglycans. This correlated with a reduced MMP-3 expression in the cartilage of syndecan-4 k.o. mice and in mice treated with anti-syndecan-4 antibodies. Proteoglycan loss was induced by IL-1 in cartilage caps isolated from 6 weeks old wt and syndecan-4 k.o. mice, and ADAMTS-5 expression was found to be upregulated by IL-1 equally in both groups. However, proteoglycan loss was reduced significantly in syndecan-4 k.o. cartilage or cartilage treated with anti-syndecan-4 antibodies. In the supernatant of syndecan-4 k.o. cartilage, we found a reduced presence of activated ADAMTS. Cartilage that was treated with NNGH showed a reduced ADAMTS-5 mediated proteoglycan cleavage. We found a reduction of phosphorylated ERK in syndecan-4 k.o. cartilage after IL-1 treatment.p> **Conclusion:** Our data demonstrate that syndecan-4 is functionally involved in cartilage degradation by hypertrophic OA chondrocytes through inhibiting the activation of ADAMTS5 mediated aggrecan cleavage. ADAMTS-5 activation depends on both direct interaction with syndecan-4 on the surface of osteoarthritic chondrocytes and syndecan-4 regulated synthesis of MMP-3, which is ERK-dependent. Inhibition of syndecan-4 may, therefore, constitute a promising strategy to interfere with osteoarthritic cartilage damage.

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ACR Concurrent Abstract Sessions

Quality Measures and Innovations in Practice Management and Care Delivery

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

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Closing Osteoporosis Care Gaps through Process Redesign: The Primary Care-Rheumatology DXA Partnership. Eric D. Newman, Jennifer Fernandez, Thomas P. Olenginski, Mark Lentz, Brian DelVecchio, Androniki Bili and Valerie Weber, Geisinger Medical Center, Danville, PA

Purpose: Assessing osteoporosis fracture risk using DXA in women >65 is a national measure of osteoporosis quality care. The Electronic Health Record (EHR) can be programmed to fire a DXA Best Practice Alert (BPA) to help improve this measure. However, a BPA is only helpful at point-of-service (clinic visit), leaving a large number of at risk patients where this quality health measure cannot be addressed. In an attempt to truly "move the bar", our Rheumatology and General Internal Medicine (GIM) departments developed a partnership redesign project to create a more efficient and more effective process for DXA testing in women >65.

Methods: Four GIM physicians agreed to pilot this program. The program process flow redesign and mailing materials were reviewed by all participants. An EHR data extract of all women > 65 who had not had a DXA within the preceding 3 years was obtained. The list was divided into weekly batches of 40 patients. Each week, the GIM physicians were sent telephone encounters with a pended DXA order to sign and return. The physicians were allowed to sign or not sign a DXA order per their discretion. After the signed orders were received, letters were sent to patients inviting them to call in for a DXA. Patients that did not call in within a week of mailing were proactively contacted. DXAs were scheduled, performed, and a consultative interpretation was reported. If the patient's risk was not high, a "normal" letter was sent to the patient on behalf of their GIM physician. High risk patients were managed per the DXA report recommendations. A spreadsheet was used for task management and to track DXA testing and reasons for not testing.

Results: 305 patients met the study criteria. 143 patients (46.9%) underwent DXA scanning. Of the 162 patients (53.1%) who did not get a DXA scan, the most common reasons included: DXA order not signed (51%), patient refused (34%), patient died (10%). Common reasons for orders not signed included frailty, co-morbid diseases, and bed-bound. The subgroup where the DXA orders were not signed was older than the group who underwent DXA (84.7 +/- 0.8 vs. 76.6 +/- 0.6, $p<0.001$), and only 13% of this subgroup was receiving empiric osteoporosis therapy. A significant increase in the quality measure "% women > 65 with DXA" was seen in all 4 physicians – overall increase from 61% pre-partnership to 74% post-partnership ($p=0.001$; see Table).

Conclusion: A proactive process redesign partnership between rheumatology and GIM resulted in a significant improvement in women over 65 receiving a DXA scan. Over half of the at-risk patients were never studied – possible reasons include process issues (physician discretion in signing orders), population issues (chronically ill GIM patients), or simply a ceiling effect on this real world benchmark. Using the data obtained in this pilot and a new process flow, a second pilot is underway with a Family Physician Group in a different population to see if the process can be further redesigned to improve quality and efficiency.

Physician	Pre-Partnership	Post-Partnership	p-value
Physician A	54%	74%	0.0001
Physician B	77%	83%	0.0016
Physician C	44%	54%	0.003
Physician D	58%	78%	0.001
Summary	61%	74%	0.001

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1917

Rheumatology Touchscreen Questionnaire to Improve Efficiency and Patient-Centric Care – Successful Development and Implementation Using Process Redesign. Eric D. Newman[1], Virginia R. Lerch[2], William T. Ayoub[3], J. B. Jones[2] and Walter F. Stewart[2], [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA, [3]Geisinger Medical Group, State College, PA

Purpose: Patient-reported outcomes (PRO) are helpful to guide rheumatologic care decisions. Validated questionnaires are rarely used routinely because of workflow challenges using paper-based instruments. Computerized questionnaires offer an advantage in obtaining, aggregating, and reporting data in real time. However, electronic questionnaire administration must take into account existing workflows and resources to be effective in busy clinical practice. We compared two workflow models using a touchscreen questionnaire (TQ) in Rheumatology practices to evaluate completeness of data capture during routine visits.

Methods: The TQ authenticated patients and administered the questionnaire, checked for errors in real time, and scored and stored results. The TQ included functional outcomes (i.e., pain, stiffness, fatigue, and global scales), fall assessment, review of systems, self-reported tender joint counts, social parameters, and 10 probes for events of interest. Two rheumatology sites were studied – a single rheumatologist practice with greater resources (personnel) and a simple exam room-centric flow (Clinic 1), and a multi-provider academic rheumatology practice with fewer resources and a more complex linear flow (Clinic 2). Plan-do-study-act cycle methodology was used for implementation in two defined cycles.

Results: Cycle 1: Authentication required a keyboard. Both sites used a full-time assistant to help patients complete this task. Use of the TQ was rapidly scaled up, with weekly debriefing and feedback to the clinic team regarding TQ completion rate. In Clinic 1, over 90% of patients were able to complete the TQ during the 1st week. Clinic 2 remained well below 70% even at 12 weeks. TQ completion rate was highly dependent on the presence of an assistant to notify the nurses that the patient had completed their TQ. Cycle 2: A 15 minute pre-visit was built into the schedule to allow sufficient TQ completion time. The TQ was redesigned so that patient authentication could be performed by TQ rather than keyboard. An instant messaging and tracking system was developed so that the existing nursing pool could monitor the patients' questionnaire progress – yellow message (questionnaire started), red message (patient needs help), green message (questionnaire completed). These redesigns eliminated the need for an assistant. The new TQ version achieved a completion rate of > 75 % in Clinic 2 in the first week and thereafter. Over 2,000 TQs have been entered to date, and its routine use has been integrated into daily practice.

Conclusion: PROs collected via questionnaire have been shown to improve efficiency and provide patient-centric care. Using process redesign techniques, we have developed a TQ-based PRO collection program and process that allows a complex rheumatology practice to achieve immediate completion rates of >75% using existing resources. The next step is to integrate the TQ results into an electronic visual display.

Touchscreen Questionnaire (TQ) Completion Rate

	Cycle 1 - TQ Version 1				Cycle 2 - TQ Version 2	
	week 1	week 4	week 8	week 12	week 1	week 4
Clinic 1 resource replete simple flow	92%	82%	74%	83%	-	-
Clinic 2 resource deficient complex flow	40%	40%	62%	54%	80%	77%

Disclosure: E. D. Newman, None; **V. R. Lerch**, None; **W. T. Ayoub**, None; **J. B. Jones**, None; **W. F. Stewart**, None.

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Quality of Preventive Care for Older Americans with Rheumatoid, Psoriatic and Osteoarthritis. J. R. Curtis[1], T. Arora[1], A.J. Taylor[1], C. O. Bingham III[2], John J. Cush[3], P. Narongroeknawin[1] and E. Delzell[1], [1]UAB, Birmingham, AL, [2]Johns Hopkins University, Baltimore, MD, [3]Baylor Research Institute, Dallas, TX

Purpose: Previous research suggests patients with rheumatoid arthritis (RA) may receive suboptimal care with respect to preventive tests and services such as DXA, vaccinations and screening tests for cancer and cardiovascular risk assessment. We evaluated the proportion of older Americans with RA and psoriatic arthritis (PsA) who received these preventive services and compared them to those with osteoarthritis (OA) (used as an internal control group).

Method: Using data from 1999-2006 from the Medicare Chronic Conditions Warehouse (CCW), we identified persons in the national 5% sample, age ≥ 65 with Medicare part A + part B not enrolled in a Medicare Advantage plan. We classified those with mutually exclusive diagnoses of RA, PsA and OA and required ≥ 2 physician visits in a 1 yr baseline period, also used to assess comorbidities and health services utilization. Over the required 5 year follow-up period, we identified tests and services that are generally recommended for older adults and the specialty of the associated provider. These services included DXA (1+), influenza (yearly) and pneumococcal vaccination (1+), hyperlipidemia testing (1+), mammography (none, 1, 2+) and colonoscopy (1+). We used multivariable dichotomous and ordinal logistic regression to estimate odds ratios to evaluate the likelihood of receiving various services among RA and PsA patients compared to OA patients, adjusting for potentially confounding factors (e.g. demographics, health services utilization, comorbidities and care from a rheumatologist.

Results: After accounting for sampling fraction, there were 139,240 RA, 6160 PsA and 747,620 OA patients who met eligibility criteria. The crude proportion who received various services is shown in Table. After adjustment, RA patients were more likely than OA patients to receive DXA (OR 2.37, 95% CI 2.23-2.51), influenza vaccination (OR 1.09, 95% CI 1.04, 1.14) and pneumococcal vaccination (OR 1.18, 95% CI 1.11-1.24) and less likely to receive mammography (OR 0.78, 95% CI 0.73-0.82) or hyperlipidemia testing (OR 0.63, 0.59-0.68). PsA patients were more likely to receive DXA (OR 2.43, 95% CI 1.87-3.15) compared to OA patients. Receipt of all other services for RA and PsA patients did not differ compared to OA patients. Of those receiving vaccination, rheumatologists administered at least 1 influenza vaccination to 17% (RA), 13% (PsA) and 2% (OA) and provided pneumococcal vaccination to 9% (RA), 5% (PsA) and 1% (OA) of patients.

Conclusion: Among older Americans in Medicare, the absolute proportion of persons with inflammatory arthritis receiving various generally-recommended preventive services and screening tests was substantially less than 100%. Using OA patients as a control group, RA patients were more likely to receive DXA and vaccinations but the same or less likely to receive hyperlipidemia testing or screening for breast or colon cancer. Most vaccinations were administered by non-rheumatologist providers. Given the high burden of comorbidities including cardiovascular disease among RA and PsA patients, strategies to improve the quality of preventive care for patients with inflammatory arthritis are needed.

Table: Proportion of patients with Rheumatoid, Psoriatic and Osteoarthritis Receiving Preventive Services during 5 Yrs of Follow-up

	RA (n = 139,240)	PsA (n = 6,160)	OA (n = 747,620)
DXA, %	61.5	56.2	40.1
Influenza vaccination, %			
None	17.4	15.9	18.5
Only 1 year	8.9	9.4	10.1
Only 2 years	11.8	12.3	12.0
Only 3 years	16.6	15.3	16.8
Only 4 years	23.8	28.2	23.0
All 5 years	21.5	18.8	19.7
Pneumococcal vaccination, %	33.0	34.7	29.1
Mammography, % (women only)			
None	29.3	18.7	28.5
Only 1	14.5	12.3	13.7
2 or more	56.2	69.0	57.8
Colonoscopy, %	65.9	71.1	64.8
Hyperlipidemia lab testing, %	83.4	90.3	87.0

Data shown as %

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Besides Disease Activity There Are Many Other Considerations Made in the Decision Whether or Not to Escalate Medication: a Qualitative Study. Laura.T.C. van Hulst[1], Wietske Kievit[2], Piet L.C.M. van Riel[1], Richard Grol[1], Liana Fraenkel[3] and Marlies E.J.L. Hulscher[1], [1]UMC St Radboud, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Yale University, New Haven, CT

Purpose: It is widely recommended that rheumatologists use validated measures to monitor disease activity and adjust medication accordingly. Despite the widespread endorsement that treatment should be escalated in patients with moderate or high disease activity, data suggests that this approach is frequently not followed in daily clinical practice. In order to improve quality of care in RA in daily clinical practice, it is important to understand the factors which influence both patients' and physicians' decisions on whether or not to escalate DMARDs in case of active disease.

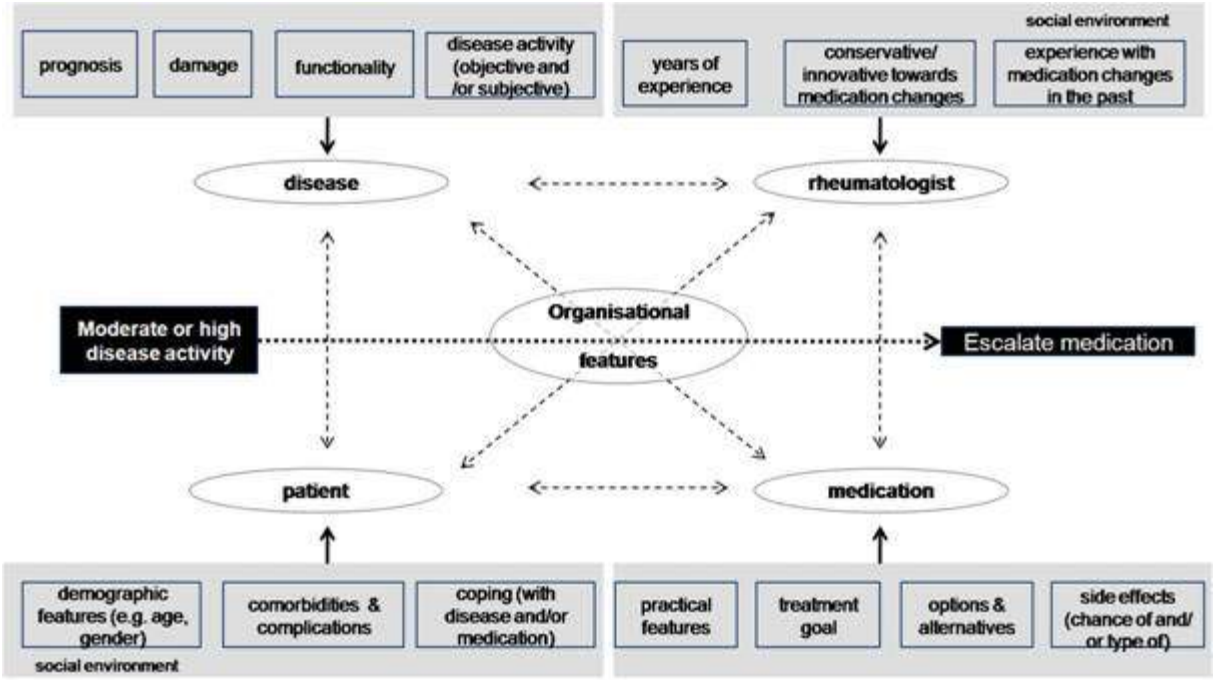
Method: Five focus groups were held (3 with RA patients and 2 with rheumatologists) to examine which factors influence rheumatologists' and patients' decisions related to escalation of DMARDs in patients who continue to have moderate to severe disease activity despite treatment with DMARDs. The focus groups were recorded and transcribed verbatim. The transcripts were analyzed on the basis of the grounded theory with Atlas.ti 6.0.11. Two analysts (LvH and WK) independently coded the transcripts. The independent codings were reviewed by the analysts. Codes were redefined until consensus was reached. Categories were derived from the final list of codes.

Results: Disease activity plays a role in the decision to escalate DMARDs for both RA patients as well as rheumatologists. RA patients emphasized that pain and fatigue were important in their decision. In contrast, rheumatologists emphasized the importance of objective disease activity parameters (e.g. joint swelling) in deciding whether or not to escalate DMARDs.

Both physicians and patients discussed the role of numerous additional factors which we divided into 4 categories: rheumatologist-related, patient-related, medication-related and organisational-related (see Figure 1). Rheumatologists felt, for example, that patient willingness to change, coping behaviour, age and patients' experiences with medication changes in the past, were important in their decision. RA patients emphasized that the route of administration, side effect profile and the availability of other options to relieve symptoms were important in their decision. The complete list of factors discussed in the focus groups is illustrated in Figure 1.

Conclusion: Besides disease activity there are many other reasons influencing the decision whether or not to escalate DMARDs which were described by 5 categories. RA patients and rheumatologists consider different factors in their decision. These findings are a first attempt to explain why medication is often not escalated in patients with moderate or high disease activity and will guide future quantitative methods to improve quality of care in RA in daily clinical practice.

Figure 1. Overview of considerations regarding escalation of DMARDs



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RAPID3 and Component Measures Are as Likely as a DAS28 and Component Measures to Identify Patients with Rheumatoid Arthritis (RA) Who Have Moderate/High Disease Activity Versus Low Activity at Presentation. Theodore Pincus[1] and C.J. Swearingen[2], [1]NYU Hospital for Joint Diseases, New York, NY, [2]MUSC, Charleston, SC

Purpose: To analyze two indices, DAS28 (disease activity score) and RAPID3 (routine assessment of patient index data), and their component measures for capacity to identify moderate/high disease activity versus low activity/remission in new patients with rheumatoid arthritis (RA) at presentation. RAPID3 is scored in ~10 seconds, versus 113 seconds for the DAS28.

Method: All patients seen at a weekly rheumatology clinic over a 25-year period from 1980 to 2004 completed a self-report questionnaire which evolved from a health assessment questionnaire (HAQ) to a multidimensional HAQ (MDHAQ). Scores for physical function (MDHAQ-FN) and pain (PN) were included on all versions of the HAQ/MDHAQ. A patient global estimate of status (PTGL) was added in 1996 to provide for a DAS28, based on swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR) and PTGL, and a RAPID3 score, based on 3 self-report measures from the Core Data Set for FN, PN and PTGL. A formal 28SJC and 28TJC were performed at certain periods, with no selection for disease severity. Values to identify moderate/high activity were regarded as >2 for SJC, TJC, and PN and PTGL on visual analog scales (0-10), >0.5 for MDHAQ-function (0-3), >28 mm/h for ESR, >3.2 for DAS28 (0-10), and >6 for RAPID3 (0-30) or RAPID3-EST (RAPID3 not including PTGL, also on a 0-30 scale, correlated with RAPID3 at r □ 0.9). The number of patients who had values greater or less than the cutpoints to define moderate/high activity was calculated for each measure and index.

Results: Overall, 82.0% of patients had moderate/high activity according to DAS28 >3.2, and 84.5% according to RAPID3 or RAPID3-EST >6 at first visit. All individual component measures indicated moderate/high activity in >80% of new patients, other than MDHAQ-function in 70.1% and ESR in 52.6% of new patients.

Table. Measurements at first clinic visit of 487 RA patients

	Range	Moderate/ High Cutpoint	Disease Activity (% new patients)	
			Low	Moderate/High
DAS28	0-10	>3.2	18.0%	82.0%
RAPID3 or RAPID3-EST	0-30	>6	15.5%	84.5%
SJC	0-28	>2	16.4%	83.6%
TJC	0-28	>2	21.0%	79.0%
ESR (mm/h)	0-150	>28	47.4%	52.6%
MDHAQ-FN	0-3	>0.5	29.9%	70.1%
PAIN	0-10	>2	15.1%	84.9%
PTGL	0-10	>2	15.0%	85.0%

Conclusion: RAPID3 is as sensitive as DAS28 to identify patients with moderate/high activity in RA who should be considered as candidates for disease-modifying antirheumatic drugs (DMARD), and ultimately biologic agents if persistently high, based on an incomplete response to therapy. These data add further evidence to the value of RAPID3 as an index to monitor status of patients with RA in usual care.

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Glucocorticoid-Induced Osteoporosis Program (GIOP): A Highly Successful Care Program with Improved Patient Outcomes After 2 Years. Cynthia K. Matzko[1], Eric D. Newman[1], Thomas P. Olenginski[1], Thomas M. Harrington[1], Gwynne L. Maloney-Saxon II[1] and G. Craig Wood[2], [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA

Purpose: Chronic glucocorticoids (GC) users have a high risk of osteoporotic fracture and their osteoporotic care is often suboptimal. Our Rheumatology Department designed a program of care called GIOP (Glucocorticoid-Induced Osteoporosis Program). GIOP uses electronic tools, pathways of care, and dedicated personnel to provide comprehensive osteoporosis care. We report on the first 200 patients entered and their 2 year follow-up.

Method: GIOP candidates were any patients taking GC ≥3 months. Baseline evaluation included demographics, patient knowledge (pre-test), GC use, 25-OH Vitamin D level, DXA, and vertebral fracture analysis (VFA) or spine X-rays. High-risk was defined as T-score below -1.0 or prevalent vertebral fracture. All patients were educated and instructed to take adequate calcium/Vitamin D, do weight bearing exercise, and implement safety strategies. Patients with Vitamin D levels below 30ng/ml were prescribed 50,000 IU supplementation. High-risk patients were prescribed medication. Patient knowledge (post-test), Vitamin D level, medication use and adherence were reassessed at 6 months, 12 months and 2 years.

Results: At baseline (n=200), the mean age was 62.7 ± 12.7 years and 68.5% of the patients were women. Personal history of fracture was seen in 9.5% of patients (2.5% hip, 4.0% spine, 2.5% wrist). The mean GC duration was 5.9 ± 7.1 years and the mean daily dose ranged from 2.5 to 15 mg of prednisone for 84% of the patients. Vitamin D levels of <30 ng/ml were seen in 74% of patients. Baseline DXA, VFA, and spine X-rays categorized 70.5% of GC patients as High-risk. Two year paired follow-up data was available in 132 patients (17 died, 5 refused follow-up, and 46 unavailable). Test scores and vitamin D levels improved significantly (p= 0.001) (Table). Forty-four % of patients were taking a lower dose of steroid at 2 years compared with baseline (p=0.001). Overall adherence to calcium, vitamin D, and prescription medication (if indicated) was 97% at 2 years. Adherence specifically to bisphosphonates or teraparatide was 99% at 2 years.

Of the 132 patients with 2-year follow-up, a baseline and at least 1 follow-up DXA were available for 128 (97%). An increase in BMD at the spine of 2.66% ($p<0.0001$) was seen for the population overall and 3.63% for the high risk patients on medication ($p<0.0001$). Over the two year follow-up, 18 of the 132 patients (14%) sustained a hip, spine, or wrist fracture (hip: n=1, spine: n=17, wrist: n=2; Table). Of these 18 patients, 8 (45%) also had a fracture at baseline.

Conclusion: Most patients entering GIOP are vitamin D deficient, high-risk and require treatment. Significant improvement was observed and sustained over 2 years in patient knowledge, Vitamin D levels following GIOP program treatment, and BMD at the spine. The mean daily steroid dose decreased. Despite the aging, high risk population, only a small percentage of patients sustained a fracture. Overall adherence to the prescribed regimen was excellent at 2 years. This well-organized, patient-centric program represents a highly successful model to improve bone health in patients requiring chronic GC.

	Baseline	2 Years
Test Scores	69 ± 21	88 ± 14
Vitamin D (ng/ml)	20.6 + 11.0	41.1 + 13.6
Patients with fracture		
Hip	2.5%	0.8%
Spine	16.0%	12.9%
Wrist	0.0%	1.5%
Any of above	18.5%	13.6%

Disclosure: C. K. Matzko, None; **E. D. Newman**, None; **T. P. Olenginski**, None; **T. M. Harrington**, None; **G. L. Maloney-Saxon**, None; **G. C. Wood**, None.

ACR Concurrent Abstract Sessions

RA Therapy: Novel Therapies in the Pipeline

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

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AIN457 Shows a Good Safety Profile and Clinical Benefit in Patients with Active Rheumatoid Arthritis (RA) Despite Methotrexate Therapy: 16-Weeks Results From a Randomized Proof-of-Concept Trial. Paul P. Tak[1], P. Durez[2], JJ. Gomez-Reino[3], B. Wittmer[4], V. Chindalore[5], F. Di Padova[6], AM. Wright[6], G. Bruin[6] and W. Hueber[6], [1]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [2]University of Louvain, Brussels, Belgium, [3]University Clinical Hospital, Santiago de Compostela, Spain, [4]Commonwealth Biomedical Research, Madisonville, KY, [5]Pinnacle Research Group, Anniston, AL, [6]Novartis Pharma AG, Basel, Switzerland

Purpose: AIN457 is a fully human IgG1κ monoclonal anti-IL17 antibody that selectively neutralizes IL-17A. IL-17 is overexpressed in synovial tissues in RA and preclinical studies support that IL-17A is a key driver of synovial inflammation and degradation of cartilage and bone. This study explores IL-17A blockade with AIN457 as a novel therapeutic approach to RA. The objective is to determine the safety, tolerability and initial evidence of clinical efficacy of AIN457 in patients with active RA despite methotrexate (MTX) therapy up to 16 weeks.

Method: This was a multicenter, randomized, double blind, parallel-group study. A total of 52 patients with active RA received either, 2 doses of 10 mg/kg AIN457 (*N*=26) three weeks apart or placebo (*N*=26). All patients were followed up to 16 weeks. This abstract expands on the previously reported 6-week results to include secondary endpoints and response rates up to 16 weeks.

Results: Patients characteristics at baseline were comparable between AIN457 and placebo groups (mean age 49.9 *vs* 49.8 yrs, median disease duration 3.9 *vs.* 2.9 yrs; median weekly MTX dose 15 mg *vs.* 12.5 mg, mean DAS28 score 5.88 *vs.* 5.84, mean tender joint count 17.6 *vs.* 17.1, mean swollen joint count 11.6 *vs.* 11.1, median C-reactive protein (CRP) 7.6 *vs.* 9.8 mg/L). AIN457 was well tolerated and has a favorable consistent PK profile with a long elimination half life of 23 days. Adverse event types and incidence rates were comparable

between the groups, with a slightly higher frequency in the AIN457 group (81% *vs.* 65%). The overall rate of infections was identical in the AIN457 and placebo group (9 events [35%] in each). No cases of neutropenia or immunogenicity were reported. Exploratory analysis showed that a greater percentage of patients treated with AIN457 2x10mg/kg achieved an ACR20 response over 16 weeks compared to placebo [*P*=0.08] (Table 1). Both ACR50 and ACR70 rates showed numerical improvements with AIN457 compared to placebo. DAS28 assessment showed greater reductions with AIN457 2x10mg/kg compared to placebo over the16-weeks period (EULAR response rates are shown in Table 1). AIN457 induced fast onset of response and sustained reductions in CRP levels through week 16 (Figure 1). This was paralleled by improvements in the patient global assessment (PGA) (Figure 2) and HAQ scores.

Conclusion: The good safety, rapid onset and encouraging efficacy of AIN457 suggest a novel therapeutic concept with the potential for improved patient outcomes. These positive results support development of AIN457 in RA and potentially other immune-mediated disorders.

Table 1: Rates of ACR and DAS28-based EULAR response in the treatment groups

Weeks since dosing	AIN457 10mg/kg (*N*=26)			Placebo (*N*=26)		
	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
16	14(54%)	7(27%)	2(8%)	8(31%)	4(15%)	0(0%)

Weeks since dosing	AIN457 10mg/kg (*N*=26)			Placebo (*N*=26)		
	None	Moderate	Good	None	Moderate	Good
16	10(38%)	8(31%)	8(31%)	16(62%)	5(19%)	5(19%)

Figure 2. Geometric mean (+/- SE) CRP concentrations over time in the treatment groups.

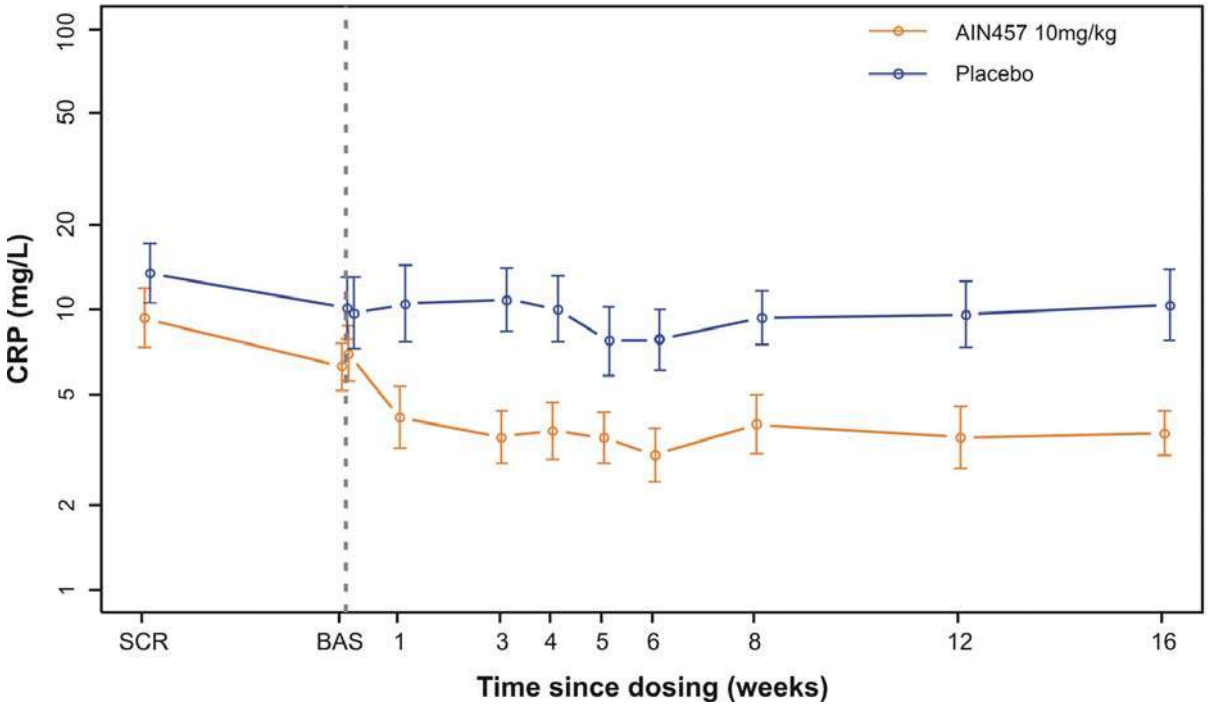
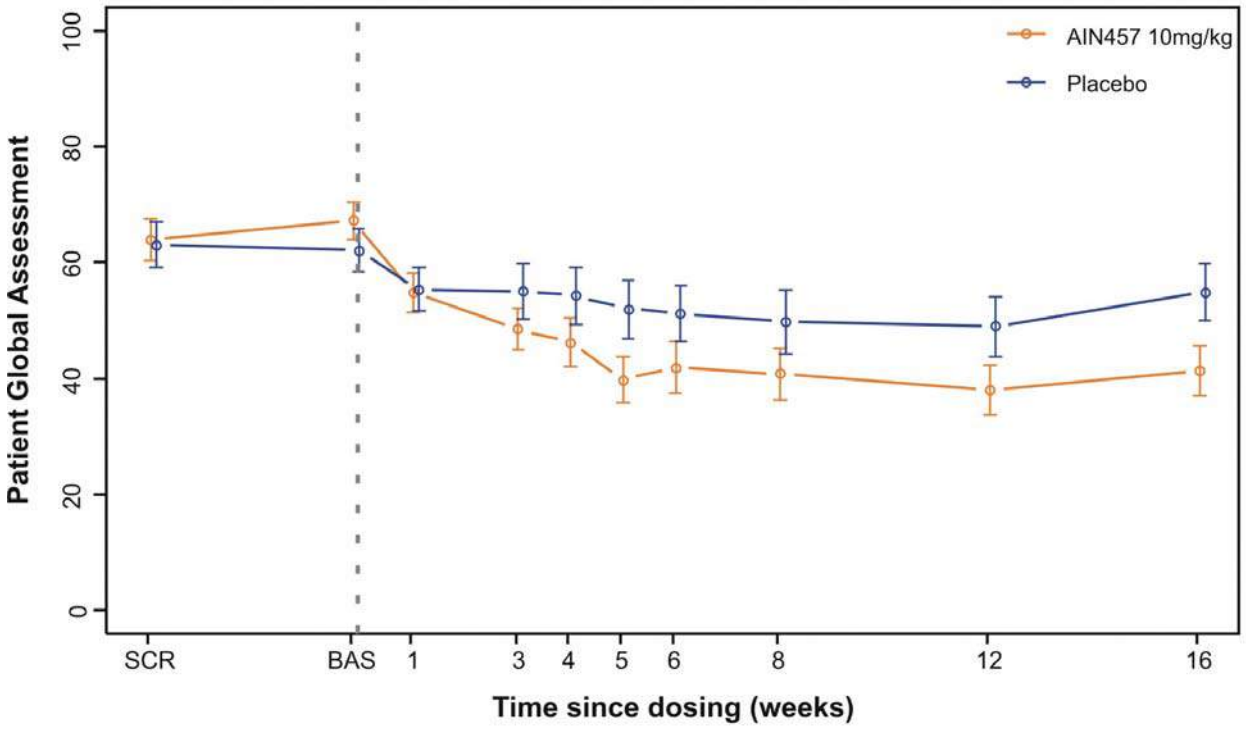


Figure 2. The mean (+/- SE) patient global assessment score over time in the treatment groups



Disclosure: P. P. Tak, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5 ; **P. Durez**, None; **J. Gomez-Reino**, Roche Pharmaceuticals, Schering Plough, 5, Roche Pharmaceuticals, Schering Plough, Bristel-Myers Squibb, Abbott, 8 ; **B. Wittmer**, Novartis Pharmaceutical Corporation, 5 ; **V. Chindalore**, Novartis Pharmaceutical Corporation, 5 ; **F. Di Padova**, Novartis Institutes for Biomedical Research, 3 ; **A. Wright**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1 ; **G. Bruin**, Novartis Pharmaceutical Corporation, 3 ; **W. Hueber**, Novartis Pharmaceutical Corporation, 3 .

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Phase 2 Study of Safety and Efficacy of a Novel Anti-BAFF Monoclonal Antibody, in Patients with RA Treated with Methotrexate (MTX). MC Genovese[1], E. Mociran[2], M. Biagini[3], S. Bojin[4] and J. Sloan-Lancaster[5], [1]Stanford U, Palo Alto, CA, [2]County Hospital, Baia Mare, Romania, [3]County Hospital, Bacau, Romania, [4]County Hospital, Covasna, Romania, [5]Eli Lilly, Indianapolis, IN

Purpose: B cell activating factor (BAFF) is a survival factor for peripheral B lymphocytes which exists in both cell surface and soluble forms. Dysregulated BAFF expression may contribute to autoimmune diseases via effects on abnormal B lymphocyte activation, proliferation, survival, and immunoglobulin secretion. LY2127399 is a novel monoclonal antibody binding both cell surface and soluble BAFF. This study was designed to explore the tolerability and efficacy of LY2127399 in Pts with active RA.

Method: This was a 24-week, randomized, placebo-controlled, double-blind study which enrolled 136 Pts with active RA despite treatment with MTX. Pts continued stable doses of MTX and received 1 of 3 dose levels (30, 60, or 160 mg) of LY2127399 or placebo (PBO) intravenously for a total of 3 doses at 3-week intervals (Weeks 0, 3, 6). Response was assessed for efficacy, PK/PD and safety. The primary endpoint was ACR20 response vs. PBO at Week 16.

Results: ACR20/50/70 and DAS28 responses showed that RA signs and symptoms improved more in Pts at each LY2127399 dose as compared with PBO. The primary objective was achieved at all LY2127399 treatment levels (Table; one-sided χ^2 test no adjustment for multiplicity), and ACR20 treatment differences remained significant at end of study (69.7%, 67.6% and 63.6% for 30, 60, 160mg respectively vs. 26.5% for PBO, $p \leq 0.001$). Initial transient increases were shown in total ($CD20^+$) B cells in all LY2127399 treatment

groups, followed by significant reductions. Importantly, B cells were not completely depleted. Mean reductions at Week 24 were 33.5%, 50.8% and 33.3% for $CD20^+$ B cells, and 35.8%, 66.9% and 63.6% for $IgD^+/CD27^-$ B cells, for the 30, 60 and 160 mg treatment groups respectively, vs. 18.3% and 17.7% respectively for placebo. Memory ($IgD^-/CD27^+$) B cells also increased in all LY2127399 groups compared with PBO by Week 1, with a return toward baseline by end of study. The nature and frequency (41% to 44%) of AEs were similar across groups; serious AEs were reported in 5 (4.9%) LY2127399- Pts and 3 (9.1%) PBO- Pts; serious infection was reported in 1 (1.0%) LY2127399- Pts and 1 (3.0%) PBO- Pts. IgM levels decreased significantly more in all LY2127399 groups combined vs. PBO; decreases in mean IgG and IgA levels were not significant compared with PBO.

Wk 16 results	**LY2127399 (30 mg) n=34**	**LY2127399 (60 mg) n=34**	**LY2127399 (160 mg) n=34**	**PBO n=34**
ACR20 (Primary) % (p value)	57.6 (0.010)	67.6 (<0.001)	51.5 (0.033)	29.4
ACR50 % (p value)	42.4 (<0.001)	32.4 (0.008)	21.2 (0.077)	8.8
ACR70 % (p value)	12.1 (0.018)	8.8 (0.038)	3.0 (0.153)	0.0
Mean ACR-N % (p value)	35.1 (0.001)	34.8 (0.001)	25.8 (0.101)	14.1
Pts with DAS28 <2.6 %	9.1	14.7	0.0	0.0
Change in DAS28 LS Mean (p value)	-1.54 (<0.001)	-1.84 (<0.001)	-1.41 (0.001)	-0.58
Change in CD20 B Cells (Cells/uL) LS Mean [baseline] (p value)	-75.7 [129.7] (<0.001)	-48.4 [197.1] (0.012)	-40.5 [152.8] (0.040)	-3.6 [173.9]

Conclusion: LY2127399 given intravenously as 3 infusions was well-tolerated and reduced the signs and symptoms of RA. Reduction of RA symptoms was not contingent upon complete B cell depletion. These results support further dose exploration of LY2127399 in RA.

Disclosure: M. Genovese, Eli Lilly, 5 ; **E. Mociran**, None; **M. Biagini**, None; **S. Bojin**, None; **J. Sloan-Lancaster**, Eli Lilly, 3, Eli Lilly, 1 .

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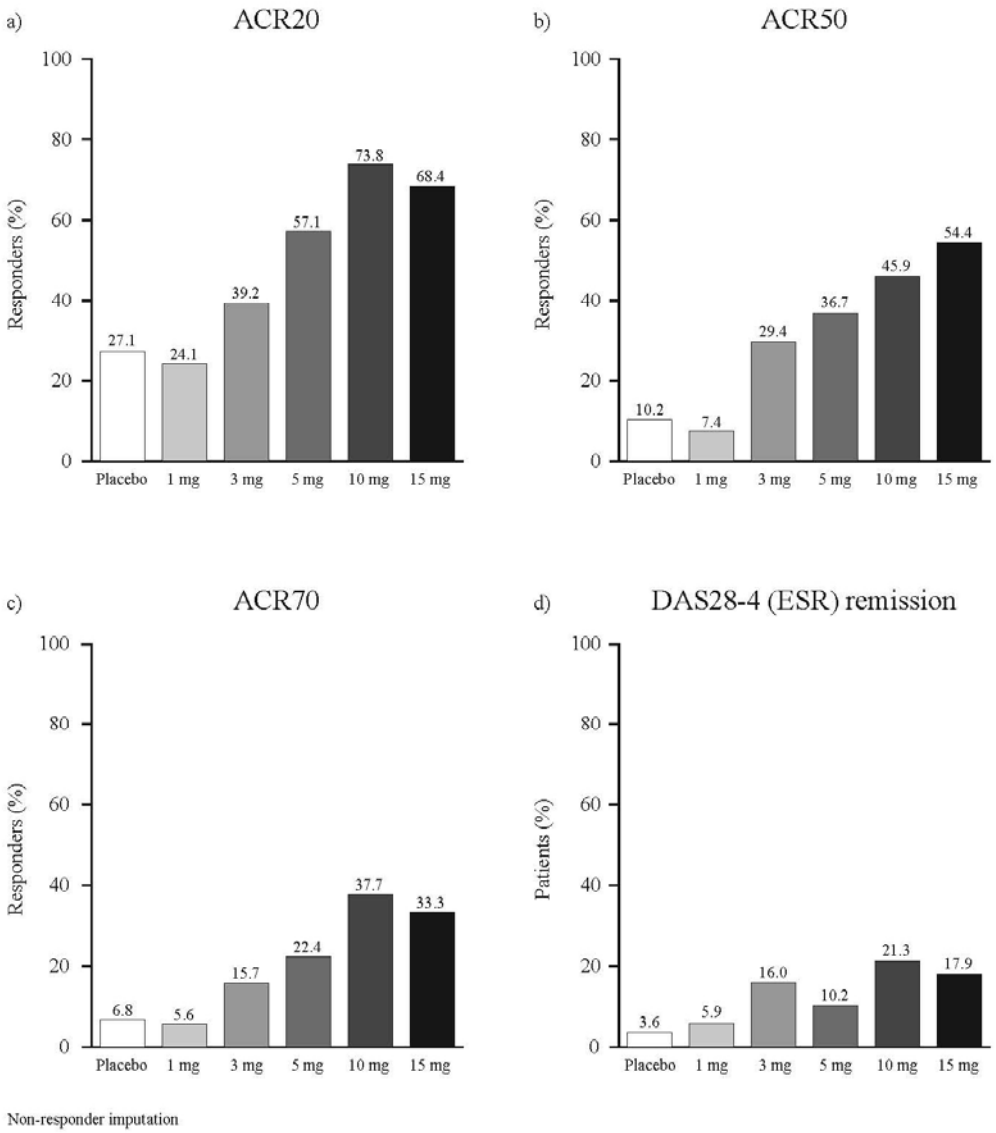
Safety and Efficacy After 24 Week (wk) Dosing of the Oral JAK Inhibitor CP-690,550 (CP) as Monotherapy in Patients (pts) with Active Rheumatoid Arthritis (RA). R.M. Fleischmann[1], M.C. Genovese[2], D. Gruben[3], K.S. Kanik[3], G.V. Wallenstein[3], B. Wilkinson[3], S.H. Zwillich[3] and J. Frain[4], [1]Metroplex Clinical Research Center, Dallas, TX, [2]Stanford University, Palo Alto, CA, [3]Pfizer Inc, New London, CT, [4]Complete Medical Communications, Macclesfield, United Kingdom

Purpose: To compare efficacy, safety, and tolerability of 5 doses of CP or adalimumab (ADA) monotherapy v PBO for treatment of RA in pts with inadequate response to DMARDS.

Methods: This study was a 6-month, double-blind, placebo-controlled Phase 2B study. Pts with active RA (≥6 tender/swollen joints, CRP >7 mg/L or ESR > ULN) were randomized to: CP 1, 3, 5, 10, 15 mg po BID, ADA 40 mg sc every 2 wks, or PBO. Pts receiving CP 1, 3 mg BID, or PBO not achieving ≥20% decrease from baseline in tender/swollen joint counts at Wk 12 were reassigned to CP 5 mg BID for the remainder of the study. All ADA pts were advanced to CP 5 mg BID monotherapy at Wk 12 and hence no ACR response rates for this group are reported after Wk 12. Data are from Wk 24 final analyses.

Results: 384 pts were randomized.

Figure 1. % responders for ACR20 (a), ACR50 (b), ACR70 (c) and DAS28-4(ESR) remission rate (d), at Wk 24



Non-responder imputation

25 (42%), 17 (32%), and 17 (33%) of placebo, 1 mg, and 3 mg BID dose groups respectively advanced to 5 mg at Wk 12 and counted as non–responders in the efficacy analysis. Previous interim results reported pts receiving 5, 10, and 15 mg CP BID consistently demonstrated statistically significant efficacy compared to placebo by ACR 20/50/70 and DAS28 at Wk12. Efficacy continued to be seen at each of these doses at Wk 24 (Fig 1).

208 (54.2%) pts experienced a total of 489 treatment emergent adverse events (TEAEs), and 14 experienced serious AEs (SAEs). The most common TEAEs across all CP arms (n=272) were UTI 20 (7.4%), diarrhea 13 (4.8%), headache 13 (4.8%) and bronchitis 12 (4.4%) and were more common at higher doses. Across all CP arms, 8 (3.0%) pts experienced SAEs. Serious infections were observed in 5 pts: 2 pts with pneumonia (CP 1 mg), 1 pt with pneumococcal pneumonia (CP 15 mg); 1 pt with acute pyelonephritis (ADA [after reassignment to CP 5 mg at Wk 12]); 1 pt with infection of ankle joint (PBO). There were 0 opportunistic infections, malignancies, or lymphomas. One pt died from stroke (CP 15 mg) not considered treatment-related.

6 pts experienced a confirmed >50% increase in serum creatinine levels from baseline (4 CP, 2 ADA; of the ADA pts, this increase occurred prior to reassignment to CP in 1 patient, and after reassignment in 1 patient). 6 (2.2%) pts on CP experienced confirmed severe anemia, and no pts experienced confirmed severe neutropenia (OMERACT criteria). The proportion of CP pts in 5, 10, 15 mg dose groups with LDL <130 mg/dl at baseline that increased to >130 mg/dl during the study were 29%, 36%, and 37%, respectively.

Conclusion: CP monotherapy dosed at 5 mg, 10 mg, and 15 mg BID demonstrated sustained efficacy at the Wk 24 study visit in pts with active RA; and a manageable safety profile.

Disclosure: R. M. Fleischmann, Abbott, Amgen, Wyeth, Celgene, Centocor, Roche, Genentech, Pfizer, Lilly, UCB, Regeneron, Array, 2, Amgen, Wyeth, Celgene, Centocor, Roche, Pfizer, Lilly, UCB, Lexicon, GSK, 5 ; **M. C. Genovese**, Pfizer Inc, 5, Pfizer Inc, 2 ; **D. Gruben**, Pfizer Inc, 3, Pfizer Inc, 1 ; **K. S. Kanik**, Pfizer Inc, 3 ; **G. V. Wallenstein**, Pfizer Inc, 3 ; **B. Wilkinson**, Pfizer Inc, 3 ; **S. H. Zwillich**, Pfizer Inc, 3 ; **J. Frain**, None.

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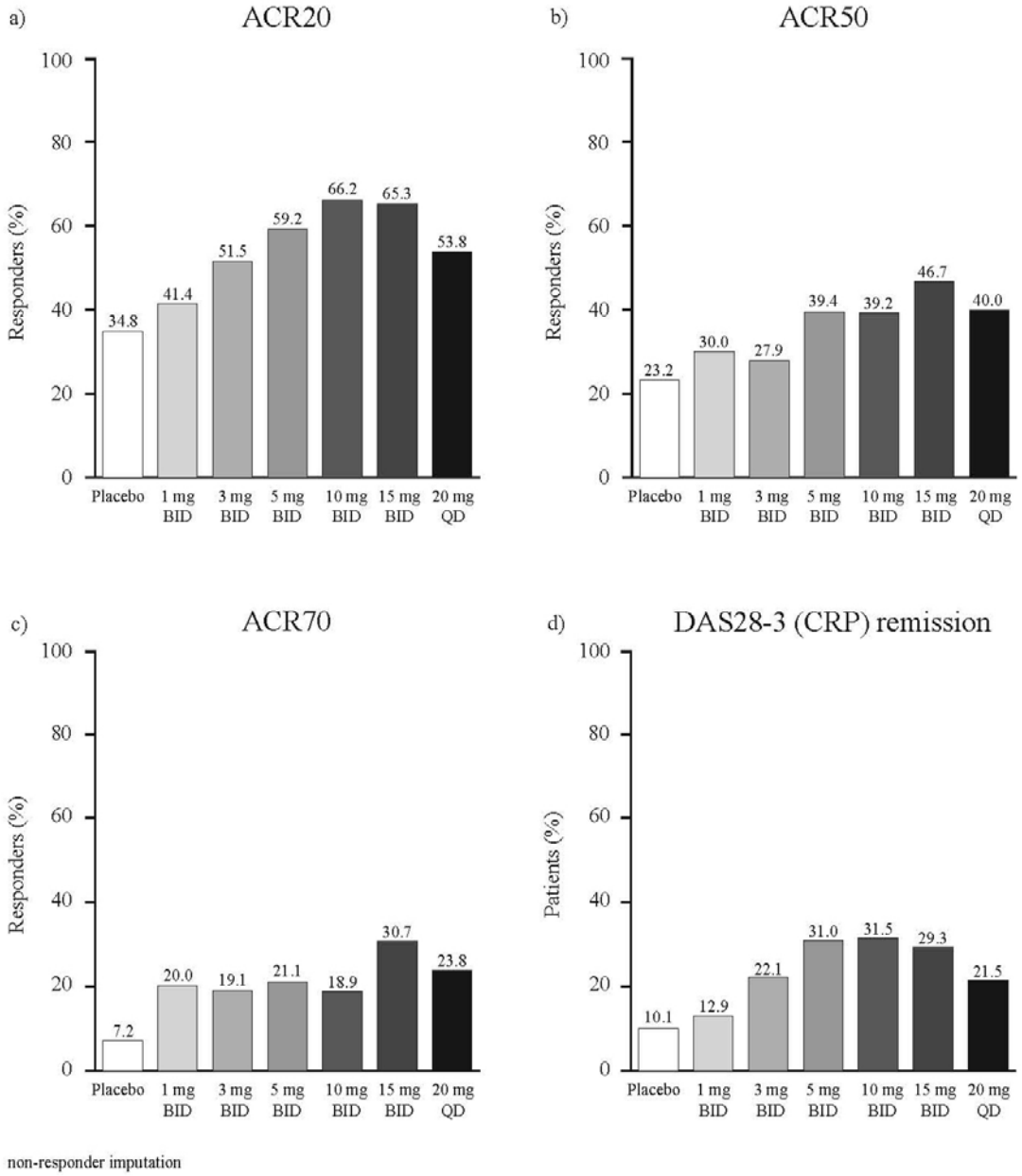
Safety and Efficacy After 24 Week (WK) Dosing of the Oral JAK Inhibitor CP-690,550 (CP) in Combination with Methotrexate (MTX) in Patients (PTS) with Active Rheumatoid Arthritis (RA). J. Kremer[1], S. Cohen[2], B. Wilkinson[3], D. Gruben[3], G.V. Wallenstein[3], K.S. Kanik[3], S.H. Zwillich[3] and J. Frain[4], [1]Albany Medical College, Albany, NY, [2]Metroplex Clinical Research Centre, Dallas, TX, [3]Pfizer Inc, New London, CT, [4]Complete Medical Communications, Macclesfield, United Kingdom

Purpose: To compare the efficacy, safety, and tolerability of 6 doses of CP compared with placebo (PBO) for treatment of active RA in pts with an inadequate response to stable background MTX alone.

Methods: This was a 24-wk, double-blind, placebo-controlled Phase 2B study. Pts with active RA (≥6 tender/swollen joints, CRP >7 mg/L or ESR > ULN) were randomized to: CP 1, 3, 5, 10, 15 mg BID, 20 mg QD, or PBO. Pts receiving CP 1 mg BID, 3 mg BID, 20 mg QD, or PBO not achieving ≥20% decrease from baseline in tender and swollen joint counts at Wk 12 (non-responders) were reassigned to CP 5 mg BID for the rest of the study (13-21 per arm). Pts remained on stable background MTX of 7.5 to 25 mg/wk. Data are from Wk 24 final analyses.

Results: 507 pts were randomized.

Figure 1. % responders for ACR20 (a), ACR50 (b), ACR70 (c) and DAS28-3(CRP) remission rate (d), at Wk 24



non-responder imputation

18 (26%), 21 (30%), 13 (19%) and 13 (16%) of PBO, 1 mg BID, 3 mg BID and 20 mg QD dose groups, respectively, were advanced to 5 mg BID at Wk 12 (non–responders in efficacy analysis). Previous interim results reported pts receiving 3 mg BID and higher had statistically significant efficacy compared with placebo by ACR 20/50/70 and DAS28 at Wk 12. Efficacy was seen at doses of 5 mg BID and higher at Wk 24 (Fig 1).

Overall, 188 (37.1%) pts had a total of 896 treatment emergent adverse events (TEAEs), and 21 (4.1%) had serious AEs (SAEs). The most common TEAEs across all CP arms (n=438) were: UTI 27 (6.2%), headache 26 (5.9%), diarrhea 25 (5.7%), nasopharyngitis 24 (5.5%), and nausea 21 (4.8%) and were more common at higher doses. The most common TEAEs across the PBO arm (n=69) were: UTI 3 (4.3%), nasopharyngitis 3 (4.3%), and pharyngitis 3 (4.3%).

5 (1.0%) pts had serious infections: 3 pneumonia (CP 3 mg BID, 5 mg BID and 20 mg QD), 1 UTI (CP 3 mg BID), and 1 respiratory tract infection (CP 10 mg BID). There were no opportunistic infections, malignancies, or lymphomas. One pt with treatment related pneumonia (CP 3mg BID) died due to complications of respiratory and cardiac failure.

6 pts had confirmed >50% increase in serum creatinine levels from baseline (5 pts in CP groups and 1 pt in PBO [reassigned to CP 5 mg BID at Wk 12]), none discontinued. 13 pts on CP and 1 pt on PBO had confirmed severe anemia (OMERACT criteria, none discontinued), and no pts had confirmed severe neutropenia (OMERACT criteria, none discontinued). There was a dose response in increases in LDL with the highest doses having the highest increase; the proportion of CP pts with a LDL <130 mg/dl at baseline that increased to >130 mg/dl at any time during the study ranged from 32% to 42% for the highest doses. 5 pts had elevations in ALT>3xULN (4 pts CP 15 mg BID and 1 pt each CP 10 mg BID, CP 20 mg QD, and PBO).

Conclusion: In pts with active RA despite MTX, CP dosed at 5 mg, 10 mg, and 15 mg BID showed sustained efficacy and a manageable safety profile through 24 wks.

Disclosure: J. Kremer, Abbott, Amgen, BMS, Centocor, Genentech, Pfizer, UCB, 2, BMS, Centocor, Pfizer, UCB, 5 ; **S. Cohen**, Pfizer Inc, Amgen, Wyeth, Proctor and Gamble, Genentech, Biogen-Idec/Roche, 2, Genentech/Roche/Amgen/ Biogen-Idec, 5 ; **B. Wilkinson**, Pfizer Inc, 3 ; **D. Gruben**, Pfizer Inc, 3 ; **G. V. Wallenstein**, Pfizer Inc, 3 ; **K. S. Kanik**, Pfizer Inc., 3 ; **S. H. Zwillich**, Pfizer Inc, 3 ; **J. Frain**, None.

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Cam-3001: A Novel Human Monoclonal Antibody against GM-CSFR-á, in Subjects with Rheumatoid Arthritis (RA)-Results of a Phi Study. Gerd-R. Burmester[1], Frank Wagner[2], Eugen Feist[3], Matthew Sleeman[4], Fabio Magrini[5] and Barbara White[6], [1]Charite, University Medicine Berlin Free University and Humboldt University of Berlin, Berlin, Germany, [2]Charité Research Organisation GmbH, Berlin, Germany, Berlin, Germany, [3]Charite University Hospital, Berlin, Germany, [4]MedImmune Ltd, Cambridge, United Kingdom, [5]Medimmune, Cambridge, United Kingdom, [6]Medimmune, Gaithersburg, MD

GM-CSF is thought to play a significant role in RA. Elevated levels of GM-CSF have been shown in tissue biopsies and synovial fluid from arthritic patients. Furthermore, recombinant GM-CSF has shown to exacerbate disease in RA patients undergoing treatment for neutropenia (1). Using phage display we developed a human monoclonal antibody (CAM-3001) to the GM-CSFR alpha chain that neutralizes GM-CSF activity. We describe the results of a Phase I single ascending dose of CAM-3001 in RA.

Purpose: The primary objective was to assess the safety and tolerability of CAM-3001 in patients with RA. Other objectives included the pharmacokinetics of CAM-3001 and the effect on biomarkers of systemic inflammation.

Method: Thirty-two subjects with mild or inactive RA (DAS28 ≤4.8) on stable methotrexate (≥3 months) received single i.v. doses of CAM-3001 or placebo in ascending doses of 0.01 and 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg. Safety was assessed throughout the study by evaluation of clinical and laboratory parameters.

Results: Adverse events were generally mild or moderate, and balanced between placebo and active treatments with no dose-relationship. There were two treatment-emergent serious adverse events (bilateral hernia, and breast cancer), neither of which was considered related to study drug. Mild transient neutropenia was seen in two subjects, and mild transient elevation of hepatic enzymes was also seen in two subjects. One subject experienced moderate urticaria of the face and neck during the infusion. Pulmonary function was also monitored and showed no clinically significant changes over the study period. Although the study was not designed to demonstrate clinical efficacy, post-hoc analysis of individual subjects with elevated CRP (>5mg/L) and ESR (>20mm/hr) at baseline showed reductions in CRP or normalization of ESR within the first 3 weeks post infusion, suggesting a potential benefit in RA. The pharmacodynamic activity of CAM-3001 pre and post dosing was also confirmed using an ex vivo GM-CSF-induced SOCS3 RT-PCR assay.

Conclusion: This is the first reported clinical study of a monoclonal antibody targeting the GM-CSF pathway in patients with rheumatoid arthritis. In this study, we show that CAM-3001 has an acceptable safety profile. Furthermore, the effects observed on acute phase reactants

following single infusion of CAM-3001 suggest a potential effect on disease activity. This will be formally investigated in future clinical studies.

References: 1) Hamilton JA Nat Rev Immunol 2008; 8: 533-44. 2) Pereira J. Acta Haematol 1994;92: 154-56.

Sponsored by MedImmune.

Disclosure: G. R. Burmester, None; **F. Wagner**, None; **E. Feist**, None; **M. Sleeman**, MedImmune, 3 ; **F. Magrini**, Medimmune Ltd, 3 ; **B. White**, Medimmune LLC, 3 .

1927

CH-1504: A Metabolically Inert Antifolate, Is An Effective and Well-Tolerated Treatment for Patients with Moderate to Severe Rheumatoid Arthritis. Edward C. Keystone[1], Lawrence A. Hewitt[2], Lee S. Simon[3], Valery Shirinsky[4] and Simon Pedder[2], [1]Professor of Medicine/University of Toronto, Toronto, ON, [2]Chelsea Therapeutics, Charlotte, NC, [3]Harvard Medical School, West Newton, MA, [4]RAMS, Novosibirsk, Russia

Purpose: Methotrexate (MTX) treatment of rheumatoid arthritis (RA) is often associated with side-effects and/or safety concerns. MTX metabolites are thought to play a significant role in MTX toxicity. Therefore, theoretically, a metabolically inert antifolate such as CH-1504, should be safer and better tolerated while providing comparable efficacy. We report results of a phase II clinical trial designed to show "Proof of Concept" for this class of compounds.

Methods: MTX naïve patients (N=201) with moderate to severe RA were enrolled in this 16 week, multi-center, randomized and double-blind study. Patients received either CH-1504 (0.25mg, 0.5mg or 1.0mg once daily oral doses) or MTX (titrated to 20.0mg once weekly). All patients received a once weekly 10mg folate supplement. Observations were made at 2, 4, 8 and 12 weeks with a treatment free follow-up at 16 weeks. The primary efficacy endpoint of the study was the ACR20 response at week 12. Secondary endpoints included DAS28 scores and the individual components of the ACR20 composite index as well as the safety and tolerability of treatment.

Results: Demographic parameters were similar in the 4 treatment groups with a mean age at enrollment for the entire study population of 54.3 ± 11.4 years, a majority being female (87%) and a mean DAS28 was 6.6 ± 0.9. At week 12 all CH-1504 treatment groups showed comparable efficacy to MTX as measured by ACR20 and DAS28 response rates. This was also seen in the key indicator sub components of the composite index including tender and swollen joints. A dose-response relationship over the dose range tested was not observed in the timeframe of this trial.

	MTX	CH-1504		
	20mg weekly	0.25mg daily	0.5mg daily	1.0mg daily
Patient Number	52	48	48	53
Efficacy				
ACR 20	38.5 %	43.8%	39.6%	34.0%
Patients with > 20% Reduction in SJC	73.1%	70.8%	83.3%	79.2%
Patients with > 20% Reduction in TJC	65.4%	58.3%	62.5%	71.7%

Mean change in DAS28	- 1.4	- 1. 0	-1.2	-1.1
Safety/Tolerability				
% Patients with ALT (>1 X ULN)	13.5	4.2	6.3	7.5
% Patients with GI related AEs	5.8	2.1	4.2	3.8
% Patents withdrawn for GI AEs	3.8	0	0	0

CH-1504 appeared safe and well tolerated at all dose levels. Adverse events (AEs) were generally mild in all arms of the study. The % of patients with serum ALT elevations above 1X upper limit of normal was lower at all doses of CH-1504 compared to MTX. The % of patients with, and dropouts because of, GI related AEs were lower at all doses of CH-1504 compared to MTX.

Conclusion: This 16 week proof-of-concept study in MTX-naïve RA patients demonstrated that CH-1504 has comparable efficacy to MTX and may be safer and better tolerated. Metabolically inert antifolates are a promising therapeutic option and warrant further study.

Disclosure: E. C. Keystone, Independant, 5 ; **L. A. Hewitt**, Chelsea Therapeutics, 3 ; **L. S. Simon**, Independant, 5 ; **V. Shirinsky**, Institute of Clinical Immunology RAMS, 5 ; **S. Pedder**, chelsea therapeutics, 3 .

ACR Concurrent Abstract Sessions

Systemic Lupus Erythematosus Outcomes-Cardiovascular and Other Outcomes

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

1928

Effect of Rosuvastatin On Homocysteine, hsCRP and Endothelial Markers in Systemic Lupus Erythematosus (SLE): A Randomized Controlled Trial. Chi Chiu Mok[1], Judy Lai[1], Chun Kwok Wong[2], Christopher Lam[3] and Cheuk Sum Lam[1], [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Department of Chemical Pathology,The Chinese University of Hong Kong,Prince of Wales Hospital, Shatin, NT, Hong Kong, [3]Chinese University of Hong Kong, Hong Kong, Hong Kong

Purpose: A randomized controlled trial to study the effect of rosuvastatin (crestor) therapy on homocysteine, hsCRP and markers of endothelial activation / injury in patients with stable SLE

Methods: Asymptomatic SLE patients who had coronary calcification (Agatston score ≥1) or Doppler ultrasound documented abnormal carotid intima-media thickness (IMT) (≥0.8mm at any site) were recruited and randomized in a double-blinded manner into 2 treatment arms: (1) rosuvastatin (10mg/day); or (2) placebo (one tab/day) for 12 months. Levels of homocysteine, hsCRP, sVCAM-1, P-selectin and thrombomodulin were measured at baseline, month 6 and month 12. SLEDAI scores were assessed at 2-month intervals.

Results: 72 patients were studied (97% women). The mean age was 50.8±9.7 years and SLE duration was 11.8±7.1 years. At baseline, their mean Agatston score was 30.9±68 and carotid IMT (all sites) was 0.67±0.13mm. The mean SLEDAI score was 1.68±1.7. The prevalence of traditional risk factors is as follows: smoking(10%), menopause(57%), diabetes mellitus(3%), hypertension(33%). Antiphospholipid antibodies were present in 28% of patients. 36 patients were randomized to receive rosuvastatin and 36 patients were randomized to the placebo arm. No statistically significant differences in clinical characteristics and baseline levels of the biomakers were observed at baseline. At month 12, a significant drop in total and LDL-cholesterol level was observed in the crestor but not in the placebo arm. The changes in the levels of the vascular / endothelial markers over time were summarized below:

Markers	Arms	baseline	Month 6	Month 12	*P
Homocysteine (umol/L)	Crestor	15.2±5.2	14.0±4.5	14.8±5.1	0.50
	Placebo	13.9±3.6	13.4±3.3	14.2±3.7	0.68

hsCRP (mg/L)	Crestor	2.58±2.7	3.07±5.71	1.64±2.0	0.009
	Placebo	3.92±10.6	3.96±9.2	5.19±9.94	0.33
sVCAM-1 (ng/mL)	Crestor	717±410	738±405	883±650	0.11
	Placebo	898±610	809±467	803±472	0.19
P-selectin (ng/mL)	Crestor	47.2±18	48.6±19.2	51.4±17.7	0.27
	Placebo	47.4±18.8	52.5±24.6	51.2±18.4	0.06
Thrombomodulin (ng/mL)	Crestor	1.33±1.07	1.27±1.98	1.19±1.10	0.40
	Placebo	0.94±0.55	0.82±0.52	0.78±0.46	0.05

*P – comparison between baseline and month 12 by paired Students' t-test

A significant decrease in the level of hsCRP was observed in the crestor arm. The difference in hsCRP level between the crestor and placebo arms was significant at month 12 (p=0.03) after adjustment for baseline hsCRP values, risk factors and the mean SLEDAI score. Trend in the levels of other biomarkers was not apparent between the two groups.

Conclusion: In SLE patients with subclinical atherosclerosis, low dose rosuvastatin leads to a significant reduction in hsCRP level after 12 months' therapy and may be beneficial in reducing the risk of arterial thrombosis in the long-run.

Disclosure: C. C. Mok, None; **J. Lai**, None; **C. K. Wong**, None; **C. Lam**, None; **C. S. Lam**, None.

1929

Pihdl Is Associated with a 19- Fold Increased Risk of Progression of Subclinical Atherosclerosis in SLE. Maureen A. McMahon[1], Lori J. Sahakian[1], Jennifer M. Grossman[1], Brian J. Skaggs[1], John D. FitzGerald[1], Christina Charles-Schoeman[1], Nagesh Ragavendra[2], Alan H. Gorn[1], George A. Karpouzas[3], Elizabeth R. Volkmann[1], M. Weisman[4], D. Wallace[5] and B H. Hahn[1], [1]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]Harbor-UCLA Medical Center, Torrance, CA, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Cedars-Sinai Med Ctr, LA, CA

Purpose: Women with SLE have an unexplained increase in atherosclerosis (ATH). We previously reported that 45% of SLE women vs. 5% of controls have pro-inflammatory HDL (piHDL), and that piHDL confers a 16-fold increased risk for the concurrent presence of carotid artery plaque. It is unknown, however, whether piHDL predicts future progression of atherosclerosis. Here we hypothesize that baseline presence of piHDL is associated with longitudinal accumulation of subclinical atherosclerosis.

Methods: Female SLE and healthy age-and gender- matched subjects not taking statins were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24-36 months. Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL.

Results: Follow-up carotid ultrasounds were completed on 83 SLE women and 31 controls. Overall, 26.5% (22) of SLE patients had accumulation of new plaques vs. 16.1% (5) of controls ($p<0.0001$). Among the 22 SLE patients in our cohort with plaque progression, 20 (90.9%) had piHDL, compared to 47.5% of SLE patients with no new plaques ($p<0.0001$). Follow-up intima media thickness (IMT) was also higher in patients with piHDL at baseline than in those without; 0.62 ± 0.14 vs. 0.52 ± 0.07 ($p<0.0001$). After multivariate analysis, the only significant factors predictive of plaque progression in SLE were the baseline presence of piHDL, with an OR of 18.8 (95% C.I. 2.2 - 161.3, p=0.007), the baseline presence of plaque (OR 20.9, (95% C.I. 1.8 – 238.9, p=0.02), and increasing age (OR of 1.1; 95% C.I. 1.03 - 1.22, p=0.004).

Conclusion: piHDL has become apparent as a strong predictor for the future progression of subclinical atherosclerosis in women with SLE.

Disclosure: M. A. McMahon, None; **L. J. Sahakian**, None; **J. M. Grossman**, None; **B. J. Skaggs**, None; **J. D. FitzGerald**, None; **C. Charles-Schoeman**, None; **N. Ragavendra**, None; **A. H. Gorn**, None; **G. A. Karpouzas**, None; **E. R. Volkmann**, None; **M. Weisman**, None; **D. Wallace**, None; **B. H. Hahn**, None.

1930

Baseline EGFR Is Predictive of Arterial Vascular Events in Patients with Systemic Lupus Erythmatosus (SLE). Wendy Zhang[1], Elaheh Aghdassi[1], Heather Reich[1], James Scholey[1], Jiandong Su[2], Wendy Lou[2] and P. R. Fortin[3], [1]University Health Network, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of Toronto, Toronto Western Hospital, University Health Network, Toronto, ON

Purpose: To determine whether baseline renal functions predict the development of cardiovascular disease (CVD) in patients with SLE by using estimated glomerular filteration rate (eGFR).

Method: An inception cohort of 437 female patients was studied between 1970 and 2007. Baseline eGFR (mL/min/1.73m^2) was calculated using serum creatinine and the abbreviated Modification of Diet in Renal Disease Study Group formula (MDRD). Arterial vascular events (VE-A) including myocardial infarction (MI), angina, transient ischemic attacks(TIA), cerebral vascular accidents (CVA) and other arterial events (OAE) were documented at up to 15 years since the first visit. Disease activity was determined using SLE disease activity index (SLEDAI). Patients were classified into those with or without VE-A (VE-A, no-VE-A). VE-A patients were further classified into VE-As that occurred within or after 3 years since the first visit (VE-A<3yr, VE-A≥3yr). Estimated GFR values were compared between groups using the t-test and the Wilcoxon test when only two groups were considered, and using analysis of variance followed by pairwise comparisons via the Tukey-Kramer method for more than two groups. The relationship between eGFR and time to VE-A was investigated using the proportional hazards model.

Results: A total of 437 females, mean age 35.5±13.9 yrs, followed for 11.3±8.24 yrs, with the baseline eGFR of 88.3±29.8 were studied. A total of 50 patients had 52 VE-A events. Among patients with VE-A, 51.9% were VE-A<3yr. VE-A group had a significantly lower baseline eGFR (72.8±27.4 vs 90.3±29.5, P<0.05) and were significantly older (44.1±16.5 vs 34.4±13.1 yr, P<0.05) than no-VE-A.

VE-A<3yr group had a significantly lower baseline eGFR than VE-A≥3yr (61.2±26.0 vs 82.6±22.7, P<0.05) . Patients who were younger than the mean age of the VE-A group and with VE-A<3 had a significantly lower baseline eGFR than the corresponding age group with VE-A≥3(61.5±26.3 vs 85.2±20.8, P<0.05). Furthermore, those who were older than the mean age and with VE-A<3yr had a significantly lower baseline eGFR than the younger patients with VE-A≥3yr (61.0±26.7 vs 85.2±20.8, P<0.05).

The following variables were included in the multivariate model: age, baseline eGFR, baseline SLEDAI, cholesterol and systolic blood pressure. Baseline eGFR, age and baseline SLEDAI were significantly associated with not only VE-A but also with the risks of VE-A (eGFR: Hazard Ratio (HR) =0.986, CI: 0.974, 0.997; age: HR=1.032, CI: 1.012, 1.052; SLEDAI: HR=1.041, CI:1.015, 1.067). For a typical female SLE patient, controlling for other risk factors, every 10 mL/min/1.73m^2 decrease of baseline eGFR increased VE-A risks by 14%, every 10-year increase of age increased VE-A risks by 32%.

Conclusion: Lower baseline eGFR, older age and higher SLEDAI score were significantly associated with increasing odds of develop VE-A sooner. Aggressive management of renal diseases and VE-A risk factors should begin from the early stages of SLE in order to prevent the development of VE-A.

Disclosure: W. Zhang, None; **E. Aghdassi**, None; **H. Reich**, None; **J. Scholey**, None; **J. Su**, None; **W. Lou**, None; **P. R. Fortin**, Canadian Institute for Health Research CIHR), 2, President, 6 .

1931

Is Cigarette Smoking Associated with Disease Activity and Damage in Patients with Systemic Lupus Erythematosus? Meenakshi Jolly[1], Ravikumar Patel[1], Rohit Aggarwal[2], Winston Sequeira[1] and Joel A. Block[1], [1]Rush University Medical Center, Chicago, IL, [2]John H. Stroger, Jr. Hospital of Cook County and Rush University Medical Center, Chicago, IL

Purpose: To determine the effect of cigarette smoking on disease activity and cumulative organ damage in patients with systemic lupus erythematosus (SLE).

Methods: The data were extracted from an ongoing prospective study on health related quality of life in patients with SLE. Consecutive consenting adult SLE patients seen in the rheumatology clinic at an academic hospital were enrolled from September 2006 to April 2008 and detailed clinical and demographic variables were collected from 216 enrolled SLE patients. Disease activity was evaluated by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and cumulative organ damage was measured by the Systemic Lupus International Collaborating Clinics Damage Index (SLICC). Smoking was defined as present if the subject reported smoking at the time of the study. Chi-Square test was used to compare the categorical data and the Mann Whitney test was used for non parametric data between the cases 'smoker' and controls 'non-smoker'. $P < 0.05$ was considered significant on one tailed test.

Results: The mean (±SD) age of participants was 42 ± 13 years and 93 % were females. The ethnic composition was: African American 60 %, Caucasian 20 %, Hispanic 14 % and Asian 6 %. Fifteen percent of subjects reported that they were "currently smoking" at the time of the study. The mean (± S.D, range) SLEDAI score was 6.3 (± 6.1, 0-35) and mean SLICC score was 1.9 (±1.9, 0-9). Smokers had greater overall disease activity than nonsmokers (mean ± S.D, median) (7.8 ± 7, 6 vs. 6 ± 6, 4; p 0.047). SLEDAI scores suggested that - presence of arthritis (33.3 % vs. 18.1 %, p 0.044) and low complement levels (45.4 % vs. 28.3 %, p 0.042) were more frequent among smokers than among nonsmokers. There were no statistically significant differences in other components of SLEDAI. There was no statistically significant difference in overall disease damage in between smokers and nonsmokers, but specifically from SLICC skin scarring/alopecia (34.3 % vs. 9.1 %, p 0.001) and skin extensive scarring/ panniculum (34.3 % vs. 6.8 %, p 0.001) were more frequent among the smokers than nonsmokers. There were no statistically significant differences in other components of SLICC.

Conclusion: Cigarette smoking is associated with greater disease activity and cumulative organ damage in SLE. Smoking cessation should be aggressively addressed among patients with SLE.

Disclosure: M. Jolly, None; **R. Patel**, None; **R. Aggarwal**, None; **W. Sequeira**, None; **J. A. Block**, None.

1932

Evolution of Disease Burden Over 5 Years in a Multicentre Inception SLE Cohort. Murray B. Urowitz[1], Dafna D. Gladman[1], Dominique Ibañez[1] and Systemic Lupus International Collaborating Clinics (SLICC)[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto, ON

Purpose: The evolution on an annual basis of disease activity and damage and the annual accrual of key autoantibodies in patients with SLE is unknown. We describe the annual occurrence of these features in an inception cohort of patients with SLE.

Method: An international research network comprising 27 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2009. Of these, 298 patients followed for a minimum of 5 years constitute the study population. Clinical disease activity was assessed using SLEDAI-2K and disease damage using the SLICC/ACR Damage Index (SLICC/DI). ANA, Anti-DNA and anticardiolipin, antibody levels and the presence of the lupus anticoagulant were assessed at each visit. Descriptive statistics were used.

Results: Of the 298 patients followed for at least 5 years, 86.6% were female, 55.4% were Caucasian, 12.1% were Black, 14.4% were Asian, 16.1% Hispanic and 2.0% other. 41.9% were married and 60.4% had at least College education. Their mean age at enrolment was 35.3 years and SLEDAI-2K at enrolment was 5.9. The duration from diagnosis to enrolment was 5.5 months.

FU	**SLEDAI-2K**		**SLICC/DI**	
	n	Mean ± std	n	Mean ± std
0	298	5.93 ± 5.54	143*	0.37 ± 0.80
1	268	3.67 ± 4.11	237	0.55 ± 0.94
2	271	3.71 ± 4.50	270	0.67 ± 1.09
3	265	3.51 ± 3.64	262	0.79 ± 1.16
4	272	3.30 ± 4.05	269	0.94 ± 1.28
5	298	3.37 ± 4.15	295	1.01 ± 1.35

*** SLICC/DI performed only in those with > 6 months disease duration.**

FU	N	ANA	Anti-DNA	ACL	LA
0	298	93.6	29.3	25.6	26.9
1	268	95.3	37.6	21.8	26.7
2	271	95.3	48.3	17.3	24.2
3	265	96.3	50.7	20.2	29.1
4	272	96.3	53.4	23.7	34.2
5	298	97.0	55.4	25.6	32.6

Mean SLEDAI-2K decreases to low levels in the first year and then remains low. SLEDAI-2K was significantly lower at each year in Caucasians compared to the combined "other" ethnicities.

Mean SLICC/DI increases progressively over the 5 years but there was no significant difference at each year between Caucasians and "others". Although ANA positivity is high at enrolment, the percent positivity increases by almost 4% over 5 years. Frequency of anti-DNA positivity is lower at enrolment but increases over 5 years. Anticardiolipin antibody does not increase over 5 years but the lupus anticoagulant increases slightly.

Conclusion: As expected disease activity in newly diagnosed patients decreases over their first 5 years but disease damage increases. However key antibody levels ran variable courses over this period. For example ANA positivity increases only slightly over 5 years. Similarly anti-DNA antibody positivity was low in the first year of disease but rose to 55% by 5 years. Anticardiolipin antibody and the lupus anticoagulant were more constant over the first 5 years of disease.

Disclosure: M. B. Urowitz, None; **D. D. Gladman**, None; **D. Ibañez**, None.

1933

Histology, Prognostic Factors, Treatment, & Outcome in SLE Patients with Non-Hodgkin's Lymphoma(NHL). S. Bernatsky[1], Rosalind Ramsey-Goldman[2], C. Gordon[3], Susan Manzi[4], O. Nived[5], S.C. Bae[6], G. Ruiz-Irastorza[7], K. H. Costenbader[8], S. Jacobsen[9], G. K Sturfelt[10], J. L. Lee[1], E. Turnbull[1] and A. E. Clarke[1], [1]MUHC, Montreal, QC, [2]Northwestern Univ, Chicago, IL, [3]Univ. of Birmingham, Birmingham, United Kingdom, [4]Univ of Pittsburgh, Pittsburgh, PA, [5]Inst of Clinical sciences, Lund, Sweden, [6]Hanyang Univ Med Ctr, Seoul, South Korea, [7]Universidad del País Vasco, Bizkaia, Spain, [8]Brigham & Women's Hospital, Boston, MA, [9]Univ Hospital, Copenhagen, Denmark, [10]Univ Hospital Lund, Lund

Purpose: To describe histology, prognostic factors, treatment & outcome of NHL in Systemic Lupus (SLE).

Methods: Lymphomas were identified via linkage with cancer registries at 7 centres, and through hospitalization & billing information at 1 centre. Histology, prognostic factors at lymphoma diagnosis, treatment & outcome were assessed from medical records. Prognostic factors were based on the International NHL Prognostic model, including age, elevated serum LDH, advanced stage, extra-nodal involvement, & poor performance status (Eastern Cooperative Oncology Group scale).

Results: Of the 35 patients who developed NHL after the SLE diagnosis, 32 were female. At the time of lymphoma diagnosis, the mean age was 52.8 years (standard deviation, SD 15.3), & mean SLE duration 13.1 years (SD 9.8, median 11.7).

Of the 28 cases where detailed histology information was available, 17 (60.7%) were diffuse large B-cell lymphomas (DLBC). In addition there were 5 follicular lymphomas, 5 marginal zone lymphomas, and 1 Burkitt's lymphoma. None of the patients with marginal zone lymphomas had Sjogren's syndrome. Data on lymphoma stage (Ann Arbor) was available for 26 cases; among these, advanced stage was seen in 18(69%). Among those with sufficient data (N=14), 11 SLE patients had ≥2 risk factors which, according to the NHL Prognostic model, confers a <50% chance of relapse-free & over-all 5-year survival

Treatment data was available for 28 of the 35 cases. Fourteen were treated with chemotherapy alone, 4 with radiation therapy alone, 2 with surgery alone and 6 with more than one therapy. Chemotherapy consisted primarily of standard CHOP (Cyclophosphamide, Adriamycin,

Oncovin, Prednisone). Rituximab was included in chemotherapy of 7 subjects, with an initially favorable response in terms of the lymphoma. Three were treated with stem cell transplants (autologous or allogenic).Two patients were not treated, one due to advanced lymphoma stage and poor prognosis. At the time of data collection, 16 of the 35 cases were deceased, including all but 3 of the subjects with poor prognostic factors at presentation.

Conclusion: These data confirm that the most common lymphoma histology in SLE is DLBC. The DLBC lymphomas make up about a third of NHL in the general population, but were twice as prevalent as this in our SLE sample. The predominance of DLBC histology in SLE may support the role of chronic antigen stimulation in the pathogenesis of lymphoma development in SLE**.** Our preliminary data suggest that SLE subjects with poor prognosis after NHL diagnosis may be identified on the basis of the International NHL Prognostic Factors model. It appears that most SLE patients diagnosed with NHL are offered standard therapy. Continued follow-up of the subjects, & expansion of the study sample, is ongoing.

Disclosure: S. Bernatsky, NIH, 2 ; **R. Ramsey-Goldman**, NIH, 2 ; **C. Gordon**, None; **S. Manzi**, Amgen, 2, Aspreva, 2, Genelabs Technologies, Inc., 2, Genentech Inc., 2, Human Genome Sciences, Inc., 2, Immunomedics, Inc., 2, Bristol-Myers Squibb Company, 2, Cellatope Corporation, 5, La Jolla Pharmaceutical, 5, MedImmune, Inc., 5, Genelabs Inc., 5, Genentech Inc., 5, Bristol-Myers Squibb, 5, Human Genome Sciences, 5, Centocor, Inc., 5, Cephalon, 5 ; **O. Nived**, None; **S. C. Bae**, None; **G. Ruiz-Irastorza**, None; **K. H. Costenbader**, None; **S. Jacobsen**, None; **G. K. Sturfelt**, None; **J. L. Lee**, None; **E. Turnbull**, None; **A. E. Clarke**, The Arthritis Society, NIH, 2 .

ARHP Concurrent Abstract Session

Surgical and Non-Surgical Approaches to Osteoarthritis

Tuesday, October 20, 2009, 2:30 PM - 4:00 PM

1934

The Influence of Hip Muscle Strength and Hip Frontal Plane Moment On the Knee Adduction Moment in People with Knee Osteoarthritis. AB Gil, Pj Sparto, Sara R. Piva and G. Kelley Fitzgerald, University of Pittsburgh, Pittsburgh, PA

Purpose: It is believed that increased hip external adduction moment may have a protective effect on progression of knee osteoarthritis (KOA) by inducing a reduction of the knee adduction moment and consequently reducing stress on the knee medial compartment. An assumption is that hip abduction strength might be a contributor to the hip external adduction moment. Although this assumption makes theoretical sense, the relationships between hip abduction strength, hip adduction moment and knee adduction moment in subjects with KOA have not been verified. The purpose of this study was to explore the association of hip abduction strength and hip frontal plane moment with knee adduction moment in subjects with KOA.

Method: Twenty-six subjects with KOA participated in this cross-sectional study. Age 67.7 ± 11 years, 50% female, BMI 29.7 ± 7.3. Hip abduction strength was measured by a hand held dynamometer. Subject was side lying with hip at 0 degrees of abduction and 5 degrees of extension. Three maximum isometric voluntary contractions were performed and the average of 3 trials was calculated. Gait analysis was performed on a level surface using the VICON system. Subjects were asked to walk at their self-selected speed. The average of 5 trials was calculated. Inverse dynamics was used to calculate moment about the hip and knee joints. Data Analysis: A multiple linear regression model was built to predict knee adduction moment. After controlling for the amount of knee varus/valgus alignment obtained from long cassette X-rays, the main effects of hip abduction strength and hip external adduction moment were entered into the model followed by their interaction term (Hip Strength x Hip Adduction moment).

Results: Knee varus/valgus alignment was significantly associated with knee adduction moment (β_{Align}=-.579, R^2_{Align}=.34, $p < .01$). Subjects with greater varus alignment had increased knee adduction moment. Once knee alignment was in the model, hip adduction moment was the only other variable that predicted knee adduction moment ($\beta_{HipAddM}$ = -.353, $R^2Change_{HipAddM}$ = .12, $p < .05$). Subjects with greater hip adduction moment had lower knee adduction moment. The two predictors explained 46% of the variability in knee adduction moment.

Conclusion: Our results confirmed the association between frontal plane hip and knee adduction moments shown by Chang et al, 2005. However hip abduction strength was not associated with knee adduction moment during gait. Hip abduction strength capacity may not be the determining factor in the relationship between hip and knee adduction moments. An alternate explanation of how the hip abductors affect the

relationship between hip and knee adduction moments may be the timing of muscle activation rather than strength. These results have potential implications on rehabilitation in that the focus may be on motor control rather than simply on hip strengthening.

FUNDING: Study supported by NIH grant R01 AR048760

Disclosure: A. Gil, None; **P. Sparto**, None; **S. R. Piva**, None; **G. K. Fitzgerald**, None.

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Effectiveness of Neuromuscular Electrical Stimulation On Knee Osteoarthritis Patients: Randomized Clinical Trial. Aline M. Imoto, Stella Peccin, Kelson NG Silva Sr., Lucas E.P.P Teixeira, Marcelo I. Abrahão and Virginia F.M. Trevisani, Federal University of Sao Paulo, Sao Paulo, Brazil

Purpose: The purpose of our study is to verify the effectiveness of an 8-week neuromuscular electrical stimulation (NMES) rehabilitation program on improving the function and pain in knee osteoarthritis' patients in comparison to an exercise program without NMES and educational program.

Methods: study design: randomized clinical trial. The sample of 150 patients was statistically randomized into three groups. The patients were evaluated by a blind assessor before and after intervention. The outcomes used were: visual analogical scale 0-10, Lequesne Index, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity of Daily Living Scale and Timed Up and Go Test. The NMES and Exercise groups were performed 2 times a week for 8 weeks. The educational group followed the manual guide for 8 weeks. For statistical analysis, the team used ANOVA to compare groups (continuous outcomes), chi-square for comparison between groups (categorical measures), paired T-test for comparison between before and after intervention. For all tests an alpha=5% was used, being considered significant $p<0,05$.

Results: The sample is described in table 1. The baseline assessment demonstrates the homogeneity of the three groups (age, Body Mass Index (Kg/m^2) gender). Considering that some patients left the study, the end sample size of our study is 125 participants (NMES (n)=42, Exercise(n)=43 , Educational(n)=40). There were statistically significant improvements in NMES and Exercise groups in terms of pain ($p<0,05$), Lequesne Index ($p<0,05$), WOMAC ($p<0,05$) (subscale pain, stiffness and function), ADLS ($p<0,05$) and Timed Up and Go Test ($p<0,05$). There were no statistical differences in any outcomes for the educational group ($p>0,05$). In comparing patients across groups, NMES and Exercise groups improved significantly versus the educational group. There were no statistical differences between the NMES and Exercise groups for the outcomes evaluated.

Conclusion: Based on the findings of our study, we conclude that NMES and Exercises are equally effective in improvement of pain and function on rehabilitation of knee osteoarthritis patients

Table 1

	NMES Group	**EX Group**	**Educational Group**	**p**
Age (years) (SD)	**60,52 (±7,06)**	**61,69 (±6,99)**	**59,37 (± 8,8)**	**.62***
BMI ((Kg/m^2) (SD)	**30,57 (± 3,58)**	**29,31 (± 4,4)**	**30,44(± 5,25)**	**.6***

Gender	**92,7% W** **7,3% M**	**91,7%W** **8,3% M**	**96,6% W** **3,4% M**	**.713 ****

Abbreviations:

NMES: Neuromuscular Electrical Stimulation

BMI: Body Mass Index

W: woman

M: man

* ANOVA

** Chi-square test

Disclosure: A. M. Imoto, None; **S. Peccin**, None; **K. N. Silva**, None; **L. E. P. P. Teixeira**, None; **M. I. Abrahão**, None; **V. F. M. Trevisani**, None.

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Factors Associated with Refusal to Participate in a Randomized Controlled Trial of Surgery Vs Non-Operative Therapy for Meniscal Tear in Knee Osteoarthritis. Debra J. Skoniecki[1], Joseph Palmisano[2], E. Losina[3], Angela S. Barraza[4], Christine E. Chaisson[2], Pamela Koeth[5], Julian C. Lagoy[6], Nina N. Niu[7], Emily K. Reinke[8] and J.N. Katz[9], [1]Brigham & Womens Hospital, Boston, MA, [2]Boston University, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Mayo Clinic, Rochester, MN, [5]Cleveland Clinic, Garfield Heights, OH, [6]Hospital for Special Surgery, New York, NY, [7]Brigham and Womens Hospital, Boston, MA, [8]Vanderbilt Orthopaedic Institute, Nashville, TN, [9]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Purpose: Adequate participation rates in surgical randomized controlled trials (RCTs) are crucial for assuring generalizable conclusions. The objective of this study was to evaluate enrollment rates and to identify factors associated with refusal to participate in a surgical RCT in patients with symptomatic meniscal tear and knee OA.

Method: The MeTeOR trial (Meniscal Tear in Osteoarthritis Research) is an NIH-funded, multi-center RCT to establish the efficacy of arthroscopic partial meniscectomy (APM) versus non-operative management of meniscal tear and knee OA. Eligibility criteria included age ≥ 45 and MRI documentation of a meniscal tear and cartilage degeneration. Patients with end stage OA (Kellgren-Lawrence (KL) grade 4) were excluded. Rates of participation were defined as the proportion who enrolled among those patients who were offered participation in the trial. To identify factors that distinguish individuals who refused the trial from those who enrolled, we examined data on demographics, OA severity as defined by KL grade, screening site and number of meniscal symptoms. We used bivariate and linear models (with GEE used to account for site effect) to determine correlates of refusal to participate.

Results: In the first year of recruitment 324 eligible individuals were identified across 5 clinical sites and 276 (85%) were offered enrollment into the trial. These 276 patients had a mean age of 58, 58% were female and 89% were Caucasian. 107 (39%) of them enrolled in the trial and 169 (61%) refused. In bivariate analyses, factors associated with refusing to participate in the trial among those who were offered enrollment included less severe KL grade and fewer meniscal symptoms. Specifically, 69% of those with KL 1refused enrollment in the trial as compared with 59% of those with KL 2 and 53% of those with KL 3 (p=0.02). Patients who refused to enroll in the MeTeOR trial had a mean of 4 ± 2 meniscal symptoms as compared with 5 ± 2 meniscal symptoms among those who enrolled (p=0.0001). The effects of KL grade and meniscal symptoms on the likelihood of refusal were confirmed in the multivariable analysis adjusting for site, race and age.

Conclusion: Participation rates in the MeTeOR trial were similar to other published surgical trials in persons with musculoskeletal conditions. Individuals with less severe OA and fewer meniscal symptoms have higher refusal rates in our surgical trial. These selection effects will need to be considered in interpreting MeTeOR trial results, particularly if OA severity and meniscal symptoms influence the trial conclusions.

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Disparities in Post-Acute Rehabilitation Care for Joint Replacement. J.K. Freburger, G.M. Holmes and M.P. Cutchin, University of North Carolina, Chapel Hill, NC

Purpose: To determine the extent to which demographic, socioeconomic, and geographic disparities exist in the use of post-acute rehabilitation care (PARC) for joint replacement and to identify factors that may contribute to these disparities.

Method: Cross-sectional analysis of two years (2005-2006) of population-based hospital discharge data from 355 acute care hospitals located in four geographically and demographically diverse states (AZ, FL, NJ, WI). Data from other sources (e.g., CMS, US Census, Area Resource file, American Hospital Association database) were merged with the hospital discharge data. The sample consisted of 201,319 adults ≥45 years of age (mean age 70 yrs; 62% female; 89% White, 4% Black, 4% Latino, 2% other) who were admitted to a short-term, acute care hospital for a hip or knee joint replacement. Individuals transferred to another acute care hospital or who died during the acute stay were excluded. The primary dependent variable was discharge destination (i.e., skilled nursing facility (SNF), inpatient rehabilitation facility (IRF), home health (HH), or home with no HH). Bivariate and multivariable analyses, including multi-level analyses, were conducted to identify disparities in PARC use and individual-level (e.g., disease severity, comorbidities), hospital-level, and community-level characteristics contributing to the disparities.

Results: 38% of the sample was discharged to a SNF, 13% to an IRF, 28% to HH, and 21% to home with no HH. In bivariate analyses, the percentage of individuals discharged to these settings varied significantly by age, sex, race, socioeconomic status (income, insurance), and geography (urban/rural county, state). After controlling for disease severity, comorbidities, sex, and age, disparities in PARC use remained. Relative to Whites, minorities (Black, Latino, Other) were more likely to be discharged to an institution (IRF or SNF) and they were more likely to receive care in an IRF than a SNF. Of individuals discharged to an institution, rural residents were also more likely to receive care in a SNF than an IRF. Individuals of lower socioeconomic status or rural residence were more likely to be discharged home and were less likely to receive home health. Of individuals discharged home, Blacks were also more likely to use HH relative to Whites. Multivariable analyses are underway to explore interactions and to determine the extent to which hospital (e.g., size, ownership, teaching status, volume, FTEs of rehabilitation staff) and community (e.g., available health care resources and sociodemographic composition at county and zip code levels) characteristics explain the disparities.

Conclusion: Factors beyond disease severity determine the type of PARC individuals receive following joint replacement. Understanding these factors is the first step in improving access to and quality of PARC. We have identified potential areas to target for improving access to PARC.

Disclosure: J. K. Freburger, None; **G. M. Holmes**, None; **M. P. Cutchin**, None.

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Understanding Early Recovery Following Primary Total Hip and Knee Replacement. Aileen Davis[1], Elizabeth M. Badley[2], Sheilah Hogg-Johnson[3], Selahadin Ibrahim[3], Anthony V. Perruccio[4], Rosalind Wong[1], Dorcas E. Beaton[5], Pierre Côté[1], Monique A. Gignac[1], David L. Streiner[6], John Flannery[7] and Nizar N. Mahomed[8], [1]Toronto Western Research Institute, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Institute for Work and Health, Toronto, ON, [4]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [5]St Michael's Hospital, Toronto, ON, [6]Baycrest Centre for Geriatric Care, Toronto, ON, [7]Toronto Rehabilitation Institute - Hillcrest Centre, Toronto, ON, [8]University Health Network, Toronto, ON

Purpose: While baseline pain and functional status are known to predict these outcomes post total hip (THR) or knee (TKR) replacement in pre-post study designs, the trajectory of recovery has not been evaluated. This research evaluates the trajectory of recovery of symptoms, mood, physical function, and social and community participation for THR and TKR through six months post surgery.

Method: Participants completed the HOOS or KOOS, measures of pain, physical function, and sports/leisure activities; the Jette Late Life Disability (LLD) and the Calderdale community mobility questions as measures of participation; the POMS (fatigue); and, the HADS

(anxiety and depression) pre surgery, 2 weeks and 1, 3 and 6 months post surgery. Outcomes were all scored such that higher scores represented more problems. Recovery was compared for THR and TKR evaluating the impact of age, sex, and body mass index (BMI).

Results: THR (n=437) patients had a mean age of 63 years, 55% were female, 34% were overweight (BMI=25-29.9) and 35% were obese (BMI>30). TKR patients (n=494) had a mean age of 65 years, 65% were female, 38% were overweight and 45% were obese. Although symptoms, mood, activity and participation levels were similar pre-surgery, THR patients improved more rapidly and had better outcomes across measures than TKR patients at all times (p 0.049 to <0.0001). Age, sex and obesity all affected outcome (p<0.05). Older individuals (>64 years) had better mood and less activity limitations at baseline and to 2 weeks post surgery for THR, and to 1 month post surgery for TKR patients. Females reported worse outcomes irrespective of joint replaced. The exception was mood and activity limitations where women with TKR had worse outcome only to 1 month post surgery. Obese THR and TKR patients had higher pre-surgery scores for all outcomes with the exception of THR patients' mood. Obese TKR patients had more activity limitations at all times.

Conclusion: People with THR and TKR have different trajectories of outcome with TKR patients recovering more slowly and having poorer outcome than THR. Age, sex and obesity differentially affect different outcomes. These data have implications for the optimal timing of TKR surgery and rehabilitation service planning for THR and TKR.

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Do Worsening Knee Radiographs Mean More Chance of Poor Functional Outcome? the MOST Study. D. White[1], Yq. Zhang[1], J. Niu[1], David T. Felson[2], Julie J.. Keysor[3], M. Nevitt[4], C. Lewis[5], J. Torner[6] and T. Neogi[1], [1]BUSM, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University, Boston, MA, [4]UCSF, San Francisco, CA, [5]UAB, Birmingham, AL, [6]UIowa, Iowa City, IA
Purpose: Radiographic knee osteoarthritis (ROA) is a chronic disease with different rates of progression. However, it is not known if people with faster progression are at higher risk of poor functional outcome than those with slower progression. Thus, we compared the incidence of poor functional outcome over 30 months among those with stable, incident, or worsening ROA.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee OA. We included people who had or developed ROA over 30 months and were not functionally limited at baseline. Knee radiographs and functional assessments were completed at baseline and 30 mo. We defined the incidence of two poor functional outcomes at 30 months using cut points shown to be risk factors for 1) total joint replacement (WOMAC physical function ≥ 36/68) and 2) persistent functional limitation (walking speed ≤1.0 m/s). We defined ROA as K/L grade ≥2 in the TF joint or patellofemoral OA based on the lateral view. We categorized ROA progression over 30 mo as follows: 1) stable K/L or JSN grades in both knees, 2) incident ROA in either knee, or 3) increase in K/L or JSN grades with existing ROA in either knee (worsening ROA). Those with new total knee replacements or existing endstage ROA (K/L=4 or JSN=3) were excluded from analyses. We evaluated the relation of ROA incidence or worsening to the incidence of poor functional outcome by calculating risk ratios adjusted for age, sex, BMI, race, depressive symptoms, number of comorbidities, and pain at lower extremity sites other than the knee, in separate analyses for each of the two outcomes.

Results: Of the 1320 subjects with ROA at 30 months (Age 63 ± 8 yrs, BMI 32 ± 6 kg/m^2, female 61%), 30% had stable ROA, 12% incident ROA, and 58% worsening of ROA. Of those without poor functional outcome at baseline, we found 5% of 957 and 10% of 873 subjects to develop poor functional outcomes at 30 mo for WOMAC and walking speed, respectively. Compared with stable ROA, we found higher risk of poor functional outcome in both those with incident ROA (adj RR 2.4-3.0) and worsening ROA (adj RR 2.3-3.3). (See Table).

Conclusion: The development of poor functional outcome is higher in worsening and incident disease, than those with stable ROA. Clinicians should consider the rate of radiographic worsening to identify those who may benefit from rehabilitation.

Table: Relation of ROA progression over 30 months with incidence of poor functional outcome at 30 months.

Incidence of poor functional outcome		WOMAC (n=957)	Walking Speed (n=857)
Stable ROA	n (incident poor functional outcome)/N (subjects without limitation at baseline)(%)	8/289 (3)	13/264 (5)

	Adj RR* [95% CI]	1.0 Ref	1.0 Ref
Incident ROA	n/N (%)	6/121 (5)	12/107 (11)
	Adj RR* [95% CI]	3.0 [0.9-10]	2.4 [1.1-5.3]
Worsening ROA	n/N (%)	33/547 (6)	63/502 (13)
	Adj RR* [95% CI]	3.3 [1.2-9.5]	2.3 [1.2-4.2]

* adjusted for age, sex, BMI, race, depressive symptoms, number of comorbities, and pain at lower extremity sites other than the knee

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ACR Concurrent Abstract Sessions

Osteoarthritis Therapeutics & Clinical Aspects

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

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Early Neuromuscular Electrical Stimulation Improves Strength and Functional Performance After Total Knee Arthroplasty.

Jennifer E. Stevens-Lapsley, Jaclyn E. Balter, Wendy M. Kohrt and Donald G. Eckhoff, University of Colorado Denver, Aurora, CO

Purpose: Muscle weakness and reduced functional capacity are present before and after total knee arthroplasty (TKA). Neuromuscular electrical stimulation (NMES) offers an innovative approach to potentially mitigate quadriceps muscle activation deficits early after TKA and restore normal quadriceps muscle function more effectively.

Method: Fifty-four patients with end-stage osteoarthritis were studied (65.7±8.8 years; 32 women, 22 men). Patients were excluded if they had uncontrolled hypertension, uncontrolled diabetes, body mass index >35, other significant lower extremity orthopaedic problems, or neurological impairments. Patients were randomly assigned to either a standard rehabilitation group (Control, n=25) or NMES group (NMES, n=29).

Quadriceps isometric strength was assessed preoperatively and again at 3wks, 6wks, and 3 months after TKA using an isomechanical dynamometer. Functional performance measures included a timed up–and-go (TUG) test, stair climbing test (SCT), 100ft walk test, and 6 minute walk test (6MW).

Rehabilitation: All patients participated in a standardized rehabilitation program for 9wks following surgery, which included 3-5 days of inpatient PT, 2wks of home PT, and 6wks of outpatient PT. Patients randomized to the NMES group also received NMES treatment (Empi 300PV) 2x/day for 15 minutes/session for 6wks beginning 2 days after surgery. Data analysis involved repeated measures with 2-way ANOVAs using baseline values as covariates for all outcome measures.

Results: Overall, significant main effects of NMES treatment were found for all outcome measures through the 3 month follow-up (quadriceps strength, TUG, SCT, 100ft walk, 6MW; $p<0.05$). Quadriceps strength loss (compared to pre-operative levels) 3wks after TKA was significantly attenuated in the NMES group (21.49±39.9% loss) compared to the control group (47.55±16.6% loss). By 6 weeks, there was a strength gain of 5.2±44.3% in the NMES group compared to a 22.15±28.7% deficit for controls.

Conclusion: Incorporating NMES into rehabilitation 2 days after TKA resulted in better quadriceps strength and functional performance than standard rehabilitation alone. Clinical Significance: Early NMES after TKA may help attenuate quadriceps strength loss and activation deficits to enhance functional performance after TKA.

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Dose-Response Vs Threshold Relationship Between Physical Activity and Function in Knee OA. D. D. Dunlop[1], J. Song[1], P. Semanik[2], L. Sharma[1] and R. W. Chang[1], [1]Northwestern University, Chicago, IL, [2]Rehabilitation Institute of Chicago, Chicago, IL

Purpose: It is not known if physical activity has a dose-response or a threshold relationship with function for persons with knee OA. Because physical activity is a key public health intervention, understanding this relationship has important implications for public health recommendations. A dose-response relationship would support advice to increase physical activity regardless of a person's current activity levels. A threshold relationship would support future research to identify what threshold target conveys functional benefits for persons with knee OA.

Methods: The Osteoarthritis (OAI) public data include n=2579 adults (aged 45-79) with radiographic knee OA (KL grade ≥2) at the baseline visit; n=2274 returned for the 1 year visit. Each person was assigned to a baseline physical activity quartile (Q1=low to Q4=high) from PASE (physical activity scores for elderly) scores. Function was assessed objectively by chair stand rate and walk rate over 20 meters. Multiple regression evaluated the relationship of PASE quartiles to functional outcomes controlling for demographics (age, gender, race, education, marital status), knee health (OA severity grade, knee symptoms, WOMAC knee pain, knee injury) and general health (BMI, comorbidity, depression, smoking, alcohol use, any hip, ankle, or foot pain).

Results: Average functional performance consistently increased with higher PASE quartiles for both 20m walk (Q1: 74, Q2: 77, Q3: 79, Q4: 82 meter/min) and chair stand performance(Q1: 25, Q2: 27, Q3: 28, Q4: 30 repetitions/min). To determine if higher physical activity levels consistently corresponds to better function among people with similar demographics and health, we examined functional differences controlling for these factors. These results (Table) showed a strong cross-sectional dose-response relationship and a statistically significant linear trend. The dose-response relationship was sustained over one year.

	Function differences between PASE baseline quartiles adjusted for demographic and health factors			
Baseline Function n=2579	Q2-Q1 (95% CI)	Q3-Q1 (95% CI)	Q4-Q1 (95% CI)	Trend Test
Walk rate	1.5 (0.3, 2.7)	3.00 (1.8, 4.2)	4.22 (2.9, 5.5)	p<.001
Chair stand	1.3 (0.2, 2.4)	1.9 (0.8, 3.0)	2.1 (0.9, 3.3)	p<.001
1 Year Function n=2274				
Walk rate	1.0 (-0.3, 2.3)	2.4 (1.1, 3.7)	3.5 (2.1, 4.9)	p<.001
Chair stand	0.8 (-0.4, 2.0)	2.1 (0.8, 3.3)	2.2 (0.9, 3.6)	p<.001

Conclusion: These findings demonstrate a strong dose-response relationship between physical activity and functional performance in persons with radiographic knee OA that is sustained over one year. This relationship persists controlling for demographic and health factors. These findings support efforts to increase physical activity at all levels to improve functional performance of persons with knee OA.

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The Joints On Glucosamine (JOG) Study: A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Structural Benefit of Glucosamine in Knee Osteoarthritis Based On 3T MRI. C. Kent Kwoh[1], Frank W. Roemer[2], Michael J. Hannon[3], Carolyn E. Moore[4], John M. Jakicic[3], Ali Guermazi[2], Stephanie M. Green[3] and Robert M. Boudreau[3], [1]University of Pittsburgh, VA Pittsburgh Healthcare System, Pittsburgh, PA, [2]Boston University School of Medicine, Boston, MA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Texas Woman's University, Houston, TX

Purpose: Prior studies of the structural benefit of glucosamine in knee osteoarthritis (KOA) as assessed by radiographs have yielded conflicting results. The aim of this study was to determine the short-term efficacy of glucosamine based on decreased worsening of structural lesions in KOA as assessed using 3T MRI.

Method: The Joints on Glucosamine (JOG) study was a 24-week double-blind placebo controlled trial of 1500 mg glucosamine hydrochloride once daily in beverage form compared to placebo. The primary outcome was decreased development of cartilage damage. Eligible participants had mild to moderate knee pain (WOMAC score > = 125). 3T MRI of both knees was performed at baseline and at 24 weeks on a Siemens Trio using the same pulse sequences used in the Osteoarthritis Initiative (OAI): sagittal fat-suppressed (FS) 2D TSE intermediate-weighted (IW); sagittal 3D dual-echo steady state (DESS) WE; and axial and coronal reformations of sagittal 3D DESS WE. Cartilage damage, bone marrow lesions (BMLs) and synovitis in each knee were scored according to the WORMS system. Baseline fixed-flexion knee x-rays were read for Kellgren-Lawrence (K-L) grade and radiographic features such as joint space narrowing using the OARSI grading system. All MRIs and x-rays were read masked to treatment assignment but not to baseline vs. follow-up order. Urinary excretion of C-terminal cross linking telopeptide of type II collagen (uCTX-II) as a biomarker of cartilage synthesis was also assessed. An Intent-to-Treat analysis with last event carried forward was performed. Negative binomial regression for cartilage defects and multivariate logistic regression for worsening BML, taking into account clustering of knees within an individual and adjusted for gender, age, BMI, baseline WOMAC, and K-L grade, were performed to determine the odds (aOR) of worsening based on treatment group assignment. These covariates were used in a linear regression model for uCTX-II.

Results: There were a total of 201 participants (49% women) with a mean age of 52, 98 were block randomized to the treatment group and 103 to the control group. The aOR of worsening cartilage defects in the glucosamine group compared to the control group was 0.9 (95% CI 0.55-1.58). The aOR for worsening in BMLs was 0.73 (95% CI 0.50-1.07).

There also was no indication that glucosamine improved uCTX-II (beta = -0.10, 95% CI -0.21-.001). There was a difference in the proportion of drop-outs by group (i.e., 16.5% in the placebo group vs. 5.1% from the glucosamine group, $p < 0.01$).

Conclusion: This short-term study provided no evidence that glucosamine results in structural benefit in knee OA as assessed using 3T MRI or uCTX.

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CRx-102 (Prednisolone/Dipyridamole Combination) Enhances Glucocorticoid (GC) Efficacy and Reduces Adverse Effects in OA Therapy: 3-12 Month Results. Kenneth Huttner[1], William J. Shergy[2], Craig Romney[3] and John C.R. Randle[1], [1]CombinatoRx, Inc., Cambridge, MA, [2]Univ of Alabama, Huntsville, AL, [3]Liberty Research Center, Tacoma, WA

Purpose: High-dose intra-articular GC is used commonly to treat OA, but oral GC is not used due to safety concerns in this patient population. CRx-102 is a combination of very low-dose prednisolone (Pd 2.7 mg/d) and dipyridamole (Dp), demonstrating synergistic enhanced anti-inflammatory GC effects *in vitro* and *in vivo*, without amplification of the GC adverse effects, approaching GC dissociation through a multi-target mechanism rather than medicinal chemistry. In previous RA and hand OA studies, CRx-102 exhibited clinically meaningful anti-inflammatory activity and was generally well-tolerated.

Methods: COMET-1 was a 14-week Ph2, double-blind, placebo-controlled, knee OA trial, with a 1-y follow-on safety extension. Subjects had screening WOMAC knee pain Q#1 VAS score of 30-80 mm with at least 10 mm flare following NSAID/Coxib discontinuation. Three CRx-102 doses (Pd 2.7 mg/d with Dp 90, 180 or 360 mg/d) were compared with Pd (2.7 mg/d) and placebo on knee OA and hand OA efficacy measurements. In the safety extension, all subjects received 1 of the 2 higher doses of CRx-102 and were monitored for long-term GC tolerability and durability of response. Intensive monitoring of weight, lipids, glucose homeostasis, HPA axis, bone density, intraocular pressure and cataract development with FDA-approved intervention rules makes this the first large, prospective, controlled study of the safety of very low-dose GC.

Results: COMET-1 enrolled 279 subjects and 141 continued in the safety extension (74% of eligible completers). With NSAID/Coxib therapy withdrawn, the CRx-102 (2.7/360) group had sustained, significant reductions in median WOMAC pain, function and stiffness scores vs. placebo, greater at D98 than the placebo and Pd groups by 17.2-19.5 mm and 5.5-8.6 mm, respectively. Accordingly, WOMAC 70% response rates were significantly greater for CRx-102 (2.7/360) vs. placebo on all three subscales at D98. Similar trends in hand pain reduction were seen in the subset of OA subjects with baseline hand pain >= 30 mm. The most commonly-reported AE was headache, with 4-5% drop-out in each active treatment arm. CRx-102 at the maximally effective dose (Pd + the vasodilator Dp at 360 mg/d) reduced both SBP and hypertension frequency vs. placebo and Pd alone. Analysis of bone metabolism demonstrated a small but significant decrease in bone formation markers in the Pd group, contrasting with a more balanced effect on formation and resorption with CRx-102 exposure accompanied by a trend to higher mean hip and femoral neck BMD.

Conclusion: COMET-1 is the first prospective RCT to demonstrate the efficacy of the dissociated glucocorticoid CRx-102 and very low-dose oral Pd in the treatment of knee OA. These effects are comparable to those of current OA therapies, including NSAIDs and Coxibs, and in conjunction with the good tolerability and long-term safety support the investigation of CRx-102 as an alternative anti-inflammatory therapy in OA.

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The Reduction in Serum Level of MMP-3 Seen in a Phase III Study in Knee Osteoarthritis Patients Is Predictive of the Protective Effect On Cartilage Volume Loss of a DMOAD Treatment. Jean-Pierre Pelletier[1], Jean-Pierre Raynauld[1], François Abram[2], Judith Caron[1], François Mineau[1], B. Haraoui[3], Denis Choquette[4] and Johanne Martel-Pelletier[1], [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]ArthroVision Inc., Montreal, QC, [3]Institut de Rhumatolgie de Montreal, Montreal, QC, [4]University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC

Purpose: Licofelone, a dual inhibitor of 5-lipoxygenase and cyclooxygenase, compared to naproxen was found to be a disease modifying drug (DMOAD) in a phase III study in knee osteoarthritis (OA) patients using quantitative MRI[1]. Very little information is available on the value of predictive and/or prognostic biomarkers in OA trials in which disease progression and cartilage volume loss were assessed using quantitative MRI. The present study explored the relationship between the protective effect of licofelone on cartilage volume loss and symptom relief, using the most relevant OA biomarkers.

Method: A subset of 155 patients selected from a clinical trial evaluating the impact of licofelone (n=81; 200 mg bid) versus naproxen (n=74; 500 mg bid) on OA knee tissue structure, were studied. The patient population had a mean age of 60.5 years, 68% were female, and the average BMI was 32.3 kg/m^2. Patients with KL grade IV were excluded. Only patients who had taken all the study medication according-to-protocol (ATP) throughout the two year period were considered for this sub-analysis. MRI acquisitions of the knee were done at baseline and two years of follow-up and the cartilage volume and bone marrow lesions quantitated. Patients underwent clinical evaluation using the WOMAC questionnaire (pain, stiffness and function). Seven biomarkers, relevant to OA structural progression, were measured at baseline and at two years: CRP, MMP-1, MMP-3, IL-6 and COMP in serum, and CTX-I and CTX-II in urine.

Results: The increase in MMP-3 and MMP-1 levels in the patients was significantly less over time in the licofelone group vs. naproxen ($p<0.0001$ and $p=0.05$, respectively). Moreover, a positive correlation was found between the baseline values of MMP-3 ($p=0.01$) and COMP ($p=0.03$) and the cartilage volume loss at two years. The extent of increase in the levels of MMP-3 ($p=0.02$) and MMP-1 ($p=0.06$) over time was found to be associated with the severity of cartilage loss. CTX-I levels at baseline also correlated ($p=0.02$) with the increase in

bone marrow lesion size in the medial compartment. The CRP levels at baseline were positively correlated with the worsening of symptoms: WOMAC total index (p=0.0009), pain (p=0.002) and function (p=0.001).

Conclusion: This study demonstrated that some serum biomarkers (MMP-3, MMP-1 and COMP) can predict the loss of cartilage in knee OA patients. However, levels of MMP-3 and to a lesser extent MMP-1 are the most useful predictive biomarkers in the monitoring of the DMOAD effect. CRP was found to be the most reliable marker for predicting the evolution of disease symptoms over time.

1. Raynauld J-P, et al. Ann Rheum Dis 2009;68:938-47.

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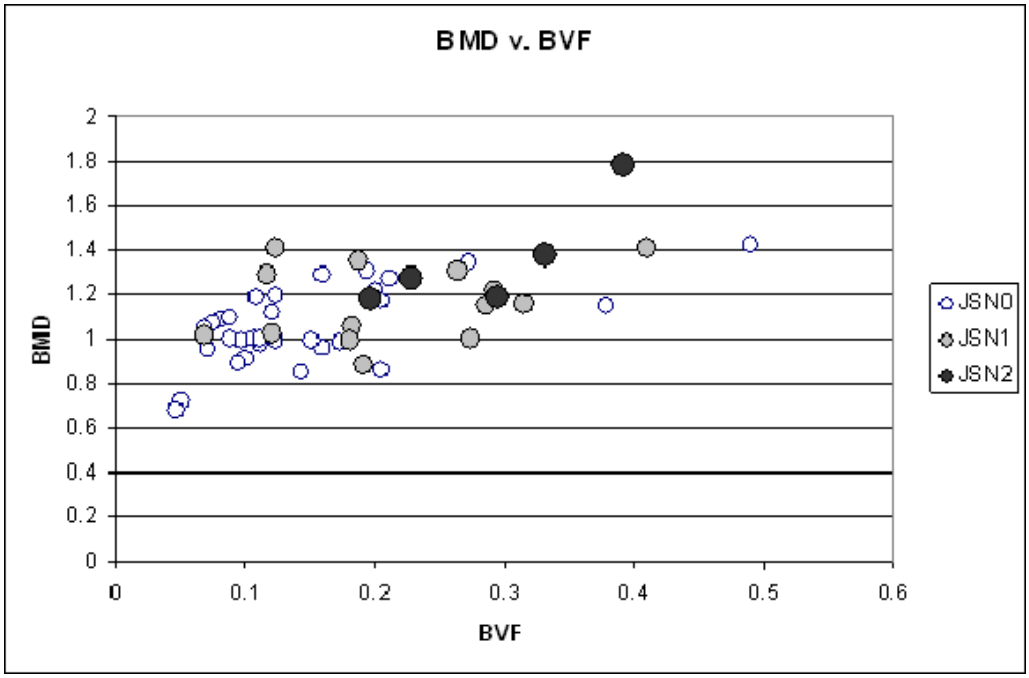
Higher Subchondral Bone Volume Is Associated with Higher DXA Bone Mineral Density and Knee OA Severity. Grace H. Lo[1], Kimberly Carr[1], Lori Lyn Price[1], Erika Schneider[2], Sharmila Majumdar[3] and Timothy McAlindon[1], [1]Tufts Medical Center, Boston, MA, [2]Cleveland Clinic, Cleveland, OH, [3]UCSF, San Francisco, CA

Purpose: There is growing evidence that the subchondral bone changes are pathologic in OA. Radiologic imaging allows for visualization of bone in vivo in humans. Apparent bone mineral density (BMD) as measured by Dual X-ray Absoptiometry (DXA) can assess the amount of mineralization within a region of interest (ROI) while MRI is able to measure bone volume fraction (BVF). Because we expected that there will be changes in mineralization in regions where there is higher bone fraction, we evaluated the relationship of tibial BMD (tBMD) with MRI measured BVF.

Methods: 50 participants of the Osteoarthritis Initiative Bone Ancillary Study who had knee DXAs and knee trabecular bone MRIs obtained at the same visit were included in this study. DXAs were obtained using a customized protocol on GE Lunar Discover Bone Densitometry scanners. We measured medial proximal tibial BMD (tBMD) including 1cm depth of subchondral bone. MRIs were obtained at 3T with 1mm slice thickness, in-plane spatial resolution of 0.2 mm X 0.2 mm, with a 12 cm imaging field-of-view, 512 X 512 matrix, 72 slice coverage with TE 4.92 msec (fat-water in-phase), TR 20 msec, flip angle 50^{o}, phase right/left, interpolation to 1024 X 1024, and no partial Fourier. MRIs were analyzed utilizing proprietary software that measured BVF in the medial proximal tibia (tBVF). We evaluated for a correlation between medial tBMD and tBVF. We then created scatter plots tBMD v. tBVF stratified by JSN and ran ANOVAs of tBMD and tBVF by JSN.

Results: The mean age was 67.2 (9.5), BMI 28.1 (4.1), and 50% were male. 31 had JSN of 0, 14 with JSN of 1, and 5 with JSN of 2. The correlation between the medial tBMD and tBVF was r = 0.64, p <0.0001. The tBMD by JSN were 1.17 g/cm^2, 1.30, and 1.60 for JSN 0, 1, and 2 respectively, p = 0.0003. The tBVF by JSN were 0.15, 0.22, and 0.29 for JSN 0, 1, and 2 respectively, p = 0.0042.



Conclusion: In regions of higher tBMD, there is greater BVF. Knees with a greater medial JSN, a marker of greater OA severity, have a higher medial tBMD and tBVF. A potential explanation for these findings is that regions of high tBMD and tBVF represent compressed subchondral bone. Further characterization of the subchondral bone in OA utilizing diverse radiologic methods will help clarify OA pathophysiology.

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ACR Concurrent Abstract Sessions

Pathogenesis of Gout, Allopurinol Dosing, the Hypouricemic Effect of Milk, and the Mortality Impact of Gout

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

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Severity of Gout and Mortality. Fernando Perez-Ruiz[1], Lorea Martinez-Indart[2], Loreto Carmona[3], Ana M. Herrero-Beites[4] and Jose I. Pijoan[5], [1]Hospital De Cruces, Barakaldo, Spain, [2]Hospital de Cruces, Baracaldo, [3]Fundación Española Reumatol., Madrid, [4]Hospital de Gorliz, Gorliz, Spain, [5]Hospital de Cruces, Baracaldo, Spain

Purpose: Recent studies have demonstrated an association of gout with an increased risk of cardiovascular (CV) mortality. The association proven is indirect, through the relation of gout with CV-related comorbidity and risk factors. The objective was to test whether the relation of mortality and gout may be direct, that is, whether the severity of gout may be associated to CV mortality.

Method: Prospective longitudinal study of all gout patients ever attended at a single Gout clinic. Baseline variables included sociodemographics, use of urate lowering drugs (ULD), number of joints affected, presence of tophi, number of flares in the previous year, prevalent CV disease, alcohol intake, and CV risk factors. Vital status was investigated in any patient who did not attend a follow-up visit.

Kaplan-Meier estimates and log-rank test were used to identify variables associated with mortality. Variables found to have a statistical association with mortality in the bivariate analysis were selected for a multivariate Cox proportional hazard regression analysis using a stepwise model. The Standardized Mortality Rate (SMR) was calculated comparing the mortality observed in the sample to the expected rate in the general population of similar age and sex (2005 National Statistics).

Results: From 1992 to November 2008, 706 patients were included, 662 (94%) of whom were men. At baseline, 436 (72%) had never received ULDs, 358 (51%) had 2 to 4 joints involved and 244 (35%) >4, and 215 (31%) had tophi. A CV disease was present in 178 (26%) cases, 153 (22%) used diuretics regularly, 142 (20%) had diabetes mellitus, 291 (41%) had arterial hypertension, and 298 (42%) had hyperlipidemia. During follow-up (range: 1 month to 14 years), 64 (9%) patients died (55 men and 9 women), with 38 (70%) attributed to CV cause. The SMR (any cause) in patients with gout was 2.37 (95% CI: 1.82 to 3.03)[men 1.57 (95% CI: 1.18 to 2.05); women 4.50 (95% CI: 2.06 to 8.54)]. The SMR (CV cause) was 3.88 (95% CI: 2.70 to 5.40). The following baseline variables were significantly associated to mortality in the bivariate analysis: age, gender, number of flares, presence of tophi, number of joints involved, secondary gout, ethanol intake, hypertension, diabetes, renal insufficiency, diuretic use, and previous cardiovascular disease. Only four of these variables were found to be independently and statistically significantly associated with mortality:

Table 1. Variables independently associated with mortality in gout patients.

	Hazard ratio	95% CI	*p*
Age (by year)	1.07	1.04 – 1.10	<.001
Serum urate (per mg/dl)	1.20	1.06 – 1.36	.004
Secondary gout	2.45	1.33 – 4.54	.004
Presence of tophi	1.84	1.12 – 3.02	.016
Prevalent CV disease	2.01	1.06 – 3.81	.033

Conclusion: Patients with gout may have an excess mortality and an excess CV mortality. Severity of gout at baseline is associated to increased mortality as much as prevalent CV disease. These results emphasize the importance of not delaying intense treatment in gout patients.

Disclosure: F. Perez-Ruiz, Ipsen, 5, Savient, 5, Pfizer Inc, 5, Ardea Biosciences, 5 ; **L. Martinez-Indart**, None; **L. Carmona**, None; **A. M. Herrero-Beites**, Ipsen, 5, Savient, 5, Pfizer Inc, 5, Ardea Biosciences, 5 ; **J. I. Pijoan**, None.

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The Acute Effect of Skim Milk On Serum Urate Concentrations: A Randomized Controlled Cross-Over Trial. Nicola Dalbeth[1], Sumwai Wong[1], Greg Gamble[1], Anne Horne[1], Barbara Mason[1], Lynette Fairbanks[2], Fiona M. McQueen[1], Jillian Cornish[1], Ian R. Reid[1] and Kate Palmano[3], [1]University of Auckland, Auckland, New Zealand, [2]Guy's Hospital, London, United Kingdom, [3]Fonterra Research Centre, Palmerston North, New Zealand

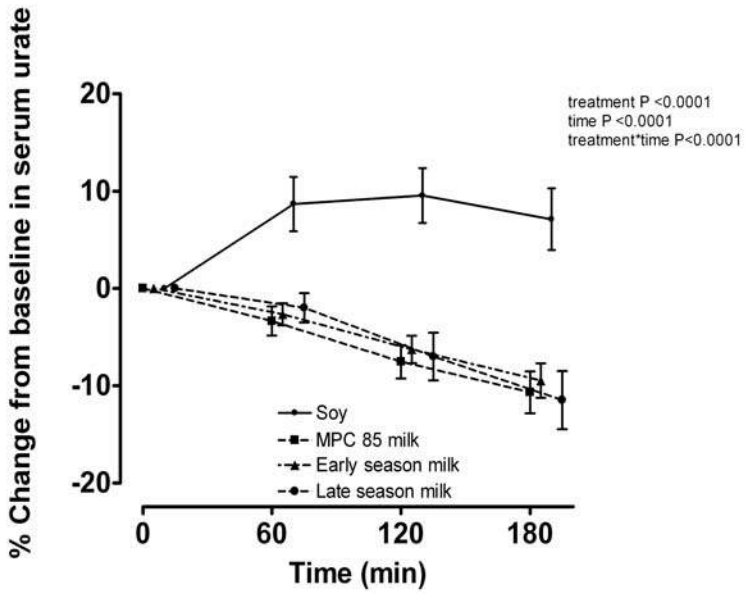
Purpose: Recent observational studies have highlighted the beneficial role of skim milk in prevention of gout. The aims of this study were to determine the acute effects of intact skim milk on serum urate concentrations, and to examine the mechanisms of the urate-lowering effects of skim milk.

Method: This was a short-term randomized controlled cross-over trial of skim milk in 16 healthy male volunteers. The following products were tested (each 80g protein); soy control, early season skim milk, late season skim milk (containing high concentrations of orotic acid, a naturally occurring uricosuric agent), and MPC 85 skim milk (an ultra-filtrated skim milk containing very low concentrations of orotic acid, purines and lactose). Each participant received a single dose of each product in random order. Serum and urine were obtained immediately before ingestion and then hourly over a three hour period after ingestion of each study product. Each study visit was separated by at least a week.

Results: Ingestion of the control soy led to an increase in serum urate by approximately 10%. In contrast, all skim milks led to a decrease in serum urate by approximately 10% ($p<0.0001$) (Figure). All products (including soy) rapidly increased the fractional excretion of uric acid (FEUA). Late season skim milk led to a greater increase in FEUA compared with MPC 85 ($p=0.02$) and early season skim milk ($p=0.052$). There were no significant differences over time or between groups in changes in serum oxypurines (xanthine and hypoxanthine) or purine-containing nucleosides (guanosine and inosine). However, all products led to an increased fractional excretion of xanthine ($p=0.004$).

Conclusion: This study has demonstrated that intact skim milk has a specific acute urate-lowering effect. These data provide further rationale for long term intervention studies to determine whether such dietary interventions play an adjunctive role in management of hyperuricaemia and gout.

Figure: Effects of soy and skim milks on changes in serum urate concentration. Data are presented as mean (95% CI).



Disclosure: N. Dalbeth, Fonterra Research Centre, 2, Abbott Laboratories, 5, Roche Pharmaceuticals, 5 ; **S. Wong**, None; **G. Gamble**, None; **A. Horne**, None; **B. Mason**, None; **L. Fairbanks**, None; **F. M. McQueen**, None; **J. Cornish**, Fonterra Ltd, 2 ; **I. R. Reid**, Fonterra Ltd, 2 ; **K. Palmano**, Fonterra Ltd, 3.

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Cellular Characterization of the Gouty Tophus: A Quantitative Analysis. Nicola Dalbeth, Bregina Pool, Greg Gamble, Timothy Smith, Karen E. Callon, Fiona M. McQueen and Jillian Cornish, University of Auckland, Auckland, New Zealand

Purpose: The gouty tophus is the hallmark of chronic gout. The aim of this study was to characterize the cellular architecture of the tophus, and to determine the presence of cytokines implicated in initiation and resolution of gouty inflammation.

Method: Sixteen fixed, paraffin-embedded, uninfected tophus samples were surgically obtained from twelve patients with microscopically proven gout. The samples were analyzed by quantitative immunohistochemistry. The number of cells present in the corona and fibrovascular zones of the tophus was analyzed by GENMOD mixed model analysis to account for repeated counts within the same individual.

Results: All results are summarized in the Table. Numerous CD68+ macrophages were present within the corona zone. The majority of these cells were mononucleated, but multinucleated CD68+ cells were also identified. Mast cells were present in all tophus samples, throughout the corona and fibrovascular zones in similar densities. In contrast, neutrophils were rarely observed. Plasma cells were present in very high numbers within the corona zone. The overall number of CD20+ B cells was much lower. However, in 5 of the 12 (42%) patients, at least one B cell aggregate was present in the fibrovascular zone. Large numbers of cells expressing IL-1β were observed, particularly within the corona zone, in both mononucleated and multinucleated cells. TGF-β1-expressing mononucleated cells were also identified. The number of cells expressing IL-1β correlated with the number expressing TGF-β1 ($r=0.59$, $p=0.03$). The number of CD68+ cells correlated with the number of cells expressing IL-1β ($r=0.64$, $p=0.02$) and TGF-β1 ($r=0.63$, $p=0.009$).

Conclusion: The tophus represents a complex and organized chronic inflammatory tissue response to MSU crystals. Both innate and adaptive immune cells are present within the gouty tophus, contrasting with the well recognized, dominant role of innate immunity in the acute gout attack. The co-expression of IL-1β and TGF-β1 within the tophus suggests that both pro- and anti-inflammatory factors present within the same lesion contribute to a cycle of chronic inflammation, attempted resolution and tissue remodeling.

Table: Summary of all results. For all cells, numbers indicate median (interquartile range) number of cells/high power field (at x20 magnification).

	Corona zone	**Fibrovascular zone**	**p**
Macrophage (CD68)	55 (22.5-83)	10 (3.5-16)	<0.0001
CD68+ multinucleated cells	8 (5-38)	0 (0-1)	<0.0001
Mast cell	24 (16-36)	18.5 (13-25.5)	0.38
Neutrophil	0.5 (0-2)	0 (0-2)	<0.0001
T cell	14 (6-32)	8 (4-24)	0.41
CD8+ T cell	9 (7-34)	18 (5-33)	0.74
Plasma cell	73 (36-113.5)	15 (6.5-40.5)	<0.0001
CD20+ B cell	0 (0-3)	8 (4-19)	0.0003
IL-1β	169 (139-228)	26 (21-34)	<0.0001
TGF-β1	27 (16-38.5)	7 (4-18.5)	0.035

Disclosure: N. Dalbeth, None; **B. Pool**, None; **G. Gamble**, None; **T. Smith**, None; **K. E. Callon**, None; **F. M. McQueen**, None; **J. Cornish**, None.

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Intracellular Calcium Oscillations in Articular Chondrocytes Induced by Basic Calcium Phosphate Crystals Lead to Cartilage Degradation. Christelle Nguyen[1], Hang-Korng Ea[1], Christian Bordat[2], Michèle Lieberherr[3] and Frédéric Lioté[1], [1]INSERM UMR-S 606, Paris-Diderot University, Lariboisière Hospital, Paris, France, [2]INRA UR 909, MIMA 2 Plateform, Jouy-en-Josas, France, [3]INSERM U567, CNRS UMR 8104, Paris-Descartes University, Cochin Institute, Paris, France

Purpose: Basic calcium phosphate (BCP) crystals, including octacalcium phosphate (OCP), carbapatite (CA) and hydroxyapatite (HA), are associated with destructive forms of osteoarthritis. However, mechanisms of cartilage breakdown induced by BCP crystals are incompletely understood. This study was designed to evaluate whether BCP crystals induce intracellular calcium (Ca^{2+}_i) variations and the role of Ca^{2+}_i in BCP-induced glycosaminoglycan (GAG) release.

Method: Bovine articular chondrocytes (BAC) and bovine cartilage explants (BCE) were stimulated by pyrogen-free OCP, CA, HA, or monosodium urate (MSU) crystals. Ca^{2+}_i levels in isolated BAC were determined with the photoactive dye Fura-2/AM, and Ca^{2+}_i oscillations by confocal microscopy using the fluoroprobe Fluo-4/AM. GAG release was measured in the supernatants of BCE cultures by 1,9-dimethylmethylen blue assay. Mechanisms of Ca^{2+}_i oscillations induced by BCP crystals were assessed by a pharmacological approach.

Results: All BCP crystals, contrary to MSU crystals, induced Ca^{2+}_i increase compared to baseline level (OCP: 2.4 ± 0.9-fold the control value, $p < 0.0001$; CA: 2.4 ± 1.8, $p = 0.003$; HA: 1.4 ± 0.4, $p = 0.005$; and MSU: 1.5 ± 0.6, $p = 0.160$). OCP crystals also induced Ca^{2+}_i oscillations within minutes. Ratio of BAC displaying Ca^{2+}_i oscillations increased with time to reach a maximum after 20 minutes of OCP crystal stimulation (49.0 ± 24.3%, $p < 0.005$), whereas no Ca^{2+}_i oscillations were observed in control BAC stimulated only by microscopy laser beam or fluid flow. OCP crystal-induced Ca^{2+}_i increase and Ca^{2+}_i oscillations involved several mechanisms including extracellular Ca^{2+} influx and Ca^{2+}_i storage and exflux. Indeed, Ca^{2+}_i oscillations induced by OCP crystals were completely abolished when experiments were performed in Ca^{2+}-free medium suggesting the role of extracellular Ca^{2+} influx. Extracellular Ca^{2+} influx involved voltage-independent and voltage-dependent Ca^{2+} channels, since Ca^{2+}_i levels decreased when BAC were pre-treated with either nickel (Ni) 5mM or verapamil 1 µM ((OCP + Ni)/OCP = 0.5 ± 0.2, $p = 0.01$; and (OCP + verapamil)/OCP = 0.6 ± 0.2, $p = 0.01$). Similarly, ratio of BAC displaying Ca^{2+} oscillations decreased rapidly when Ni was added, and was completely abolished by thapsigargin, an inhibitor of Ca^{2+}_i storage in endoplasmic reticulum. Finally, BAPTA 1 µM, a Ca^{2+}_i chelator, significantly decreased BCE GAG release induced by OCP crystals (1.1 ± 0.4-fold the control value vs. 1.7 ± 0.1, $p = 0.01$, in presence and in absence of BAPTA, respectively).

Conclusion: These results suggest that Ca^{2+}_i signalling is a major pathway involved in BCP crystal effects on articular chondrocytes. They highlight a new pathophysiological mechanism and give rise to a new therapeutic target in diseases related to BCP crystal deposition.

Disclosure: C. Nguyen, None; **H. K. Ea**, None; **C. Bordat**, None; **M. Lieberherr**, None; **F. Lioté**, None.

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Increasing Allopurinol Dose Above the Recommended Range Is Effective and Safe in Chronic Gout, Including in Those with Renal Impairment – a Pilot Study. Lisa Stamp[1], J.L. O'Donnell[2], M. Zhang[3], C. Frampton[4], M. Barclay[3] and PT Chapman[3], [1]University of Otago, Dunedin, New Zealand, [2]Canterbury Health Laboratories, Christchurch, [3]Christchurch Hospital, Christchurch, New Zealand, [4]University of Otago, Christchurch, New Zealand

Purpose: Allopurinol is the most commonly used urate lowering therapy. Recommended dosing guidelines based on creatinine clearance (CrCL) have been published. However, many patients fail to achieve adequate serum uric acid (SUA) reduction with recommended doses. The aim of this study was to determine whether using allopurinol above recommended doses leads to adequate reduction in SUA without increase in toxicity.

Methods: Patients with gout on stable dose allopurinol for at least one month were recruited. Recommended allopurinol dose was defined by the Hande criteria based on CrCL. Allopurinol dose was gradually increased to obtain the target SUA ≤6mg/dL. Patients were seen monthly until SUA was ≤6mg/dL for 3 consecutive months. Then patients were seen 3 monthly until at least 12 months after study entry. Data were analyzed using allopurinol mg/day above recommended dose in 50mg increments (R+).

Results: 90 patients were enrolled. Mean age 58.3years (27-83yrs), 87.8% male, and 78% European. At the initial visit, 52 had SUA >6mg/dL, of whom 7 were on lower than recommended doses of allopurinol. 45 patients had the dose of allopurinol increased above the recommended range. Baseline mean CrCl in the dose escalation group was 61.9mls/min (19-132) and mean SUA was 7.4 mg/dL (6-10.8mg/dL). Three patients developed rashes (2 receiving concomitant frusemide) and discontinued allopurinol or ceased dose escalation.

Six patients were lost to follow-up. All patients were included in the analysis until lost or stopped allopurinol. Of the 36 patients who completed the entire 12-month study period, 31 (85%) patients achieved a SUA ≤6mg/dL at the 12 month end point. Of the 5 patients who had SUA>6mg/dL 2 had undetectable plasma oxypurinol indicating non-compliance. There was a significant reduction in SUA at all allopurinol doses above recommended ($p<0.001$). The percentage decrease in SUA from baseline was -12.6% R+50mg, -20.8% R+100mg, -25.9% R+150mg, -36.2% R+200, -30% R+250mg and -35.6% R+300mg. 18/45 patients were receiving frusemide or a thiazide diuretic. There was no significant difference between baseline SUA in those receiving diuretic treatment or not. Baseline doses of allopurinol were higher in those patients on frusemide (248 vs 180mg/d $p=0.003$). Patients on frusemide were just as likely to achieve SUA ≤6mg/dL as patients not on frusemide (72% vs 88.5% $p=0.24$). Other than the three patients with rashes there were no significant toxicities.

Conclusion: Increasing the dose of allopurinol above the recommended range led to a significant reduction in serum urate. 86% of patients achieved a SUA ≤6mg/dL. There was no increase in toxicity with higher doses of allopurinol in this cohort, including those with renal impairment.

Disclosure: L. Stamp, WYETH, 6 ; **J. L. O'Donnell**, None; **M. Zhang**, None; **C. Frampton**, None; **M. Barclay**, None; **P. Chapman**, None.

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Dynamics of Transcription Regulation of Urate Crystal Inflammation in a Synovium-Like Tissue. Christian T. Mayer[1], John W. Tobias[1], Joseph P. Menetski[2], H. R. Schumacher Jr.[3] and Frank Pessler[4], [1]University of Pennsylvania, Philadelphia, PA, [2]Merck Research Labs, NJ, [3]U Penn & VA Med Ctr, Philadelphia, PA, [4]Technical University Dresden Children's Hospital, 01307 Dresden, Germany

Purpose: Monosodium urate (MSU) crystals, the causative agent of gout in humans, elicit acute inflammation driven by innate immunity, including TLRs 2 and 4 and the Nalp3 inflammasome. Whereas much has been revealed about the cellular aspects of MSU crystal inflammation, very little is known about molecular effects of the crystals on intact tissues, including the synovial membrane. We have begun to define major steps in transcriptional reprogramming in the murine air pouch (a structure closely resembling the human synovial membrane) during a complete time course of MSU crystal inflammation.

Method: MSU crystals (2 mg in 1ml PBS) were injected into 6-day-old murine air pouches (n=36). Six pouches each were harvested at 0h (control pouches), 1h, 4h, 9h, 18h, 27h, and 50h after crystal injection. The pouch exudates were obtained by lavage with 2ml PBS, and the pouch membranes then meticulously dissected away from the adjacent subcutaneous tissue. Leukocyte density in the pouch exudates was used to measure the degree of inflammation. Total RNA was extracted from the dissected membranes and reverse transcribed into cDNA. Using custom low-density PCR arrays, we then analyzed the expression of 94 target mRNAs encoding pro- and anti-inflammatory cytokines, inflammasome constituents, MMPs, transcription factors, and factors involved in apoptosis, cell cycle, and prostaglandin metabolism. Normalized expression data were analysed with the Partek Genomic Suite and SpotFire Decision Site bioinformatics software programs.

Results: Averaged over all mRNAs, transcriptional induction was 100-fold, peaked 4h after crystal injection, and gradually returned near baseline by 50h. Euclidian distance similarity calculation confirmed that transcriptional reprogramming was most intense at 4h. Leukocyte density in the pouch exudate also normalized by 50h, but differed kinetically in that it peaked 5h after the maximum of transcriptional reprogramming. Hierarchical clustering analysis revealed 3 clusters of temporally coregulated mRNAs: (1) an early burst that included major pro- (e.g., IL-1b, IL-6, TNFa) and anti-inflammatory (IL-10) cytokines; (2) a more sustained second wave including MMPs, the anti-inflammatory enzyme arginase, surface receptors involved in prostaglandin synthesis, TLR signalling; and (3) a prolonged resolution phase characterized by increased expression of CD68 and the anti-inflammatory factors PPAR-g, h-prostaglandin D synthase, and TGF-b.

Conclusion: On the basis of gene expression analysis, MSU crystal inflammation in a synovium-like tissue can be separated into three distinct phases (Fig. 1). Modulating the relative extent and/or duration of each phase may be a major effect of anti-inflammatory pharmacological interventions.

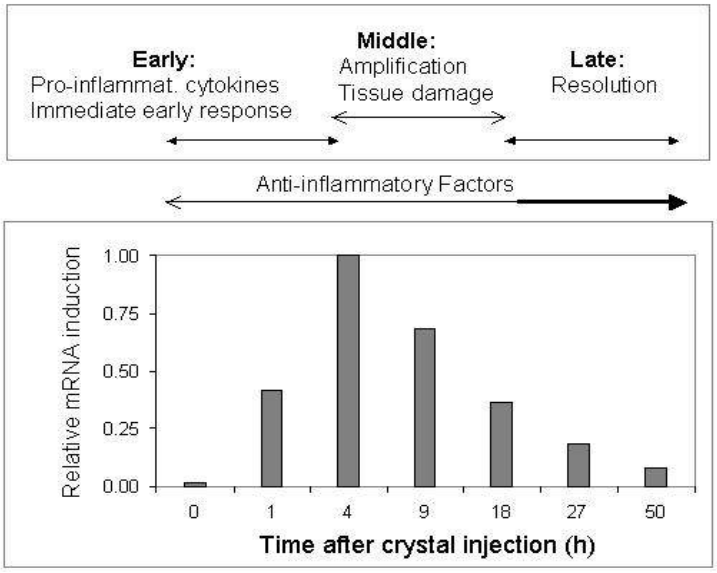

Fig. 1. Summary of the 3 phases of transcriptional reprogramming of MSU crystal inflammation in the murine air pouch membrane.

Disclosure: C. T. Mayer, None; **J. W. Tobias**, None; **J. P. Menetski**, None; **H. R. Schumacher**, Takeda, 5, Regeneron, 5, Pfizer , 5, Savient, 5 ; **F. Pessler**, None.

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Therapy: Safety

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

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Long-Term Safety of Rituximab: Long-Term Follow-up of the RA Clinical Trials and Retreatment Population. Ronald F. van Vollenhoven[1], Paul Emery[2], Clifton O. Bingham III[3], Edward C. Keystone[4], Roy M. Fleishmann[5], Daniel E. Furst[6], Katherine Macey[7], Marianne T. Sweetster[8], Patricia B. Lehane[7], Pamela Farmer[9] and Simon G. Long[7], [1]The Karolinska Institute, Stockholm, Sweden, [2]Leeds General Infirmary, Leeds, United Kingdom, [3]Johns Hopkins University, Baltimore, MD, [4]Professor of Medicine/University of Toronto, Toronto, ON, [5]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [6]UCLA, Los Angeles, CA, [7]Roche Products Ltd, Welwyn Garden City, United Kingdom, [8]Biogen Idec Inc., Cambridge, MD, [9]Genentech, Inc., South San Francisco, CA

Purpose: To evaluate the long-term safety of rituximab (RTX) in RA patients (pts) in clinical trials.

Methods: Pooled analysis of safety data from pts treated with RTX in combination with methotrexate (MTX) in a global clinical trial program. All pts were offered retreatment with RTX based on clinical need. Pts receiving placebo during placebo-controlled study periods were pooled to provide a placebo population.

Results: As of September 2008, 3095 pts had been treated with RTX providing 7198 pt-years (pt-yrs) of exposure. Over 750 patients had been followed for >3 years with 2365, 1581, 1038 and 497 pts receiving ≥2, ≥3, ≥4 and ≥5 courses, respectively. Other than infusion-related reactions (IRR), the safety profile of RTX was similar to the pooled placebo population (Table). In the RTX group, the most frequent

adverse event (AE) was IRR (35%), most of which were CTC grade 1 or 2 and occurred after the first infusion of the first course (23%), with <1% considered serious. The rates of serious AEs (SAEs) and infections remained stable over time and also between RTX courses. The rate of serious infection was 4.25 events/100 pt-yrs and was comparable to that observed in the placebo population (4.33 events/100 pt-yrs). The most frequent serious infections were of the lower respiratory tract, predominantly pneumonia (1%). No cases of TB or reactivation of hepatitis B were reported. Serious opportunistic infections were uncommon, but included one confirmed case of *Pneumocystis jiroveci* pneumonia in each of the RTX and pooled placebo groups and one case of progressive multifocal leukoencephalopathy (PML) in the RTX group. The causal relationship of PML to RTX in this case was unclear due to recognized risk factors including carcinoma of the oropharynx treated by chemoradiotherapy. Rates of MI and stroke were consistent with the general RA population. The standardized incidence ratio (SIR) for malignancy compared with the SEER 2008 database was 1.06 (95% CI 0.81–1.37). The most frequently reported malignancy (excluding non-melanoma skin cancer) was breast cancer (SIR 0.69; 95% CI 0.35–1.24).

	All exposure	**Pooled placebo**
No. pts (n)	3095	819
Total pt-yrs	7198	832
IRR (%)	35%	22%
SAE rate/100 pt-yrs	16.5	15.7
(95% CI)	(15.59–17.47)	(13.3–18.7)
Infection rate/100 pt-yrs	97.4	103.7
(95% CI)	(95.14–99.7)	(97–110.9)
Serious infection rate/100 pt-yrs	4.25	4.33
(95% CI)	(3.8–4.75)	(3.1–6)

Conclusion: In prolonged follow-up of RA pts treated with RTX in clinical trials, RTX has remained well tolerated over multiple courses with a stable safety profile similar to the pooled placebo population.

Disclosure: R. F. van Vollenhoven, Schering-Plough, 2, Abbott Immunology Pharmaceuticals, 2, Wyeth Pharmaceuticals, 2, Roche, 2 ; **P. Emery**, Roche Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 9 ; **C. O. Bingham**, Genentech and Biogen IDEC Inc., 2, Wyeth Pharmaceuticals, 2, Bristol-Myers Squibb, 2, UCB, 2, Abbott Laboratories, 5, Amgen, 5, Cypress Biosciences, Inc., 5, Genentech and Biogen IDEC Inc., 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5, Osiris Therapeutics, 5, Roche Pharmaceuticals, 5, Targeted Genetics, 5, UCB, 5 ; **E. C. Keystone**, Abbott Laboratories, 2, Centocor, 2, Amgen, 2, Abbott Laboratories, 5, Centocor, Inc., 5, Amgen, 5 ; **R. M. Fleishmann**, Abbott Laboratories, 1, Merck Pharmaceuticals, 1, Proctor and Gamble, 1, Amgen, 2, Wyeth Pharmaceuticals, 2, Abbott Laboratories, 2, Centocor, Inc., 2, UCB, 2, Genentech and Biogen IDEC Inc., 2, Roche Pharmaceuticals, 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2, Bristol-Myers Squibb, 2, Regeneron, 2, XDx, 2 ; **D. E. Furst**, Gilead, 9, Genentech and Biogen IDEC Inc., 9, Centocor, Inc., 9, Biogen Idec, 9, Bristol-Myers Squibb, 9, Amgen, 9, Actelion Pharmaceuticals US, 9, Abbott Immunology Pharmaceuticals, 9, Xoma, 9, Wyeth Pharmaceuticals, 9, UCB, 9, Novartis Pharmaceutical Corporation, 9, Nitec, 9, Merck Pharmaceuticals, 9, Gilead, 9, Genentech and Biogen IDEC Inc., 9, Centocor, Inc., 9, Biogen Idec, 9, Bristol-Myers Squibb, 9, Amgen, 9, Actelion Pharmaceuticals US, 9, Abbott Immunology Pharmaceuticals, 9, Xoma Corporation , 9, Wyeth Pharmaceuticals, 9, UCB, 9, Roche Pharmaceuticals, 9, Novartis Pharmaceutical Corporation, 9, Nitec, 9, GlaxoSmithKline, 9, Gilead, 9, Genentech and Biogen IDEC Inc., 9, Bristol-Myers Squibb, 9, Amgen, 9, Actelion Pharmaceuticals US, 9, Abbott Immunology Pharmaceuticals, 9, Merck Pharmaceuticals, 9, Nitec, 9, Abbott Immunology Pharmaceuticals, 9, Actelion Pharmaceuticals US, 9, UCB, 9 ; **K. Macey**, Roche Pharmaceuticals, 3 ; **M. T. Sweetster**, Biogen Idec, 1, Biogen Idec, 3 ; **P. B. Lehane**, Roche Pharmaceuticals, 3 ; **P. Farmer**, Genentech and Biogen IDEC Inc., 3 ; **S. G. Long**, Roche Pharmaceuticals, 1, Roche Pharmaceuticals, 3 .

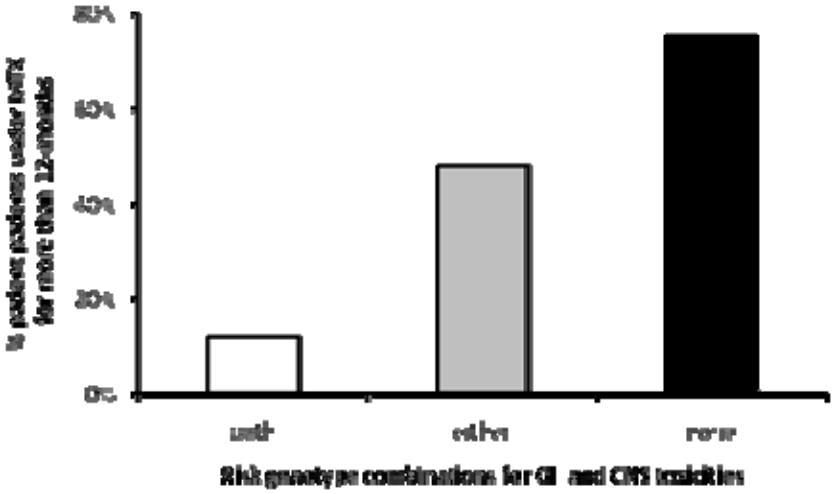
1953

Gene-Gene Interactions Among Folate, Purine and Pyrimidine Gene Pathways Impact Methotrexate Tolerability in Rheumatoid Arthritis. Thierry Dervieux[1], Judith Wessels[2], Tahar van der Straaten[2], Jason Moore[3], Nadia Penrod[3], Henk-Jan Guchelaar[2] and Joel M. Kremer[4], [1]Cypress Bioscience, San Diego, CA, [2]Leiden Medical Center, Leiden, Netherlands, [3]Dartmouth-Hitchcock Medical Center, Lebanon, [4]Albany Medical College, Albany, NY

Purpose: Dose-limiting gastrointestinal and neurological toxicities are common in patients with rheumatoid arthritis (RA) treated with the antimetabolite Methotrexate (MTX). We sought to evaluate whether gene-gene interactions (epistasis) in folate, purine and pyrimidine gene pathways contributed to these idiosyncrasies in RA.

Method: A total of 158 patients under MTX for more than three months were evaluated. MTX side effects were defined as those affecting the gastrointestinal tract (nausea, diarrhea, stomatitis, dyspepsia, elevation of aspartate aminostransferase (AST)>twice the upper limit normal) or the central nervous system (headache, lethargy). Fourteen single nucleotide polymorphisms were measured. Detection and interpretation of non-linear gene-gene interactions was performed using multifactor dimensionality reduction (MDR) which reduces genetic information to one-dimension by combining higher and lower-risk genotype combinations into two separate groups.

Results: Gastrointestinal and neurological side effects were observed in 23% and 21% of patients, respectively. MDR analysis identified epistatic interactions among variants in Methylene Tetrahydrofolate Reductase (MTHFR A1298C), Inosine-Triphosphate Pyrophosphatase (ITPA C94A) and γ-Glutamyl Hydrolase (GGH -354 G/T). These contributed to MTX-induced gastrointestinal idiosyncrasies, with a 7.3-fold higher likelihood of these adverse events in patients having the higher-risk genotype combination (vs. without; CI95%: 3.2-16.8;p<0.001). Interactions among MTHFR A1298C, Thymidylate Synthase (TSER*2/*3), and Serine HydroxyMethyltransferase (SHMT C1420T) variants contributed to neurological toxicities which were 10.1-fold more likely to occur in patients carrier of a predisposing risk-genotype combination (CI 95%: 4.3-23.8; p<0.001). Altogether, the presence of risk genotype combinations for gastrointestinal or neurological toxicities (52%) was associated with an 8.9-fold higher likelihood to present gastrointestinal or neurological toxicities (CI 95%: 3.6-21.9; p<0.001). There was a 2-fold overrepresentation of patients without predisposing risk genotypes in those who received MTX for more than 12-months (72%) versus those who received MTX for less than 12-months (37%) (p<0.001). Seventy-two percent of patients receiving MTX after 12 months did not carry either predisposing risk genotype combinations, while only 12% who carried both predisposing risk genotypes continued treatment beyond this time period (p<0.001).



Conclusion: These hypothesis generating data indicate that gene-gene interactions contribute to MTX-induced adverse events in RA and suggest that the presence of risk genotypes may impact the rate of MTX discontinuation.

Disclosure: T. Dervieux, Cypress Bioscience, 1 ; **J. Wessels**, None; **T. van der Straaten**, None; **J. Moore**, Cypress Bioscience, 5 ; **N. Penrod**, None; **H. J. Guchelaar**, None; **J. M. Kremer**, None.

1954

Liver Enzyme Levels in Patients Receiving Tocilizumab with Methotrexate: 1-Year Results From the LITHE Study. J. Kremer[1], Alain Cantagrel[2], C. Montecucco[3], R. Malamet[4], R. Pilson[4] and M. H. Schiff[5], [1]Albany Medical College, Albany, NY, [2]JE 2510, Purpan University Hospital, Toulouse, France, [3]IRCCS Policlinico S Matteo, Pavia, Italy, [4]Roche, Nutley, NJ, [5]University of Colorado, Denver, CO

Purpose: The effect of tocilizumab (TCZ) + methotrexate (MTX) on liver enzyme levels was analyzed in patients (pts) in the 2-y, phase 3, double-blind, randomized controlled study LITHE. One-year findings are presented.

Method: Pts with radiographic evidence of joint damage and inadequate response to MTX were randomized to placebo + MTX (control), TCZ 4 mg/kg + MTX (TCZ4), or TCZ 8 mg/kg + MTX (TCZ8). TCZ or placebo was infused every 4 wks; MTX dose was 10-25 mg/wk. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) levels were assessed at baseline and every 2 wks to wk 8, then every 4 wks to wk 52. Results of liver enzyme testing were not required prior to infusions; TCZ interruption and/or MTX dose reduction/interruption (ie, treatment modification) were applied as deemed necessary by investigators (1-3x upper limit of normal [ULN]) or per protocol prior to later infusions (>3x ULN).

Results: The population included 399 TCZ8, 399 TCZ4, and 392 control pts. ALT and AST increased from normal at baseline to >3× ULN in 9% and 3% of TCZ8 pts, 7% and 2% of TCZ4 pts, and 0.8% and 0.3% of controls during 52 wks, respectively (Table). TBILI shifts occurred in 0.3% of TCZ8 pts. Most pts with single occurrences of ALT or AST elevations normalized without treatment modification in TCZ8 (44/67; 56/72), TCZ4 (64/77; 64/75), and control (37/46; 32/39) pts. More TCZ8 pts than TCZ4 or control pts had ALT or AST elevations >ULN in ≥6 of 12 monthly determinations (Table). More pts with ≥6 ALT or ≥6 AST elevations started the study with normal levels than with elevated levels (Table). Treatment modifications were used for ≥6 ALT and ≥6 AST elevations in 56/95 and 21/34 TCZ8 pts, 17/36 and 5/10 of TCZ4 pts, and 3/11 and 1/3 controls, respectively. In the entire population, 3, 8, and 12 pts were withdrawn due to transaminase level elevations from the control, TCZ4, and TCZ8 groups, respectively. Liver biopsies were conducted at investigator discretion for 3 TCZ8 pts. TBILI (primarily indirect) of >3× ULN was seen in 1 TCZ8 pt and was not associated with ALT/AST level elevations. No drug-induced liver injury (as indicated by hepatic dysfunction or clinical signs of hepatitis) was seen.

Conclusion: Most pts with ALT/AST elevations >ULN ≥6 times in 12 mos underwent some form of treatment modification. These recurrent ALT/AST level elevations were manageable and not associated with known liver injury or hepatitis. Clinicians should obtain liver enzyme levels at baseline, monitor for elevated ALT/AST levels, and adjust treatment accordingly.

Table

	PBO + MTX n=392	TCZ4 + MTX n=399	TCZ8 + MTX n=399
ALT			
Normal at baseline→ >1-3× ULN, % (n)[a]	23.7 (93)	46.1 (184)	51.6 (206)
Normal at baseline→ >3×ULN, % (n)[a]	0.8 (3)	7.0 (28)	9.0 (36)
Patients with ≥6 elevations, % (n)	2.8 (11)	9.0 (36)	23.8 (95)
Normal at baseline, n	5	30	73
Elevated at baseline, n	6	6	22
AST			
Normal at baseline→ >1-3× ULN, % (n)[a]	19.4 (76)	39.6 (158)	50.6 (202)
Normal at baseline→ >3× ULN, % (n)[a]	0.3 (1)	1.8 (7)	2.8 (11)
Patients with ≥6 elevations, % (n)	0.8 (3)	2.5 (10)	8.5 (34)
Normal at baseline, n	1	10	31
Elevated at baseline, n	2	1	3
Total Bilirubin			
Normal at baseline→ >1-3× ULN, % (n)	1.3 (5)	6.0 (24)	10.0 (40)
Normal at baseline→ >3× ULN, % (n)	—	—	0.3 (1)

[a] Patients had 1 or more elevations.

Disclosure: J. Kremer, Roche Pharmaceuticals, 5 ; **A. Cantagrel**, Roche Pharmaceuticals, 2, Wyeth Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 8 ; **C. Montecucco**, None; **R. Malamet**, Roche Pharmaceuticals, 3 ; **R. Pilson**, Roche Pharmaceuticals, 3 ; **M. H. Schiff**, Roche Pharmaceuticals, 5 .

1955

Long-Term Safety and Tolerability of Tocilizumab Treatment in Patients with Rheumatoid Arthritis and a Mean Treatment Duration of 2.4 Years. Ronald F. van Vollenhoven[1], D. Siri[2], R. Furie[3], J. Krasnow[4], E. Alecock[5] and R. Alten[6], [1]Karolinska Univ Hosp, Stockholm, Sweden, [2]CAICI Institute, Rosario, Argentina, [3]NS-LIJHS, Lake Success, NY, [4]Roche, Nutley, NJ, [5]Roche, Welwyn, United Kingdom, [6]Schlosspark-Klinik, Berlin, Germany

Purpose: The safety of tocilizumab (TCZ) as monotherapy or with DMARDs has been demonstrated in patients with rheumatoid arthritis (RA) in phase 3 clinical trials and long-term extension studies. The objective of this analysis was to assess the longer-term safety of TCZ in patients with RA using pooled data from the ongoing long-term extension studies and an ongoing phase 3 trial.

Method: The study population included all patients who received at least 1 dose of TCZ in the 24-week, phase 3 clinical trials (OPTION, AMBITION, RADIATE, TOWARD), in the phase 3 clinical trial (LITHE), in a phase 1 study, or in the ongoing, open-label extension studies (GROWTH95, GROWTH96). Safety data were pooled and analyzed from the time of the initial TCZ exposure to the cutoff date of February 6, 2009.

Results: TCZ was administered to 4009 patients, mean treatment duration was 2.4 years, and total treatment exposure was 9414 patient-years (PY). The rate of withdrawals because of adverse events (AEs) was 5.8/100 PY and was driven by elevated liver enzyme levels, infections, and benign and malignant neoplasms. Overall rate/100 PY of serious AEs was 14.91, of serious infections was 4.7, of deaths was

0.53, and of deaths from infection was 0.13. Rates/100 PY of upper and lower GI perforations were 0.01 for stomach/duodenum, 0.03 for small intestine, 0.02 for appendix, and 0.19 for large intestine. Malignancies occurred at an overall rate of 1.16/100 PY, without excess of any one type. Overall rates/100 PY for myocardial infarction and stroke were 0.25 and 0.19, respectively, and did not increase with TCZ exposure. Total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels increased at week 6 and remained relatively stable over time; 313 (7.8%) patients who initiated lipid-lowering therapy during treatment with TCZ generally responded to treatment without complications. The incidences of ALT and AST elevations >3× the upper limit of normal were 3.6% and 1.4%, respectively, during the first 24 weeks of treatment, and the rates did not increase over time. Transaminase elevations were not associated with clinically apparent hepatitis or hepatic dysfunction.

Conclusion: These results demonstrate that no new safety signals have emerged with prolonged exposure to TCZ. Transaminase elevations were not associated with clinically important events. During longer-term treatment with TCZ (median duration greater than 2.5 years), the risks for AEs and serious AEs were stable over time and laboratory changes could be effectively managed. These data support a favorable benefit/risk ratio for TCZ in patients with moderate to severe RA.

Disclosure: R. F. van Vollenhoven, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 ; **D. Siri**, None; **R. Furie**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5 ; **J. Krasnow**, Roche Pharmaceuticals, 3 ; **E. Alecock**, Roche Pharmaceuticals, 3 ; **R. Alten**, Roche Pharmaceuticals, 5 .

1956

Does the Risk of Infections in Anti-TNF Treated Patients Decrease Over Time? Joachim Listing[1], Anja Strangfeld[2], Matthias Schneider[3], Winfried Demary[4], Hans Joachim Bergerhausen[5], Christina Bungartz[2] and Angela Zink[2], [1]DRFZ, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]MNR-Klinik, Duesseldorf, [4]Rheumatologist in Private Practice, Hildesheim, Germany, [5]Wedau Kliniken, Duisburg, Germany

Purpose: Data of the German biologics register RABBIT were used to determine the influence of anti-TNF treatment, outcome of this treatment, confounding by indication, and dropout processes on the risk of developing serious infections. Our objective was to investigate whether there is a decline in the risk of serious infections in patients with rheumatoid arthritis (RA) receiving TNFα inhibitors and if so what are the reasons for.

Method: RABBIT is an ongoing prospective cohort study. Patients are enrolled in the biologics groups at start of an approved biological therapy or at start of a new DMARD treatment after at least one DMARD failure. At fixed time points at follow-up rheumatologists assess the clinical status, report treatment details and adverse events according to ICH guidelines.

Results: Data of 5,044 RA patients was available for the analysis. Among them 3,270 received TNFα inhibitors and 1,774 DMARDs at study entry. Crude rates of serious infections increased slightly in DMARD treated patients from 2.4 /100 patient years (PY) in the 1st year to 2.5, 2.8/100 PY in the 2nd and 3rd year respectively (p=0.74) whereas in anti-TNF treated patients a significant decrease (p<0.0001) from 5.0/100 (PY) in the 1st year to 3.1/100 PY in the 2nd and to 2.0/ 100 PY in the 3rd year was observed. Already in the first year there were highly significant differences in the crude infection rates of anti-TNF treated patients who completed treatment for at least 12 months (1.8/100 PY), switched to treatment with DMARDs (10.2/100PY) dropped out or switched to non-anti-TNF biologics (16.8/100 PY). This selection process led to a lower exposure time under anti-TNF treatment in the 2nd (56% of time) or 3rd year (68% of time) in patients with serious infections in the 1st year. This process caused a depletion of susceptibles since patients with one serious infection in the first year were at a significantly higher risk of developing a serious infection in the following years. By applying marginal structural models to account for time-varying risk factors and selection processes at follow-up (confounding by indication, dropouts) we could explain the decrease in the relative risk (RR) of serious infections under anti-TNF treatment compared to DMARD in the second year (crude RR: 1.3, adjusted RR: 2.0 (95% CI: 0.8 – 4.9). According to these models the decrease was mainly caused by confounding by indication at follow-up. A similar result was found for the 3rd year (adjusted RR: 1.7 (95%CI: 0.6 - 4.7).

Conclusion: Patients with serious infections were at higher risk of further infections and were less likely treated with anti-TNF agents at follow-up. Our data suggest that the depletion of susceptibles is a main cause for the observed decrease in the serious infection rates of anti-TNF treated patients.

Disclosure: J. Listing, None; **A. Strangfeld**, None; **M. Schneider**, None; **W. Demary**, None; **H. J. Bergerhausen**, None; **C. Bungartz**, None; **A. Zink**, None.

1957

Safety of Rituximab in Combination with a TNF Inhibitor and Methotrexate in Patients with Active Rheumatoid Arthritis: Results From a Randomized Controlled Trial (TAME). M. Greenwald[1], W. Shergy[2], J. L. Kaine[3], M. T. Sweetser[4], K. Gilder[5] and M. D. Linnik[6], [1]Desert Medical Advances, Palm Desert, CA, [2]Univ of Alabama, Huntsville, AL, [3]Sarasota Arthritis Center, Sarasota, FL, [4]Biogen Idec, Cambridge, MA, [5]Biogen Idec, San Diego, [6]Biogen Idec, San Diego, CA

Purpose: Rituximab (RTX) improves signs and symptoms and slows joint damage progression in patients (pts) with rheumatoid arthritis (RA). This study explored the safety of RTX in combination with a TNF inhibitor (etanercept or adalimumab) and MTX in pts with active RA.

Methods: Pts with active RA (swollen joint count ≥5 and tender joint count ≥5) receiving a stable dose of etanercept (50 mg qw) or adalimumab (40 mg q2w) and methotrexate (10-25 mg qw) for at least 12 weeks were eligible. Pts were randomized 2:1 and treated with 500 mg RTX or placebo (PLA) on Days 1 and 15. After Wk 24, eligible pts could enter open-label treatment with RTX. The primary endpoint was the proportion of pts who experience ≥1 serious infection through Wk 24. Secondary endpoints evaluated additional safety and efficacy parameters.

Results: Fifty-one pts received at least one dose of study treatment (33 RTX, 18 PLA). The concomitant TNF inhibitors were balanced between treatment groups: etanercept (76% vs 78%) and adalimumab (24% vs 22%) for RTX and PLA, respectively. Baseline characteristics were balanced between groups, including disease duration (10.5 yrs), duration on TNF inhibitor (2.2 yrs), HAQ (1.4) and CRP (0.92 mg/dL) with the exception of oral steroid use (36% RTX vs. 17% PLA). Through Wk 24, there was 1 (3%) serious infection (pneumonia on Day 45) in the RTX group and 0 in PLA. Any infection was reported in 18 (55%) RTX pts and 11 (61%) PLA pts with an average duration of 12.6 days (sd 9.6) and 14.5 days (sd 5.2), respectively. Grade 3 infections were reported in 3 (9%) RTX pts (pneumonia on Day 45, influenza on Day 105 and postoperative infection on Day 116) and 0 PLA pts. There were no grade 4 infections. There were 2 (6%) pts with serious adverse events in RTX and 0 in PLA. Through Wk 24, there was 1 serious infection in 15.55 pt-yrs of exposure in the RTX group (6.43 events per 100 pt-yrs, 95% CI: 0.91-45.65) and none in PLA. Overall data, including the open label extension phase, revealed no further serious infections in 46.35 pt-yrs (2.16 events per 100 pt-yrs, 95% CI: 0.30-15.32) in pts receiving 1 or 2 courses of RTX. At Wk 24, the percentage of pts with ACR20 and ACR50 responses was 30% vs 17% and 12% vs 6% for RTX and PLA, respectively.

Conclusion: The preliminary safety profile of RTX in combination with a TNF inhibitor (etanercept or adalimumab) and MTX was consistent with the safety profile of RTX with MTX in other RA trials without a TNF inhibitor, with no new safety signals seen. A larger open-label study evaluating the safety profile of RTX in combination with TNF inhibitors and non-biologic DMARDs is in progress.

Disclosure: M. Greenwald, Genentech and Biogen Idec, 2 ; **W. Shergy**, Genentech , 8 ; **J. L. Kaine**, None; **M. T. Sweetser**, Biogen Idec, 3 ; **K. Gilder**, Biogen Idec, 3 ; **M. D. Linnik**, Biogen Idec, 3, Biogen Idec, 1 .

ACR Concurrent Abstract Sessions

Sjögren's Syndrome

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

1958

The Distribution of Inflammatory Cells at the Autoimmune Minor Salivary Gland (MSG) Lesions of Sjögren's Syndrome (SS) Varies According to Lesion Severity: Correlation with Adverse Prognostic Factors. MI Christodoulou[1], Ek Kapsogeorgou[1], NM Moutsopoulos[2] and HM Moutsopoulos[1], [1]Athens Medical School, Athens, Greece, [2]NIDCR, Bethesda, MD

Purpose: The MSG lymphocytic infiltrates of SS patients extend from mild to severe. They mainly consist of T and B cells, while antigen presenting cells have been reported in heavy lesions. However, the variation of the infiltrating mononuclear cell (MNC) types in SS lesions of distinct severity is not well defined. Herein, we study the distribution of the infiltrating MNC types in SS lesions of variable severity and possible correlations with adverse prognostic factors.

Method: SS patients with mild (n=11), intermediate (n=13) or severe (n=15) MSG lesions (Tarpley score 1, 2 or 3/4, respectively) were studied. Total T, $CD4^+$T, CD8+T, Treg, and B cells, macrophages (MΦ), interdigitating (iDC) and follicular dendritic cells (fDC) and natural-killer (NK) cells were identified immunohistochemically by antibodies to CD3, CD4, CD8, FOXP3, CD20, CD68, S100, fascin and CD56, respectively. Positively stained cells were counted field by field in each MSG section and expressed as incidence (% total infiltrating MNC). One-way ANOVA for linear trend, Spearman's correlation, Tukey's multiple comparison statistical tests and multivariate linear regression analysis (backward stepwise) were applied.

Results: T cells were found to predominate in mild lesions, whereas B cells in severe. The differential distribution of T cells was attributed to $CD4^+$T cell variation, while $CD8^+$T cells remained unchanged. Compared to mild or severe infiltrates, higher Treg incidence was detected in intermediate lesions. MΦ and iDC incidence was positively and negatively associated with lesion severity, whereas similar percentages of NK cells were detected in all SS groups (Table). Total T, $CD4^+$T cell and iDC incidence was negatively, whereas B cell and MΦ incidence was positively correlated with biopsy focus score. Multivariate analysis revealed positive correlations between the incidence of Treg / NK cells and serum C4 levels, Treg / B cells and extraglandular manifestations, fDC and cryoglobulinemia, MΦ and purpura, and T/$CD4^+$T cells and arthritis, and negative correlations of T, $CD4^+$T, iDC and NK cells with extraglandular manifestations and MΦ with arthritis.

			Infiltrating	MNCs	(mean	percentage	± SE)		
MSG Lesions	T	$CD4^+$T	$CD8^+$T	Tregs	B	MΦ	iDC	fDC	NK
Mild	58.6±2.9	41.7±2.4	16.4±2.0	1.3±0.4	34.7±3.2	2.4±0.6	1.3±0.2	2.3±0.5	0.03±0.01
Intermediate	48.1±1.9	35.1±2.4	13.3±1.8	2.8±0.5	45.2±2.2	3.8±0.8	0.5±0.1	1.6±0.3	0.04±0.01
Severe	40.3±2.4	23.5±2.7	16.7±0.9	1.4±0.3	50.3±2.7	6.6±1.4	0.5±0.1	1.9±0.4	0.05±0.01

Conclusion: The distribution of the infiltrating MNC populations at the SS lesions varies according to lesion severity and correlates with certain adverse prognostic factors. The significance of this differential distribution and the operating aetiopathogenic factors need to be elucidated.

Disclosure: M. Christodoulou, None; **E. Kapsogeorgou**, None; **N. Moutsopoulos**, None; **H. Moutsopoulos**, None.

1959

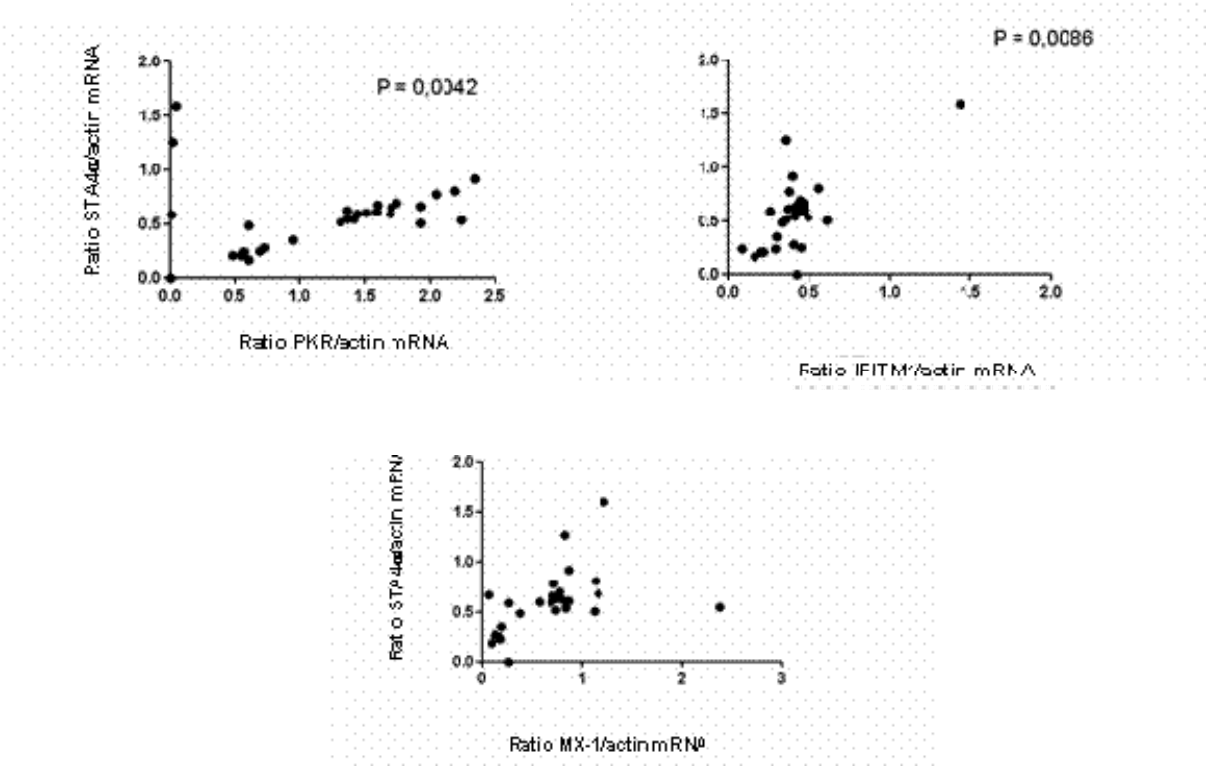
STAT4 Polymorphism Is a Confirmed Genetic Risk Factor for Sjögren's Syndrome That Could Be Involved in Type 1 Interferon Pathway Signalling. Corinne Miceli-Richard[1], Nicolas Gestermann[2], Pascale Loiseau[3], Xavier Puéchal[4], Eric Hachulla[5], Jacques-Eric Gottenberg[6] and Xavier Mariette[7], [1]Hôpital Bicêtre, Le Kremlin Bicêtre, France, [2]Bicêtre hospital, INSERM U802, Le Kremlin Bicêtre, France, [3]Hôpital Saint-Louis, Paris, France, [4]Centre Hospitalier Du Mans, Le Mans, France, [5]National scleroderma centre, Lille Cedex, France, [6]University Hospital of Strasbourg, Strasbourg, France, [7]Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France

Purpose: Signal transducer and activator of transcription 4 (STAT4) is a transcription factor activated mainly by interleukin 12 (and to a lesser extent by type 1 IFN) which promotes secretion of type 2 IFN by Th1 cells. *STAT4* gene polymorphisms have been significantly associated with various autoimmune diseases – rheumatoid arthritis, lupus and primary Sjögren's syndrome (pSS) by 2 independent groups. The functional consequences of STAT4 associated polymorphisms are poorly understood with limited data available yet. This study aimed to confirm or not the association between *STAT4* gene polymorphism and SSp and to assess the functional relevance of the at-risk genotypes on STAT4 mRNA level of expression (a and b subunits).

Method: We analyzed *STAT4* rs7582694 polymorphism in an exploratory cohort of 190 pSS patients and 152 controls, and in a second independent cohort of 192 pSS patients, all of Caucasian origin. This polymorphism was genotyped by Taqman genotyping assay (Applied Biosystem). STAT4a and STAT4b mRNA levels were assessed in PBMCs from 30 pSS patients and correlated with the level of expression of PKR, MX1 and IFITM1 as surrogate markers of the type 1 IFN induction pathway.

Results: The *STAT4* rs7582694 C allele was found among 28% of pSS patients compared with 17% in controls ($P=1.4.10^{-3}$ - OR 1.83 (95% CI 1.26 – 2.65). In the replication pSS cohort, *STAT4* rs7582694 C allele frequency was comparable (30%). The overall OR for pSS in the combined cohorts was 1.92 (95% CI 1.37 – 2.68 – $P=1.10^{-4}$). This OR was even higher when considering pSS patients and controls homozygous for the rs7582694 C allele, suggesting a recessive effect of the *STAT4* at-risk allele: OR 3.96 (95% CI 1.38 – 11.30.20; $P=6.10^{-3}$). The association was present both in patients with and without anti-SSA/SSB antibodies. *STAT*a and STAT4b mRNA levels in PBMCs were not significantly determined by rs7582694 genotypes (P=0.99 and P=0.17, respectively) but STAT4a was strongly correlated with the IFN type I induced genes mRNA levels: PKR ($P=4.10^{-3}$), MX-1 ($P=2.10^{-4}$) and IFITM-1 ($P=8.10^{-3}$).

Conclusion: These results confirm a replicated association of *STAT4* polymorphism with pSS with a potential recessive effect on disease susceptibility. Our results do not support the functional relevance of the at-risk genotypes on STAT4a and STAT4b mRNA level of expression. Unexpectedly, STAT4a mRNA expression was highly correlated with the level of expression of type 1 interferon induced genes, supporting a possible involvement of STAT4 not only in type 2 IFN but also in type 1 IFN production.



Disclosure: C. Miceli-Richard, None; **N. Gestermann**, None; **P. Loiseau**, None; **X. Puéchal**, None; **E. Hachulla**, None; **J. E. Gottenberg**, None; **X. Mariette**, None.

1960

Activation of Innate Immunity Leads to Accelerated Development of Sjogren's Syndrome-Like Disorder in NZB/W F1 Mice.

Seshagiri Rao Nandula, Yogesh Scindia, Harini Bagavant and Umesh Deshmukh, University of Virginia, Charlottesville, VA

Purpose: To determine whether chronic activation of innate immunity in genetically susceptible individual will lead to accelerated adaptive immune response and development of Sjogren's syndrome (SS).

Methods: Female NZB/W F1 mice were treated every other day for 2 weeks, either with TLR3 agonist poly (I:C) or PBS. Mice were monitored for the development of SS-like disorder by checking pilocarpine induced saliva flow. Submandibular glands (SMG) were analyzed for lymphocytic infiltration and cell types within the infiltrates were characterized by immunohistochemistry. Gene expression levels of inflammatory cytokines within the SMG were determined by real time PCR. Sera were analyzed for presence of autoantibodies to Ro60 and La. Antibody deposition within the SMG was studied by immunofluorescence.

Results: Repeated injections of poly I:C rapidly induced salivary gland dysfunction that was independent of systemic or localized adaptive immune response. The glandular function recovered completely within 2-3 weeks after the cessation of poly I:C treatment. However, by 4 months post-treatment, the mean saliva volume in poly I:C treated group was significantly lower than the PBS treated group and was associated with severe lymphocytic infiltration within the SMG. The lymphocytic infiltrates were mainly composed of CD4+ T and B cells. In comparison with PBS treated mice, the SMGs from poly I:C treated mice showed significantly higher levels of Il-12a, IL-21 and IL21R gene expression . While IL-17F expression was detected in both groups, IL-17A expression was undetectable. Characterization of CD4+ T cells within the infiltrates showed presence of ICOS+, CXCR5+ cells. The levels of anti-Ro60 and anti-La antibodies were significantly higher in the poly I:C treated group and the SMG from these mice showed IgM and IgG deposition.

Conclusion: Our data suggests a biphasic model for SS development. In the initial phase, chronic activation of innate immunity causes glandular dysfunction. This predisposes the salivary gland for an assault by accelerated adaptive immune response in the later phase. An ensuing localized T-B cell response causes glandular destruction and loss of function. Our data also demonstrates for the first time that IL-21 producing follicular T helper cells (Tfh) and their interaction with B cells within the SMG could be critical for the pathogenesis of SS. Thus, the Il-21 pathway might provide a promising target for future immunotherapy of SS.

Disclosure: S. R. Nandula, None; **Y. Scindia**, None; **H. Bagavant**, None; **U. Deshmukh**, None.

1961

MicroRNA Profiling of Minor Salivary Glands Identifies Disease and Inflammation Biomarkers in Sjögren's Syndrome Patients.

Ilias Alevizos[1], Siddhartha Bajracharya[2], Stefanie Alexander[2], Roy J. Turner[3] and Gabor G. Illei[2], [1]NIH/NIDCR, Bethesda, MD, [2]NIDCR, NIH, Bethesda, MD, [3]Bethesda, MD

Purpose: Sjögren's Syndrome (SS) is an autoimmune disorder characterized by lymphocytic infiltrates in salivary and lacrymal glands, causing xerostomia and dry eyes. The diagnosis of Sjögren's Syndrome is based on a number of diagnostic criteria, including subjective and objective mouth and eye dryness, a minor salivary gland (MSG) biopsy with inflammatory focus and presence of specific autoantibodies. MicroRNAs (miRNAs) are a group of small RNAs, 18-22 nucleotides in length, involved in the regulation of development, cell differentiation, proliferation, function and survival. MicroRNAs are considered master regulators of gene expression, as one microRNA can alter the expression of hundreds of mRNAs. Clinically, the use of microRNAs in biomarker applications is very promising since microRNAs possess characteristics that render them excellent candidates for such applications, i.e resistance to degradation, isolation from all types of body fluids including saliva and urine, and isolation from FFPE samples.

Method: We used 24 Agilent microRNA microarrays to profile miRNAs isolated from healthy volunteers and Sjögren's patients' minor salivary glands (MSGs) with normal and low salivary flows and high (focus score of 12) and low focus scores (focus score of 1 or 2). We developed novel methods for data normalization by identifying microRNAs that can serve as housekeeping genes for this dataset and in extension for minor salivary gland microRNA expression measurements. The results were analyzed with the scope of identifying microRNAs that correlate with the physiologic status of a MSG as it is defined by whether the sample belongs to a healthy volunteer or SS patient, what is the focus score of that minor salivary gland, and if the salivary flow associated with that specimen is normal or decreased

Results: Through intensive bioinformatics analysis we identified disease, functional and inflammatory biomarkers for SS. The expression of the most promising microRNAs was validated in independent samples. For the functional biomarker discovery, of particular interest was the upregulation of several members of the mir-17-92 cluster in normal salivary flow high focus score when compared to low salivary flow high focus score MSGs, denoting that a different type of lymphocytic proliferation might be present in functional salivary glands. For the inflammation biomarkers, we identified two microRNAs, the ratio of expression level of which can give a very good representation of the inflammatory status of the minor salivary glands. The ratio of expression levels of those 2 microRNAs correlated very well with the inflammatory status of the MSGs in independent samples, including intermediate focus scores of 4-7.

Conclusion: Examining changes in miRNA expression can provide biomarkers for both the inflammatory process and the dysfunction associated with Sjögren's syndrome.

Disclosure: I. Alevizos, None; **S. Bajracharya**, None; **S. Alexander**, None; **R. J. Turner**, None; **G. G. Illei**, None.

1962

Role of the Urokinase Plasminogen Activator Receptor in Mediating Impaired Apoptotic Cardiocyte Clearance by Anti-SSA/Ro-SSB/La Antibodies in the Pathogenesis of Congenital Heart Block. Paraskevi Briasouli, Elena V. Komissarova, David Alvarez, Jill P. Buyon and Robert M. Clancy, NYU School of Medicine, New York, NY

Purpose: Organ injury induced by antibodies characteristic of Sjogren's Syndrome, while varied in the adult and fetus, may share in common a link between apoptosis and ultimate fibrosis. In congenital heart block (CHB), surface binding of maternal anti-Ro/La antibodies to apoptotic cardiocytes decreases removal by healthy cardiocytes. Membrane bound fibrinolytic components and the plasminogen activation cascade are involved in apoptosis. Dysregulation of the urokinase Plasminogen Activator/urokinase Plasminogen Activator Receptor (uPA/uPAR) system leads to cardiac fibrosis in mice and data implicate uPAR as a ‘'don't eat me" signal. The relevance of uPAR to CHB pathogenesis was addressed by investigating whether binding of anti-Ro/La to apoptotic cardiocytes alters uPAR expression thereby providing a molecular explanation for impaired clearance.

Methods and Results: Initial experiments evaluated Ro/La and uPAR localization on healthy and apoptotic cardiocytes. In permeabilized healthy cardiocytes, IgG fractions from mothers whose children had CHB containing anti-Ro and La antibodies (CHB IgG) stained the nucleus while anti-uPAR localized to the plasma membrane and vesicular compartments. In cardiocytes rendered apoptotic (exposure to TNFα, cyclohexamide, IFNγ and plating on pHEMA, or staurosporine), CHB IgG bound the cardiocyte surface and colocalized with anti-uPAR (not isotype control) supporting the proximity of Ro/La and uPAR. After crosslinking, uPAR migrated as a high molecular weight conjugate only on the apoptotic cells supporting an altered distribution of uPAR. Flow cytometry also demonstrated anti-uPAR binding to apoptotic cardiocytes (31 MFU ± 7 vs 19.3 ±8 (isotype control); p =0.008; n=5). The consequence of anti-Ro/La surface binding to the expression/function of uPAR as a “don't eat me” signal was assessed. Preincubation with CHB IgG, significantly increased the binding of anti-uPAR to apoptotic cells (58 MFU ± 8 vs 31 ± 7; p = 0.0013; n= 5). In contrast, binding of anti-HLA, and three other ‘'don't- eat me" molecules: anti-CD31 (pecam-I scavenger receptor), anti-CD47 (thrombospondin scavenger receptor), and anti-calreticulin were not increased after incubation with CHB IgG. To determine the functional effect of increased uPAR expression, apoptotic cells were cocultured with healthy cardiocytes for 5 hours, washed to remove unbound apoptotic cells, and fixed. CHB IgG significantly inhibited efferocytosis (58 ± 4.5% engulfment after incubation with control IgG vs 33 ± 3.0% with CHB IgG ; p= 0.002; n=6). Preincubation of the apoptotic cardiocytes with anti-uPAR but not anti-HLA, significantly reversed the CHB IgG inhibition (33 ± 3.0 % vs 63 ± 3.0 %; p = .001; n=6).

Conclusion: These data suggest that one potential mechanism accounting for the anti-Ro/La inhibition of efferocytosis by healthy cardiocytes exploits enhanced expression/function of uPAR, which may mediate injury in CHB via its capacity to act as a “don't eat me” signal.

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1963

Effect of Rituximab Treatment On Salivary Gland Immunohistology in Patients with Primary Sjögren's Syndrome. R.P.E. Pollard[1], J.E. van der Wal[1], S. Ihrler[2], F.K.L. Spijkervet[1], J. Pijpe[1], J.M. Meijer[1], P.M. Kluin[1], C.G.M. Kallenberg[1], A. Vissink[1] and H. Bootsma[1], [1]University Medical Center Groningen, Groningen, Netherlands, [2]Ludwig Maximilians Universität, München, Germany

Purpose: To assess the shift in B-, T- and plasma cells in parotid gland tissue induced by rituximab (anti-CD20) therapy in patients with primary Sjögren's syndrome (pSS).

Method: In a double-blinded placebo-controlled trial paired incisional parotid biopsies were taken in 25 patients with pSS before and 12 weeks after rituximab/placebo treatment. Until now, biopsy samples of 5 rituximab-treated and 5 placebo-treated patients were studied. The relative amount of parotid parenchyma, lymphocytic infiltrate and fat, the focus score, and the presence of lymphoid follicles and lymphoepithelial lesions were evaluated. B/T-cell ratio of the lymphocytic infiltrate was analyzed by immunohistochemistry (CD79a, CD20, CD3). In addition, distribution of plasma cells expressing different classes of immunoglobulins (IgA, IgG) was quantified.

Results: In all rituximab-treated patients a reduction in B/T-cell ratio was seen at 12 weeks, while no reduction in B/T-cell ratio was seen in the placebo-treated patients. Moreover, focus score and lymphoepithelial lesions were reduced in rituximab-treated, but not in placebo-treated patients. Finally, rituximab treated patients showed on average an increase in the proportion of IgA positive plasma cells (from 65±19% to 72±23%) while in placebo-treated patients, the plasma cell proportion containing IgA tended to decrease (from 66±18% to 64±16%).

Conclusion: Our preliminary data show a tendency of a rituximab-mediated shift in immunoglobulin class of plasma cells in glandular tissue of pSS patients towards a normally present dominance of IgA-class in conjunction with a decrease in focus score. Extended data are in progress.

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ACR Concurrent Abstract Sessions

T cells in Autoimmune Diseases

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

1964

TL1A-DR3 Interactions: An Attractive Target for Immunotherapy. Yun-Jeong Song[1], Francoise Meylan[1], Ivan Fuss[2], Todd Davidson[3], Ethan Shevach[4] and Richard Siegel[2], [1]NIAMS, NIH, Bethesda, MD, [2]NIH, Bethesda, MD, [3]Bethesda, MD, [4]NIAID, NIH, Bethesda, MD

Purpose: Molecules in the TNF-Receptor superfamily have diverse roles including regulatory functions in immune system. One of the newer members of the receptor superfamily is DR3 (death receptor-3; TRAMP, LARD, WSL-1, TNFRSF25). Like TNFR1, DR3 recruits TRADD and can mediate dual signals that lead to inflammation through NFκB signaling or cell death through caspase activation. Unlike TNFR1, DR3 is specifically expressed in lymphocytes, with the highest level on T cells. The sole known ligand for DR3 is the TNF superfamily member TL1A (TNF like cytokine 1A; TNFSF15). Using DR3 knockout mice, we have recently shown that TL1A-DR3 interactions play a key role in experimental autoimmune encephalomyelitis (EAE) and in an ovalbumin-induced asthma model, facilitating local T cell accumulation at the site of inflammation, while not affecting systemic priming, T cell polarization or host defense against Toxoplasma gondii (Meylan et al, 2008 Immunity 29:79). Other studies have suggested a role for TL1A and DR3 in various human diseases and animal disease models, including rheumatoid arthritis (RA), collagen-induced arthritis (CIA), and inflammatory bowel disease (IBD).

Method: Given the role of DR3 in mediating local effector T cell function in diverse autoimmune disease models, blocking TL1A-DR3 interactions may be an attractive therapeutic strategy for autoimmune disease. We have generated anti-TL1A antibodies to explore this possibility, and to further assess the role of TL1A-DR3 signaling pathway in normal and pathological T cell immune responses.

Results: We have found these antibodies to be useful in identifying TL1A producing cells and quantifying TL1A in cell supernatants and sera. In addition, selected clones were able to block functional TL1A-DR3 interactions, blocking T cell co-stimulation and apoptosis induced by TL1A in vitro. When administered prior to the onset of disease, anti-mouse TL1A mAb blocks the T-cell dependent TNBS colitis model

and ameliorates collagen-induced arthritis (CIA). We will present data on the efficacy of anti-TL1A mAb in preventing bone erosion in CIA and in other models of arthritis and autoimmunity such as experimental allergic encephalomyelitis (EAE).

Conclusion: These antibodies will be also useful in further studying the role of TL1A-DR3 interactions in the normal and diseased immune system, which may lead to the development of TL1A blockade as a novel therapy for autoimmune diseases.

Disclosure: Y. J. Song, None; **F. Meylan**, None; **I. Fuss**, None; **T. Davidson**, None; **E. Shevach**, None; **R. Siegel**, None.

1965

The Immune Response to Citrullinated Peptides in the Pathogenesis of Rheumatoid Arthritis. Maria Bellatin[1], Donglan Xia[1], Margarita Fallena[2], Nancy J. Olsen[3], David R. Karp[2] and Peter Stastny[1], [1]UT Southwestern Medical Center, Dallas, TX, [2]UT Southwestern Med Ctr, Dallas, TX, [3]Univ ofTX Southwestern Med Ctr, Dallas, TX

Purpose: An immune response against citrullinated peptides is closely associated with the development of Rheumatoid Arthritis (RA). Genetic factors, controlled by the Major Histocompatibility Complex (MHC) and environmental stimuli such as smoking appear to play a role. In the present experiments we wanted to investigate the contribution of B cells to the pathogenesis of RA by analyzing their capacity to produce autoantibodies against citrullinated peptides in vitro.

Method: B-cell enriched preparations were isolated from the peripheral blood of 66 patients with definite RA (with 60 or 91 % CCP-positive) and 54 matched healthy persons (all CCP-negative). Cultures of B cells with a feeder layer of EL4 cells producing CD40-ligand and a supply of T-cell factors were incubated for 14 days under conditions known to allow antibody secretion. Culture fluids were tested for appearance of antibodies against citrullinated peptides by an ELISA assay with a commercially available CCP3 kit. The role of RA-associated MHC genes was investigated by high resolution typing for HLA class II. The possible effect of smoking was determined by taking a smoking history of each of the participants in this study.

Results: Production of antibodies against CCP was detected in many of the cultures. It was found in 44/66 cultures from RA patients (67%) and in 21/54 B-cell cultures from healthy controls (39%). The difference between the two groups was significant ($p=0.003$). The two groups were also different in regards to the amount of anti-CCP antibodies produced ($p<0.02$) and the frequency of positive wells in the cultures ($p<0.0001$). Patients with RA-associated MHC genes were more likely to have B cells producing anti-CCP (Odds ratio (OR) =5.3, $p=0.007$). Interestingly, such a relationship was also seen in the cultures from healthy persons without R.A.; production of anti-CCP was seen more frequently in normal controls having RA-associated MHC genes (OR=4.9, $p=0.008$). Past and present smoking was associated with an increased frequency of cultures producing anti-CCP in these healthy control subjects (OR=3.2, $p=0.04$).

Conclusion: In vitro production of autoantibodies by peripheral blood B cells was investigated in RA patients and controls. The immune response to citrullinated peptides was stronger and more frequent in RA patients, but almost 40% of normal subjects had some B cells capable of producing anti-CCP. Both genetic and environmental factors appeared to influence this immune response in the two groups of persons we have studied. This view of the B cell repertoire may offer a window to the events leading to the development of autoimmunity and disease in persons with susceptibility for the development of RA.

Disclosure: M. Bellatin, None; **D. Xia**, None; **M. Fallena**, None; **N. J. Olsen**, None; **D. R. Karp**, None; **P. Stastny**, None.

1966

T Cell Lymphopenia Represents a Risk Factor for the Development of $CD4^+$ T Cell-Mediated Autoimmune Arthritis. Ryan Martinez, Na Zhang, Sarada Nandiwada, Bryce A. Binstadt and Daniel L. Mueller, University of Minnesota Medical School, Minneapolis, MN

Purpose: Rheumatoid Arthritis development has been associated with “premature aging” of the naïve $CD4^+$ T cell repertoire, perhaps reflecting dysregulated Ag-dependent T cell clonal expansion and a need for exuberant homeostatic proliferation to prevent frank T cell lymphopenia. Previously, we demonstrated that lymphopenia represents a barrier to T cell clonal anergy induction. We now questioned whether the development of autoimmune arthritis could result from a defect in clonal anergy induction, in the setting of T lymphopenia.

Method: Recipient (B6xB6.g7)F1 mice that naturally express glucose 6-phosphate isomerase (GPI)/I-A^{g7} peptide/MHC class II complexes were injected with purified B6 strain, GPI-reactive KRN TCR-transgenic naïve $CD4^+$ T cells to elicit the production of anti-GPI autoantibodies and development of arthritis.

Results: Wildtype recipients of KRN T cells produced only modest anti-GPI IgG1 Ab, and only rarely developed arthritis. Consistent with this result, the KRN T cells in these mice underwent an abortive clonal expansion, developed an anergic $Folr4^{high}$ $CD73^{high}$ phenotype, and became unresponsive to Ag re-challenge. In contrast, lymphopenic $TCRalpha^{-/-}$ (B6xB6.g7)F1 recipient mice induced a robust and sustained KRN T cell clonal expansion that failed to lead to either high level Folr4 and CD73 expression or proliferative anergy. Furthermore, these mice produced higher levels of anti-GPI Ab and developed intense inflammatory arthritis. Reconstitution of $TCRalpha^{-/-}$ (B6xB6.g7)F1 mice with an adoptive transfer of mature syngeneic polyclonal $CD4^+$ T cells resulted in the appearance of $Foxp3^+$ $CD25^+$ $CD4^+$ T regulatory cells and restored the ability of these mice to induce anergy in the KRN T cells to resist arthritis development.

Conclusion: These experiments demonstrate that T cell lymphopenia and T regulatory cell deficiency predispose the individual to autoimmune arthritis when autoreactive $CD4^+$ T cells fail to develop anergy upon encounter with self-antigen.

Disclosure: R. Martinez, None; **N. Zhang**, None; **S. Nandiwada**, None; **B. A. Binstadt**, None; **D. L. Mueller**, None.

1967

Maintenance of T Cell Rap1 Signaling Protects Mice against Collagen-Induced Arthritis. Joana R.F. Abreu[1], Sarah Krausz[1], Wendy Dontje[1], Aleksander M. Grabiec[1], Daphne de Launay[1], Margriet J. Vervoordeldonk[1], Paul P. Tak[2] and Kris A. Reedquist[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: The small GTPase Rap1 is inactivated in autoreactive T cells from the synovium of rheumatoid arthritis (RA) patients, contributing to chronic reactive oxygen species by these cells. This suggests an important role for Rap1 in determining the quality of T cells responses *in vivo*. Our goal was to determine if maintaining Rap1 signaling in murine T cells could modify disease onset or severity in collagen-induced arthritis.

Method: Arthritis was induced in wild-type (WT) and RapV12 transgenic (expressing constitutively active Rap1 in the T cell compartment) C57BL/6 mice by intradermal immunization with chicken collagen type II emulsified in complete Freund's adjuvant, and the immunization repeated at Day 21. Arthritis severity was monitored 3 times per week in a blinded manner using a semi-quantitative score (0-4 per paw, 16 points maximum). Hind paw ankle joint thickness was measured using a dial caliper. Mice were sacrificed at day 60 and hind paws preserved for histological and radiological analysis. In a second experiment, mice were sacrificed at Day 40, and blood, spleen and lymph nodes harvested from mice. Serum anti-collagen antibody titers were measured by ELISA. Splenic and lymph node cells were phenotypically assesed for expression of CD3, CD4, CD8, CD44, CD62L, CD103 and FoxP3. Cells were also stimulated for 6 hours with PMA/I, followed by intracellular staining for TNF, IFN-gamma, and IL-17. T cells were stimulated in vitro and assessed for expression of costimulatory proteins needed to direct B cell immunoglobulin (Ig) class switching.

Results: Disease incidence in RapV12 mice (20%) was severely reduced compared to WT mice (100%). Arthritis scores observed in WT mice (8+/- 1.51, mean +/- SEM) were also significantly reduced in RapV12 mice (1+/-0.68) ($p<0.001$). Infiltration of synovial tissue (WT=2.33+/-0.49 ; RapV12=0+/-0) ($p<0.001$) or cartilage erosion (WT= 2.5+/-0.5; RapV12= 0+/-0($p<=0.001$) was not detectable in RapV12 mice. Radiological scores in RapV12 mice (0.643+/-0.199) were also signficantly reduced compared to WT mice (2 +/-0.296) ($p<0.001$). Anti-collagen IgG2a and IgG2b antibody titers were reduced by 75% in RapV12 mice compared to WT mice ($p<0.05$). Total T cell numbers and percentages of CD3+, CD4+, CD8+ T cells (both naive and effector/memory), CD4+FoxP3+ Tregs, and Th17 cells were equivalent in WT and RapV12 mice. RapV12 mice had a significant decrease in the percentage of TNF-secreting CD8+ T cells ($p<0.05$). CD4+ T cells stimulated in vitro failed to upregulate ICOS and CD40L proteins needed by follicular T helper cells to promote B cell Ig class switching.

Conclusion: Maintenance of T cell Rap1 signaling in murine T cells reduces disease incidence and severity in the collagen-induced arthritis model, associated with decreases in the function of cytotoxic T cells, and development of IgG2a and IgG2b auto-antibodies. Strategies aimed at restoring Rap1 function in RA synovial T cells may have therapeutic benefit in RA.

Disclosure: J. R. F. Abreu, None; **S. Krausz**, None; **W. Dontje**, None; **A. M. Grabiec**, None; **D. de Launay**, None; **M. J. Vervoordeldonk**, None; **P. P. Tak**, None; **K. A. Reedquist**, None.

1968

Novel Delineation of Human FoxP3 Expressing CD4+ T Cell Subsets Reveals a Perturbed Homeostasis of FoxP3+ Treg Subsets During Active SLE. Makoto Miyara[1], Alexis Mathian[1], Julien Haroche[1], Guy Gorochov[2] and Zahir Amoura[3], [1]Centre Hospitalier Universitaire Pitié-Salpêtrière, APHP, Paris, France, [2]Inserm Umrs-945, Pitié-Salpêtrière Hospital, Paris, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France

Purpose: Conflicting results are reported in the literature regarding the prevalence of circulating FoxP3 expressing Tregs during active SLE. We have recently demonstrated that human FoxP3 expressing $CD4^+$ T cells are not homogeneous in function[1]. Our results have shown that FoxP3 and CD45RA expression enables the delineation of human FoxP3 expressing cells into three subsets: (1) $CD45RA^+FoxP3^{lo}$ Resting Tregs (rTregs), (2) $CD45RA^-FoxP3^{hi}$ activated Tregs (aTregs) and (3) cytokine-secreting $CD45RA^-FoxP3^{lo}$ non-Tregs[1]. We thus applied this new definition to active SLE.

Method: Our study included 16 patients with a diagnosis of SLE, established according to the American College of Rheumatology criteria, with an active disease (SLEDAI >3) and 31 healthy donors. CD45, CD4 and FoxP3 expression by PBMCs were analyzed by flow cytometry. Statistical comparisons were performed using the non parametric Mann-Whitney U test.

Results: There was a decrease in the proportion of aTregs (1.16 ± 0.71 *vs* 1,63 ± 0,52 % in healthy donors; p=0.002), and an increase in the proportions of rTregs (3.83± 2.02 vs 2,43 ± 0,89 %; p=0.006). Notably, $CD45RA^-FoxP3^{lo}$ non-Treg fraction increased to form a distinct population in active SLE (9.64 ± 9.0 % vs 3.13 ± 1.1; p<0.0001).

Conclusion: These results argue for perturbed homeostasis phenomenon in Treg subsets during SLE. Our recent findings indicate that rTregs are the thymic derived precursor of aTregs and that aTregs are susceptible to apoptosis[1]. Thus, death of aTregs and increased compensatory thymic output of rTreg cells might occur during active SLE. The increase in $FoxP3^{lo}CD45RA^-$ non Treg cells can account for the discrepancy in the prevalence of Tregs found in the literature. The role of cytokine secreting $FoxP3^{lo}$ non Treg CD4+ T cells, that were consistently increased during SLE flares, remains to be determined.

[1]Miyara et al. Functional delineation and differentiation dynamics of human $CD4^+$ T cells expressing the FoxP3 transcription factor. Immunity june 2009

Disclosure: M. Miyara, None; **A. Mathian**, None; **J. Haroche**, None; **G. Gorochov**, None; **Z. Amoura**, None.

1969

All-Trans Retinoic Acid Restores the Stability and Functionality of Ntregs in the Inflammatory Milieu. Xiao H. Zhou[1], Ning Kong[2], Julie Wang[1], Hejian Zou[3], Huimin Fan[4], David Brand[5], Zhongmin Liu[4] and Song Guo Zheng[1], [1]University of Southern California, Los Angeles, CA, [2]University of Southern California, Los Angeles, CA ; Huashan Hospital, Fudan University, Shanghai, China, [3]Huashan Hospital, Fudan University, Shanghai, China, [4]East Hospital, Tongji University, Shanghai, China, [5]VA Medical Center, Memphis, Memphis, TN

Purpose: Natural CD4+CD25+Foxp3+ cells (nTregs) play an important role in the maintenance of immune tolerance. Recent studies revealed that nTregs are plastic and unstable when stimulated with IL-6. They can be converted into either Th1, or Th17 or Th2 cells and lose phenotypic and functional characteristics in inflammatory milieu. all-trans Retinoic Acid (atRA) not only promotes $Foxp3^+$ cell development, but restrains Th17 cell differentiation induced by IL-6+TGF-β. We hypothesize that atRA alters the plasticity of nTregs and restore their suppressive activities in an inflammatory milieu.

Method: nTregs isolated from DBA/1J or Foxp3 knock-in mice were stimulated with IL-6 in the presence or absence of atRA, and intracellular IFN-γ, IL-4, IL-17 expression was determined by FCM. nTregs were also pretreated by anti-CD3/CD28 with atRA or DMSO and these cells were re-stimulated with IL-6. IL-6 R and phosphorylated STAT3 expression in nTregs pretreated with atRA and control were analyzed by FCM and qRT-PCR. The suppressive activity in vitro of both nTregs pretreated with atRA or DMSO was compared using CFSE dilution of T responder cells that were stimulated with anti-CD3 in the presence of IL-6. $3x10^6$ of both pretreated nTregs were i.v. injected

into DBA/1J mice on the day 28 after immunization with CII and CFA. The clinical severity of collagen-induced arthritis (CIA) was evaluated by visual judge, measuring specific anti-CII IgG subsets and histological examination.

Results: While 30% of nTregs were converted to Th17 cells when stimulated with IL-6, addition of atRA blocked Th17 conversion from nTregs. Similarly, atRA- but not DMSO-pretreated nTregs are also resistant to Th17 conversion when stimulated with IL-6. atRA-nTregs expressed lower levels of CD126 (IL-6Rα chain) and phosphorylated STAT3 compared to DMSO-nTregs when stimulated with IL-6. atRA- but not DMSO-nTregs maintained the suppressive activity in the presence of IL-6. Adoptive transfer of atRA- but not DMSO-pretreated nTregs to DBA/1 mice at day 28 after immunization with CII/CFA significantly reduced the severity of CIA. atRA-nTregs also suppressed CII-specific IgG production. Using CFSE-labeled donor cells, we were able to observe that majority of nTreg cells lost Foxp3 expression, converted to IL-17-prodcuing cells, and >20% converted into Th2 cells in draining lymph nodes at one week after adoptive transfer to the established CIA. Conversely, atRA-nTregs maintained Foxp3 expression and did not convert to Th1, Th2 and Th17 cells in a similar inflammatory milieu.

Conclusion: atRA alters Treg plasticity and restores the functionality of nTregs in the inflammatory milieu. Decreased IL-6 receptor and its signal molecule expression on atRA-pretreated nTregs possibly contribute to their stability and functionality in established CIA. This study may provide a novel therapeutic approach for the treatment of Rheumatoid Arthritis.

Disclosure: X. H. Zhou, None; **N. Kong**, None; **J. Wang**, None; **H. Zou**, None; **H. Fan**, None; **D. Brand**, None; **Z. Liu**, None; **S. G. Zheng**, None.

ACR Concurrent Abstract Sessions

Vasculitis II

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

1970

Hidden Diagnoses in Temporal Artery Biopsy Paraffin Blocks: The GRACG Study. Pierre Duhaut[1], Jean Schmidt[1], Denis Chatelain[1], Fabienne Bellarbre[1], Amar Smail[1], Valery Salle[1], Sylvie Bosshard[2], Jean -Charles Piette[3], Hélène Pellet[2], Henri Sevestre[1], Jean-Pierre Ducroix[1] and GRACG study members[4], [1]Amiens University Hospital, Amiens, France, [2]Claude Bernard University, Lyon, France, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [4]Amiens, France

Purpose: The necessary length of the temporal artery biopsy (TAB) has been largely discussed, but there are currently no guidelines for the management of TAB by the pathologist. Usually, several transversal sections are embedded in the paraffin blocks, leaving a large proportion of the TAB unexplored; then, several levels are cut within each section, leaving a large proportion of each section unexplored. The number of levels cut in the paraffin blocks may vary from 1 to more than 10, and is usually close to 3. Our goal was to assess 1- the proportion of diagnoses left in the paraffin blocks after usual processing; 2- the optimal way of processing biopsies in the laboratory of pathology.

Method: Consecutive bilateral negative TAB were extracted from the laboratory database, and the paraffin blocks were systematically re-processed. First, 6 new levels distant from 50 µm were cut, and then, new levels distant from 100 µm were cut until exhaustion of the blocks. All slides were reviewed by an independent pathologist with a pre-formatted form collecting all pathological items of the TAB. The pathologist was unaware of the final clinical diagnosis of the patients, and clinical charts were reviewed afterward. Pre- and post-review diagnoses were compared.

Results: One hundred and forty five bilateral negative TAB were included. After new slicing, 17 new cases of vasculitis were diagnosed (12% of all TAB). Among these, 5 were located in the 3 layers of the arterial wall (3 of them with giant cells), 3 showed signs of healed arteritis (with small foci of inflammatory cells), 1 showed evidence of necrotizing vasculitis in small vessels distant from the temporal artery, and 8 evidence of small vessel vasculitis surrounding the adventice of temporal artery. Involvement was unilateral in 15 cases out of 17. Thirteen diagnoses were found in the 6 first new levels, and 4, in the last, 100 µm-distant levels.

These new findings confirmed the suspected clinical diagnosis in 7 cases (‘negative’ TAB GCA : 5; ANCA vasculitis:2), and changed the former clinical diagnosis in 10 cases (‘pure’ PMR: 4; unexplained inflammatory syndrome:2; headache without further precision : 2; ‘suspicion of lymphoma’ without pathological evidence: 2).

Conclusion: Undiagnosed vasculitis was found in 12 % of the paraffin blocks after new processing. Although the diagnostic value of small vessel vasculitis may be discussed, the new findings would have modified the initial clinical diagnosis in 10 cases. Since 76 % of newly diagnosed vasculitis were found in the 6 new first levels, we suggest that these levels should be systematically performed in case of negative TAB, and further exploration could depend on the strength of clinical suspicion of temporal arteritis or vasculitis.

Disclosure: P. Duhaut, None; **J. Schmidt**, None; **D. Chatelain**, None; **F. Bellarbre**, None; **A. Smail**, None; **V. Salle**, None; **S. Bosshard**, None; **J. -. C. Piette**, None; **H. Pellet**, None; **H. Sevestre**, None; **J. P. Ducroix**, None.

1971

Aortic Involvement in Patients with Newly Diagnosed Giant Cell Arteritis (GCA). A Prospective Study Using Computed Tomography (CT) Angiography. Sergio Prieto-González, Pedro Arguis, Ana García-Martínez, Georgina Espígol-Frigolé, Montserrat Butjosa, Itziar Tavera, Josep M. Grau, José Hernández-Rodríguez and Maria C. Cid, Hospital Clínic. IDIBAPS. University of Barcelona, Barcelona, Spain

Purpose: Recent studies have shown that 22.5% of GCA patients develop aortic aneurysms during follow-up. Examination of necropsy or surgically removed specimens has evidenced that GCA may target the aorta. More recently, positron emission tomography has shown to be able to detect fluorodeoxyglucose uptake by the aorta in patients with active GCA, but the prevalence and topography of aortic involvement has not been accurately evaluated by imaging techniques in prospective studies. Our objective was to prospective assess the prevalence, topography and characteristics of aortic involvement (aortitis and dilatation) in patients with newly diagnosed GCA using CT angiography.

Method: From July 2007 to June 2009, 32 patients were diagnosed with biopsy-proven GCA in our institution. Nine patients were excluded because of allergy to iodine (1), no consent to participate (1) or steroid treatment for >3 days (7 patients). Aortic CT angiography was performed to the remaining 24 patients, and the following features were evaluated: presence of aortitis (defined by contrast-enhanced circumferential aortic wall thickness ≥ 2 mm without adjacent atheroma), and significant dilatation (diameter > 4 cm in the ascending aorta, at least 4 cm in the rest of the thoracic aorta and loss of normal progressive reduction in the abdominal aortic calibre). Controls matched for gender, age and cardiovascular risk factors, were consecutively recruited from patients with no chronic inflammatory diseases, who underwent CT angiography for diagnosis or follow-up of neoplasia.

Results: The study group consisted of 13 women and 11 men, aged 80 years (range 67-89). None of the patients had previously diagnosed aortic valvulopathy or aneurysm. Structural abnormalities were detected in 18 patients (75%). Seventeen patients (70%) had aortitis and 3 patients (12,5%) had significant dilatation of the ascending aorta. Two patients had both findings, but dilatation was not coincident with aortitis in the same segment. Aortitis preferentially involved the thoracic descending aorta which was affected in 16 (94%) of patients with aortitis. The aortic arch was involved in 13 (76,5%) patients, the abdominal aorta in 8 (53%), and the ascending aorta in 3 (23%). No aortic abnormalities were observed in the control group.

Conclusion: Aortitis, as assessed by CT angiography, is highly frequent in patients with GCA at the time of diagnosis. Aortic dilatation is already present in 12,5% of patients at baseline evaluation. Aortic dilatation exclusively occurred in the ascending aorta and was no associated with CT angiography evidence of aortitis, suggesting the contribution of hemodynamic factors. Supported by SAF 08/04328. MTV3 06/0710.

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1972

Adding Hydroxychloroquine to Prednisone Does Not Improve the Outcome in Giant Cell Arteritis: A Double Blind Randomized Controlled Trial. Laurent Sailler[1], Maryse Lapeyre-Mestre[2], Loïck Geffray[3], Philippe Letellier[4], Eric Liozon[5], Philippe Montané de La Roque[6], Mohamed Hamidou[7], Eric Oziol[8], Nadine Magy[9], Philippe Arlet[10], Jean-Louis Montastruc[11] and and the investigators of the Horton-hydroxychloroquine trial, [1]Université de Toulouse, Laboratoire de Pharmacoépidémiologie, EA3696, Toulouse, France, [2]Université de Toulouse, Laboratoire de Pharmaco-épidémiologie, EA3696, Toulouse, France, [3]CHG de Lisieux, Lisieux, France, [4]CHU Côte de Nacre, Caen, France, [5]CHU de Limoges, Limoges, France, [6]CHG du Val d'Ariège, Foix, France, [7]Hôtel Dieu, Nantes, France, [8]CHG, Béziers, France, [9]CHU, Hôpital jean Minjoz, Besançon, France, [10]CHU Purpan, Toulouse,, France, [11]Université de Toulouse, Laboratoire de Pharmacologie Médicale et Clinique, Toulouse, France

Purpose: Few drugs have corticosteroid sparing effects in the treatment of giant cell arteritis (GCA). Hydroxychloroquine is a well tolerated immunomodulatory drug that may have a corticosteroid sparing potential according to its immuno-pharmacological properties and previous clinical data (*Le Guennec et al, Rev Rhum 1994*). Our objective was to evaluate the glucocorticosteroid (GC) sparing effect of hydroxychloroquine (HCQ) in the treatment of non-complicated GCA.

Method: This was a double blind randomized controlled trial. Patients with a non-complicated, newly diagnosed, biopsy confirmed GCA randomly received corticosteroids plus placebo or plus 400 mg HCQ per day for up to 96 weeks. The primary end point was being in remission with 5 mg prednisone or less for at least 3 months at the end of the follow-up. Analysis was made on an intent-to-treat basis using the Kaplan-Meier method and the log-rank test to compare the survival curves, and the Cox proportional hazard ratio to identify variables associated with the outcome. All patients have given their informed consent. The study has been registered on the clinicaltrial.gov web site (identifier: NCT00430807).

Results: 74 patients were randomized to receive placebo (n=38) or hydroxychloroquine (n=36). Among them, 10 were excluded before beginning the study drug (7 for cancellation of earlier approval, 1 for a severe GC-induced psychosis, 2 due to a major deviation). Among the 64 remaining patients (mean age: 74.4 ± 6.5 years), 32 received the placebo and 32 HCQ. Fourteen out of 32 HCQ and 21 out of 32 placebo patients reached the primary endpoint (log-rank test: p= 0.22). Twenty HCQ patients and 14 placebo patients experienced at least one relapse (p=0.13). The median cumulative corticosteroid doses were 7146 mg (range: 4643-9493) in the HCQ group and 6687 mg (range: 4563-10444) in the placebo group (p=0.9). The study drug was stopped due to adverse reactions in 8 HCQ patients (skin eruption in 6). In a *post hoc* analysis, receiving HCQ was independently associated with an increased risk of relapse after week 24 (HR = 2.52 [IC95% 1.14-5.57], p = 0.02). Polymyalgia rheumatica symptoms at the baseline (HR: 0.38 [0.15-0.96], p=0.04) and male gender (HR: 0.44 [0.17-0.93], p=0.03) were associated with a lower risk of relapse.

Conclusion: The early administration of hydroxychloroquine did not improve the outcome in non-complicated giant cell arteritis and was not always well-tolerated.

Disclosure: L. Sailler, None; **M. Lapeyre-Mestre**, None; **L. Geffray**, None; **P. Letellier**, None; **E. Liozon**, None; **P. Montané de La Roque**, None; **M. Hamidou**, None; **E. Oziol**, None; **N. Magy**, None; **P. Arlet**, None; **J. L. Montastruc**, None.

1973

Long-Term Surgical and Medical Outcome in Takayasu Arteritis: Vascular Procedures Performed in Active Patients Have a Poor Outcome. Muge Bicakcigil, Kenan Aksu, Sevil Kamali, Servet Akar, Omer Karadag, Huseyin T. Ozer, Fatos Onen, Sibel Z. Aydin, Neslihan Yilmaz, Zeynep Ozbalkan, Askin Ates, Ayse Cefle, Veli Cobankara, Mesut A. Onat, Ercan Tunc, Yasar Karaaslan, Nurullah Akkoc, A. Eftal Yucel, Gokhan Keser, Sedat Kiraz, Murat Inanc and Haner Direskeneli, Turkish Takayasu's Arteritis Study Group, Istanbul, Turkey

Purpose: Takayasu's arteritis (TA) is a rare chronic inflammatory disease of unknown etiology. There are only a few reports discussing the follow-up, course and surgical and medical prognosis of TA patients.We aimed to evaluate long-term outcome of medical and surgical treatments in TA.

Method: 184 patients (F/M: 171/13), mean age: 40.9 years followed at 13 Rheumatology centers are prospectively evaluated in terms of clinical and vascular prognosis. Mean follow-up time was 76 months .We defined active disease using NIH guidelines, and remission and sustained remission were assessed according to criteria defined by *Hoffman et al.*

Results: The great majority of 184 patients (79%) required other immunosuppressive agents, in addition to glucocorticosteroids to achieve and maintain disease remission. After the treatment, remission was observed in 89% of the patients and 51% of those patients that maintain disease remission had sustained remission at the last visit, whereas 18% were still currently active. In 78 (42%) patients, relapse was observed during follow-up. After initiation of treatment, first remission was achieved at 11.3 months. During follow-up, in 127 patients sustained remission was observed at least once.

In serial angiographic evaluations, angiographic progression was observed in 28 % of the patients. Regression analysis have shown relationship only with complete remission duration (p=0.02, OR=0.9 CI=0.92-0.99) and progression. Patients showing progression had significantly less sustained remission duration (66 months vs 32 months, p=0.02). Outcome of angiographically followed 77 vascular interventions were evaluated in terms of restenosis and complications. Restenosis was observed in 27 (35%). There was a significant relationship with the disease activity at the time of vascular procedure in terms of restenosis in regression analysis (p=0.04, OR=3.6, CI=1-13) Restenosis was observed significantly lower in the group with medical treatment started before intervention 8/34 (23%), compared to the non-treated group 19/45 (45%)(p = 0.04). Restenosis was also observed more frequently in active TA patients at the time of procedure compared to inactives(active: 21/45 (80%) vs inactive 6/30 (20%), p= 0.02). During follow-up 10 (5.4%) patients died.

Conclusion: Although glucocorticoids and immunosuppressive treatments are effective in the treatment of TA and complete remission could be achieved in 69% of the patients. Angiographic progression was observed less in patients that have longer periods of sustained remission. This observation suggests that new therapeutic agents in TA treatment. Our results also showed that in terms of restenosis, vascular interventions must be performed at inactive stages and in patients under treatment, except in emergency cases.

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1974

Microendothelial Cells Regulate Functional Selection of Proinflammatory T Cells in Takayasu's Arteritis. Jiusheng Deng[1], Kisha Piggott[1], Brian R. Younge[2], Jorg J. Goronzy[1] and Cornelia M. Weyand[1], [1]Lowance Center for Human Immunology and Rheumatology, Atlanta, GA, [2]Mayo Clinic, Rochester, MN

Purpose: Takayasu's arteritis (TA) is a primary vasculitis that targets the aorta and its branches and causes aortic arch syndrome, aneurysm formation, aortic insufficiency, stroke, heart attacks, and hypertension. The typical histomorphology shows T-cell and macrophage infiltrates in the arterial media and adventitia, often clustering around vasa vasorum. T cells with proinflammatory features are end-differentiated effector cells that derive from distinct subsets (e.g. IFN-g-producing Th1 cells, IL-17-producing Th17 cells, IL-4-producing Th2 cells) with specialized differentiation requirements, tissue trafficking patterns, and effector mechanisms. Here, we have explored which T-cell effector subsets contribute to TA and how recruitment of these T cells to the aortic wall is orchestrated.

Method: IL-17- and IFN-g-producing CD4 T cells were quantified in the peripheral blood of patients with active TA and age-matched healthy controls by intracellular staining and FACS analysis. Biopsies from TA-affected aortas were analyzed for IL-17, IFN-g, and chemokine receptor transcripts by qPCR. Cytokine and chemokine production in tissue-residing and tissue-infiltrating cells were examined by immunohistochemical staining. Vessel wall inflammation was induced in noninflamed human aortas after engraftment into SCID mice and adoptive transfer of human peripheral blood mononuclear cells.

Results: In TA patients (n=10) with active disease the frequency of circulating Th17 cells was four-fold increased compared to age-matched controls (n=10) (2.85% vs 0.70%, *P*=0.0001); whereas IFN-g-producing Th1 cells were less than two-fold elevated (19.3% vs 13.3%, *P*=0.0018). In aortic wall extracts, the chemokine receptor most expressed was CCR6, followed by CCR5 and CCR3, suggesting a dominant role for $CCR6^+$ T cells. Functional analysis of wall-infiltrating T cells confirmed strong enrichment of IL-17-producing cells (16.6%) whereas IFN-g producers were represented at frequencies similar to those in the circulating blood (14.8%). Production of the CCR6-attracting chemokine CCL20 was localized to microendothelial cells of the vasa vasorum tree, often favoring microvessels in the proximal adventitia. In adoptive transfer experiments, $IL\text{-}17^+$ T cells preferentially accumulated in the aortic wall. The induction of aortic wall inflammation could be disrupted by blocking the CCL20-CCR6 axis.

Conclusion: T cells occupying the aortic wall lesions in TA are functionally selected and dominated by IL-17-releasing CD4 T cells. Due to the expression of the chemokine receptor CCR6, IL-17-producing T cells are responsive to the chemokine CCL20, which is secreted by

endothelial cells of the vasa vasorum tree. These data place dysfunctional microendothelial cells at the top of the pathogenic cascade of TA and identify the CCL20-CCR6 axis as critical in aortic wall inflammation.

Disclosure: J. Deng, None; **K. Piggott**, None; **B. R. Younge**, None; **J. J. Goronzy**, None; **C. M. Weyand**, None.

1975

Pediatric Takayasu Arteritis: Significance of Central Nervous System Manifestations. Daniela S. Ardelean[1], Rayfel Schneider[2], Earl D. Silverman[3], Ronald M. Laxer[2], Pascal Tyrell[4], Michael Seed[2], Shi-Joon Yoo[2] and Susanne M. Benseler[2], [1]Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]The Hospital for Sick Children and University of Toronto, Toronto, ON, [4]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON

Purpose: To describe the clinical, laboratory and imaging characteristics of children with pediatric Takayasu arteritis (TA), their treatment regimens and identify risk factors for adverse long-term outcome

Methods and Study: A single-center cohort study of consecutive children diagnosed with TA between 01/1986 and 12/2008. **Inclusion:** 1) Age ≤ 18 year-old; 2) follow-up ≥12 months. **Exclusion:** Follow-up ≤ 12 months (3 patients).

Data: Demographics, clinical, laboratory, magnetic resonance/conventional angiography characteristics and treatment regimens were collected. **Outcome:** 1) *Adverse outcome*: death or persistent disease activity at last 2 follow-ups, 2) *disease flares.* Predictors at presentation for adverse outcome *(*demographic, clinical, laboratory, imaging characteristics and treatment choices) were compared between the group with and without adverse outcome. **Analysis:** Descriptive statistics, uni-/multivariable logistic regression.

Results: Demographics: A total of 18 TA patients were included; 6 boys, 12 girls (ratio 1: 2). Median age at diagnosis was 10.0 years (range 0.6-18); median follow-up 36 months (range 12-156). **Presenting features:** Hypertension (HTN) in 8 (44%). *CNS manifestations in 9 (50%),* all had ≥ 2 distinct CNS features including severe headache in 5 (28%), hypertensive seizures in 5 (28%), arterial ischemic stroke in 5 (28%). Claudication in 3 (17%), murmur in 1 (5%) and 1 unstable angina. Constitutional features in 2 (11%); 1 (5%) had uveitis. Confirmed TB was present in 2/18 (11%). **Inflammatory markers at presentation:** elevated ESR in 9/ 16 tested (56%), anemia in 7/18 (39%), high IgG in 2/13 tested (15%), elevated CRP in 2/9 (22%) and thrombocytosis in 3/18 (15%).**Vascular imaging:** stenoses in 100%, dilations in 4(22%); vessel wall enhancement in 5/18 (28%), aneurysms in 2/18 (11%). Overall 12 (67%) had supra and infra-diaphragmatic vasculitis; 5 (28%) infra-diaphragmatic TA and 1 supra-diaphragmatic vasculitis. **Treatment:** 13 children (72%) treated with corticosteroids; 12 (67%) received an additional agent: MTX in 5 (28%), cyclophosphamide in 6 (33%), azathioprine in 5 (28%), MMF in 1; two refractory patients received infliximab; 7 (39%) required surgical interventions. **Outcome:** 1) *adverse outcome* in 7/18 (39%): 2 deaths, persistently active disease in 5; 2) *flares* in 4/18 (22%), all on immunosuppresion. Infra-diaphragmatic involvement (p=0.01) and anemia (p=0.03) reached statistical significance.

Conclusion: Children with TA commonly presented with CNS manifestations and or HTN. In children with stroke, TA has to be considered. More than one third of children with TA had an adverse outcome. Children with infra-diaphragmatic TA and anemia at presentation have a significantly increased likelihood of adverse outcome.

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ARHP Concurrent Abstract Session

Physical Function and Disability in Rheumatoid Arthritis

Tuesday, October 20, 2009, 4:30 PM - 6:00 PM

1976

Association of Physical Function and Disability with Physical Activity in Women with Rheumatoid Arthritis. Sara R. Piva[1], Gustavo J. M. Almeida[1], Yanique Murphy[1] and M. C. Wasko[2], [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Purpose: Measures of physical function (PF) and disability traditionally have been used as the primary outcomes of rehabilitation in patients with rheumatoid arthritis (RA). While informative about the patient's ability to perform everyday tasks, they do not provide information about the amount of everyday tasks one performs, defined as physical activity (PA). Studies demonstrated that PA is associated only to a small degree with PF and disability and perhaps represent independent constructs. The purpose of this study was to determine the cross-sectional associations between measures of PA and measures of PF and disability prior and after controlling for social and biomedical characteristics in women with RA.

Method: Forty seven women with RA, mean age 58 ± 6 years. PA was measured by a portable activity monitor worn for 7 days, and was characterized in 2 ways: daily average # of steps, and daily energy expenditure during moderate levels of PA (EEPA). Disability was measured by the Health Assessment Questionnaire (HAQ). PF was measured by self-selected gait speed and the timed 5-chair rise test. Non-normally distributed variables were square root-transformed. Analyses: Step 1- Pearson coefficients were calculated between PA, PF and disability. Step 2- Pearson or Spearman coefficients were calculated between social and biomedical characteristics and PA, PF and disability. Step 3- partial correlations between measures of PA and measures of PF and disability were calculated controlling for associated social and biomedical characteristics.

Results: Results are reported in the Table. Associations between measures of PA and measures of PF and disability, although significant, were small (r = -.23 to .48). After controlling for social and biomedical characteristics, the associations were not significant (r= .07 to .28).

Conclusion: Small associations between measures of PA and measures of PF and disability are explained by patient's social and biomedical characteristics. The results indicate that measures of PF and disability may represent constructs different than PA and suggest that measures of PA should be included in rehabilitation research in RA.

Step 1. Associations between PA and measures of PF and disability					
			PF		Disability
			Gait Speed	Chair Rise	HAQ
PA	EEPA		.37*	-.23	-.38**
	# of steps		.39**	-.41**	-.48**
Step 2. Associations of social and biomedical characteristics with PA, PF, and disability					
	PA		PF		Disability
	EEPA	# of steps	Gait Speed	Chair Rise	HAQ
Age	-.24	-.21	-.25	.30*	.27
Race†	.03	.06	.12	-.22	-.20
BMI	-.03	-.18	-.36*	.10	.10
Marital Status†	-.19	-.04	-.06	.04	.10
Education	.27	.31*	.35*	-.35*	-.28
Comorbidities†	-.13	-.26	-.17	.24	.34*
RA Duration	-.09	.39*	.06	.39**	.37*
RA Activity (DAS28)	-.21	-.18	-.28	.21	.30*
Step 3. Associations between PA and measures of PF and disability controlling for age, BMI, education, comorbidities, disease duration and activity					
			PF		Disability
			Gait Speed	Chair Rise	HAQ
PA	PAEE		.25	-.07	-.28
	# of steps		.24	-.27	-.27

† Spearman Rho; * $p < .05$; ** $p < .01$

Disclosure: S. R. Piva, None; **G. J. M. Almeida**, None; **Y. Murphy**, None; **M. C. Wasko**, None.

1977

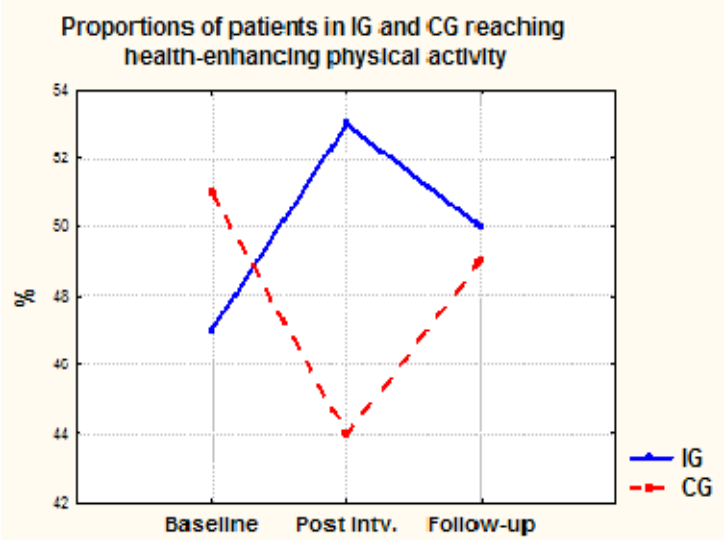
Maintenance of Health-Enhancing Physical Activity in Rheumatoid Arthritis After a One-Year Coaching Intervention – A Long-Term Follow-up. Emma Swärdh[1], Nina Brodin[1], Jon Lampa[2], Christina H. Opava[1] and the PARA Study Group, [1]Karolinska Institutet, Huddinge, Sweden, [2]Stockholm, Sweden

Purpose: The recommendation of at least 30 minutes' moderately intense physical activity on most, preferably all, days may serve as a useful and feasible self-management strategy for individuals with rheumatoid arthritis (RA) to improve or maintain general health. However, support from health professionals is often necessary in adopting and maintaining this behavior. The present aim was to investigate

the long-term effect on perceived general health, physical activity, pain, disease activity, and activity limitation of a one-year coaching program to adopt health-enhancing physical activity in patients with early RA.

Method: At baseline, 228 patients with early RA, from 10 rheumatology clinics in Sweden, were assigned at random to an intervention group (IG, n=94) or a control group (CG, n=134). The intervention was assessed one year after baseline, and followed up two years after baseline. The IG was coached by physical therapists during the first year to adopt health-enhancing levels of physical activity (30 minutes/day, moderately intensive, ≥ 4 days/week). No coaching was given during the subsequent year between post-intervention and follow-up. Follow-up assessment consisted of a postal questionnaire on physical activity behavior and of visual analog scales for ratings of general health perception and pain, the functional disability index of the HAQ and the DAS 28 collected at regular medical check-ups.

Results: Sixty-five (69%) participants in the IG and 92 (69%) in the CG completed the entire study period by filling in and posting the follow-up questionnaire on physical activity behavior two years after baseline. No long-term differences in changes between the IG and the CG in any of the outcome variables were found between baseline and follow-up. However, different variations in physical activity behavior were observed in the two groups.



Conclusion: The present study, which was performed within ordinary clinical practice, is one of the first to evaluate the coaching of individuals with RA to adopt health-enhancing physical activity. Whereas improved self-reported health was found at the end of the one-year coaching program, as previously reported, no long-term increases in self-reported health or in physical activity behavior were found in the present follow-up. This may partly be because the intervention lacked several important behavioral elements for physical activity maintenance.

Disclosure: E. Swärdh, None; **N. Brodin**, None; **J. Lampa**, None; **C. H. Opava**, None.

1978

Adherence to An 8-Week Yoga Program for RA and OA: Who Drops out and Why? Steffany Haaz[1], Clifton O. Bingham III[2] and Susan J. Bartlett[3], [1]Johns Hopkins School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins, Baltimore, MD

Background. Physical activity is integral to comprehensive arthritis management, yet long-term adherence averages 50-60% over several months. We have previously shown yoga is a safe, effective and enjoyable physical activity for arthritis patients, though long term-adherence in unknown.

Purpose: To identify factors associated with adherence to yoga tailored for people with rheumatoid (RA) and osteoarthritis (OA).

Methods: In this RCT, 75 persons ages 18-65 with OA or RA were recruited through arthritis clinics and area rheumatologists. Participants were 96% female, 55% Caucasian, aged 52.3±11.9 years. 36 (48%) had RA and 39 (52%) had OA and were randomized to immediate yoga (IY) or waitlist control (WC) followed by participation in the yoga program. Yoga classes, held biweekly for 8 weeks, included poses (asanas), breathing (pranayama), chanting, relaxation and meditation. Poses were designed to accommodate joint limitations and individual abilities. Instruction was provided for weekly home practice.

Adherence was assessed as: 1) attendance at ≥13 classes (protocol) and 2) completion of study requirements (study). Baseline predictors included sociodemographic and disease characteristics, depressive symptoms (CES-D), self-efficacy (ASES) and selected markers of physical fitness (4) and health status (4). Logistic regression was used to identify baseline predictors of protocol and study adherence.

Results: Of 75 patients screened, 40 were assigned to IY and 35 were assigned to WC. There were no differences between treatment groups in sex, race, disease diagnosis or duration. The WC group was slightly older than the IY group (55.9±1.5 vs. 49.2±2.1, p=.01).

There was a trend for those randomly assigned to IY to attend any classes (83% vs. 63% WC respectively p=.059), which did not change when controlling for differences in age between groups.

Overall, 69% were classified as protocol adherent (73% IY vs. 64% WC, p=.48). Caucasian race was the only baseline characteristic associated with starting or completing the yoga intervention (odds ratio [OR] = .33, 95% CI=.11, .97 and OR=.25 95% CI=.09, .94 respectively). Study adherence was 71% (63% IY vs. 80% WC, p=.10). Attending college and Caucasian race were the only predictors associated with study adherence (OR=2.4 95% CI= .10, .75 and OR=.26 95% CI=1.1, 4.9 respectively). However, after controlling for age and race, education was no longer predictive. While race was repeatedly associated with adherence, the contribution to predicting any form of adherence was low. Trends toward significance were found for hypothesized markers of physical function, physical fitness and self-efficacy. Common reasons for attrition were change in eligibility, life events and class logistics (time, location).

Conclusion: Arthritis patients who begin yoga may be likely to persist with it over time. Risk of drop-out appears highest in minority persons and before starting classes. Better understanding of minority barriers to participation and other factors affecting adherence is needed. Clinicians may wish to consider recommending yoga to arthritis patients, particularly when adherence to exercise has been problematic.

Disclosure: S. Haaz, None; **C. O. Bingham**, None; **S. J. Bartlett**, None.

1979

Predictors of Physical Therapy Service Use in Persons with Rheumatoid Arthritis. Maura D. Iversen[1], Nancy A. Shadick[2] and Riku Chhabriya[3], [1]MGH Inst of Hlth Professions and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham & Women's Hosp, Boston, MA, [3]MGH Inst of Hlth Professions, Boston, MA

Purpose: Although physical therapy (PT) is recognized as a key component of rheumatoid arthritis (RA) management and has been shown to improve function and reduce disability in persons with RA, the literature demonstrates that PT services are underutilized. This study aimed to identify factors associated with use of PT among patients with RA.

Method: 772 patients prospectively recruited from a large hospital registry, completed questionnaires, received a physical examination at baseline and completed a 12- month follow-up survey. Measures included: demographic data (age, gender, marital status, race, employment, disability, income, co-morbidities, education) as well as self- efficacy, social support (BSNI), function (MDHAQ), quality of life (EuroQoL), disease activity (RADAI). Self-reported use of PT services (yes/no) was assessed at 12-months. Descriptive statistics were used to characterize the sample. Bivariate comparisons were conducted to identify variables for logistic regression analysis. Using a modified liseral approach, variables were selected and entered into the regression, based on the International Classification of Function (ICF) framework, to develop a parsimonious set of predictors.

Results: 93.6% were Caucasians, 82.3% female with mean age of 56.29 (±13.57) years. 64.7% were married, half of the sample was employed, 9.8% reported to have disability in past 6 months and 36.6% had annual income >= $90,000. Of 772 patients, 118 (15.3%) patients used PT services. The majority of patients had 1 to 8 PT visits. Within our sample, 29.4% of patients reported no prior participation in exercise and 27.1% performed exercises on a regular basis. On average, Patients reported a moderate amount of fatigue (mean VAS 43.23

(± 28.45 SD). and mild disease activity (median RADAI = 3.26; range = 0-10). These patients were fairly independent, reporting only mild restrictions in activities of daily living (median MDHAQ = 0.68, range = 0-3). Despite the limited clinical manifestation of disease impact, these patients reported relatively poor quality of life (median EQ Index = 0.82; range = 0-1).

Using bivariate analysis, factors most predictive of PT use were: disability, RADAI, income, EuroQoL, co-morbidities, MDHAQ and BSNI. In the multivariate regression, the most significant predictors were RADAI (OR=1.14; 95%CI=1.02-1.28); co-morbidities (OR=1.5; 95%CI=1.04 - 2.07); EuroQoL(OR=0.06; 95%CI=0.01-0.32), BSNI (OR=1.05; 95%CI=1.01-1.10) and disability (OR=2.00; 95%CI=1.01-3.93).

Conclusion: Patients with more active disease, higher number of co-morbidities, and who reported being disabled, having a low quality of life and greater social support were more likely to receive PT services. This model explained 86% of the variance in PT service use.

Disclosure: M. D. Iversen, None; **N. A. Shadick**, Crescendo biosciences, 2, Amgen, 2, Bristol Myers Squibb Foundation, 2, Biogen Idec, 2 ; **R. Chhabriya**, None.

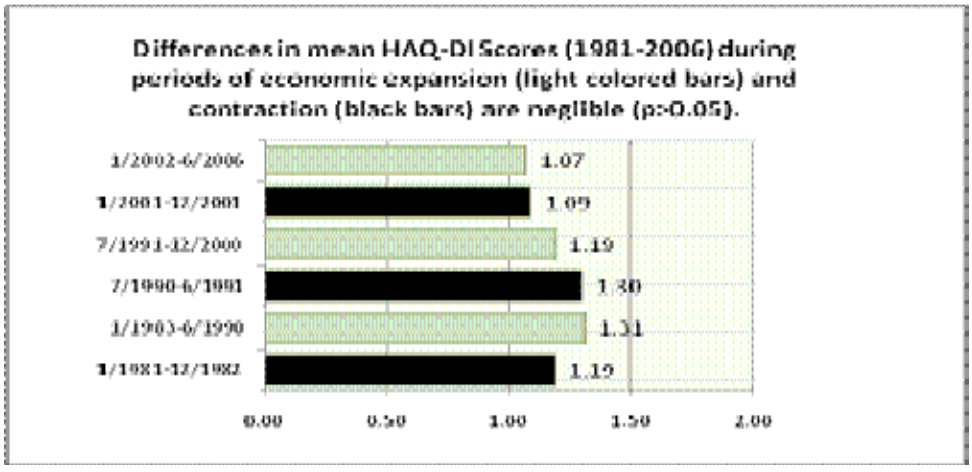
1980

Effects of Economic Fluctuations and Seasonal Variability On HAQ-DI Scores in Rheumatoid Arthritis. Bonnie Bruce[1], James F. Fries[2] and Bharathi Lingala[3], [1]Stanford Dept of Medicine, Palo Alto, CA, [2]Stanford Univ Medical Ctr, Palo Alto, CA, [3]Stanford University, CA

Purpose: Self-reported health status outcomes could be in part influenced by economic fluctuations or seasons (e.g., winter worse than summer) and are largely understudied. We examined 25.5 years of Health Assessment Questionnaire Disability Index (HAQ-DI) administrations to study the effects of economic expansion and contraction and seasonal variability.

Method: We used 6-month HAQ-DI scores (0-3; 3=worst) from 51 semi-annual mailings (1981-2006) collected from a longitudinal panel study of adults with rheumatoid arthritis (RA). We used the National Bureau of Economic Research criteria to define economic expansion and contraction. Periods of economic contraction were defined as 1/1981-12/1982, 7/1990-6/1991, and 1/2001-12/2001. Seasons were defined as Winter/Spring and Summer/Fall. We describe our findings using measures of central tendency and examine the data using parametric and nonparametric statistics as appropriate.

Results: Subjects (n=1413/mailing) were white (90%), female (76%), had 12 education years, RA for 18 years, and a mean HAQ-DI score of 1.21±0.80. There were no differences in subject characteristics between periods of economic expansion or contraction (age – 59 vs. 61 years, disease duration – 17 vs. 18 years, p>0.05). The overall mean physical function score was similar for the 43 HAQs (21.5 years) collected during economic expansion years compared to the 8 HAQs (4 years) collected during periods of contraction (1.21±0.11 vs. 1.19±0.09, p=0.65). HAQ-DI scores were not different for winter-spring (26 HAQs) compared to summer-fall (25 HAQs) (1.20±0.80 vs. 1.21±0.81, p=0.83). Reporting did not differ between males and females for economically or seasonally defined periods.



Conclusion: In this study with large numbers of RA patients, we found consistent reporting of disability scores without effects during periods of economic expansion or contraction or between seasons. The effects of economic fluctuations or seasons on HAQ-DI scores are negligible.

Disclosure: B. Bruce, None; **J. F. Fries**, None; **B. Lingala**, None.

1981

Is Nurse-Led Care for RA Patients Clinically Effective? Mwidimi Ndosi, Jackie Hill and Claire Hale, University of Leeds, Leeds, United Kingdom

Purpose: To determine the effectiveness of nurse-led care (NLC) by comparing the outcomes of RA patients seen by clinical nurse specialists or rheumatologists (RLC). We hypothesized that the outcomes of the NLC would not be inferior to those obtained by RLC.

Methods: This was a 4-centre RCT. Patients were randomised on a 1:1 basis to either NLC of RLC based on their primary outcome, DAS28 scores which were measured at baseline (M0), 3 months (M3) and 6 months (M6). Secondary outcomes were measured at the baseline and 6 months and included the Health Assessment Questionnaire (HAQ), Arthritis Self Efficacy Scale (ASES), Hospital Anxiety and Depression Scale (HAD) and the Leeds Satisfaction Questionnaire (LSQ). The clinical nurse specialist and the rheumatologists saw patients on 3 occasions and undertook their normal practice. An independent assessor performed all joint counts.

Repeated measures models were used to assess:

1) within-subject (time) effects - how DAS28 changed from M0 to M3 & M6

2) between-subjects (group) effects – how differently each group performed over time (group*time effects)

<>For the secondary outcomes, mean differences (MD) were computed and the unpaired t-test was used to test the difference between the groups' MD's

Results: The cohort comprised 14 males and 39 females whose median age was 61 years (Range = 30 – 86). 27 were allocated to NLC and 26 to RLC. On study entry there was no significant difference in any variable between the 2 groups.

On study completion, there were improvements in DAS28 for all patients (M0, M3 & M6 = 3.40, 3.20 & 3.12 respectively; $p = 0$ .34), but this was a small effect size (eta-squared = 0.03). Interestingly, patients under the NLC had consistent improvements (M0, M3 & M6 = 3.29, 3.19 &3.05 respectively) while those under RLC had an improvement by month 3 then a plateau by month 6 (M0, M3 & M6 = 3.53, 3.36 & 3.37 respectively). Despite this difference, group effects were non-significant (p = 0.67, eta squared = 0.01).

The HAQ demonstrated that disability was significantly decreased for all patients (MD = -0.6, p = 0.01) but those under NLC were significantly greater (MD = -0.7) than RLC (MD = -0.5; p = 0.05).

The LSQ showed that overall satisfaction significantly decreased (MD = -1.05, p = 0.01) and there were no between group differences (p = 0.10).

There were no significant improvements in ASES (MD = -0.6, p = 0.78) or HAD scores (MD = 0.2, p = 0.86) and no between group differences (p = 0.66 & 0.87) respectively.

Conclusion: Despite the small effect size on DAS28, NLC demonstrated at least similar outcomes to RLC. In addition, NLC delivered greater improvements on disability than RLC and in this respect NLC provided added value. Surprisingly, satisfaction decreased for both groups which is inconsistent with previous studies which have reported increased satisfaction with NLC.

The overall results suggest that NLC for RA patients is clinically effective and not inferior to RLC. Given that RA is a variable disease, a longer multi-centre study is needed to take account of this.

Disclosure: M. Ndosi, None; **J. Hill**, None; **C. Hale**, None.

ARHP Concurrent Abstract Session

Cardiovascular Disease in Rheumatic Conditions

Wednesday, October 21, 2009, 7:45 AM - 8:45 AM

1982

Identification of Cardiac Risk Factors in Hospitalized Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis.

Eileen J. Lydon[1] and H. Michael Belmont[2], [1]NYUHJD, New York, NY, [2]Hosp for Joint Disease, New York, NY

Purpose: Patients with systemic lupus erythematosus(SLE) and rheumatoid arthritis(RA) have a higher incidence of coronary heart disease than the general population. Since recent data support the hypothesis that inflammation associated with RA and SLE contributes to accelerated atherosclerosis cardiovascular events are not solely explained by traditional risk factors, but undoubtedly these classic hazards do contribute to the burden of atherosclerosis. Therefore, aggressive efforts to identify cardiac prevention measures are essential in this cohort. Identifying patients in a hospitalized setting is an opportunity to target, educate and treat more patients.

Method: During 2007-2008 in-patients at NYUHJD with RA or SLE had their cardiac risk assessed and were given appropriate treatment recommendations as derived from the 2001 Adult Treatment Panel III National Cholesterol Education Program as well as the 2004 implications of recent clinical trials published in Circulation. A fasting lipid panel was performed then a ten year risk assessment was calculated using the Framingham point scores and LDL goals identified. Patients with metabolic syndrome were also identified. Recommendations included the initiation of LDL lowering therapy, hypertension treatment, smoking cessation, and therapeutic lifestyle changes (TLC) (e.g. diet and exercise intervention).

Results: 87 enrolled,76F,11M; 27SLE, 60RA. Low Risk 40/87(46%), Moderate 32/87(37%), Moderately High 5/87(6%), High 10/87(11%). Unmet LDL: 14/87(16%), Statin initiated 13/14(93%). HTN: 10/87(11%), Treated 9/10(90%). Cigarette Smoking: 6/87(7%). BMI: Under 2/87(2%), WNL 34/87(39%), Over 26/87(30%), Obese 25/87(29%). Metabolic Syndrome:10/87(11%). TLC:19/87(22%).

Conclusion: Cardiovascular disease is the leading cause of morbidity and mortality in patients suffering from SLE and RA and classic risk factors are not adequately managed in the community. Targeting in-patients easily allows for risk factor modification such as initiating LDL lowering and hypertensive therapy, obtaining a fasting lipid panel, educating, assessing learning needs, consulting nutritionists, physical therapists and making appropriate outside referrals. These results also highlight that statins are insufficiently prescribed which is especially relevant in this population as in addition to lipid lowering, they may have anti-inflammatory properties. In conclusion, the in-patient hospital setting can serve as a valuable opportunity to provide effective cardiac prevention strategies in this high risk population.

Disclosure: E. J. Lydon, None; **H. M. Belmont**, None.

1983

Cardiovascular Risk and Depression in Systemic Lupus Erythematosus (SLE). L. J. Julian, P.P. Katz, J. Yazdany, A.O. Hersh, L. Trupin, A. Galvin, L.A. Criswell and E.H. Yelin, UCSF, SF, CA

Purpose: Cardiovascular (CV) disease has emerged as a major cause of morbidity and mortality in SLE. In the general population, the link between depression and CV disease is well established; however, few studies have evaluated this relationship in SLE. This study evaluated traditional and SLE-specific factors as predictors of the prevalence and incidence of depression in a large observational cohort of persons with SLE.

Methods: Participants included 725 persons with confirmed SLE (ACR criteria), participating in annual survey interviews over 6 years. Depression symptom severity was evaluated by the Centers for Epidemiological Studies Depression Scale (CESD). Statistical analyses included multivariate linear regression predicting concurrent depression, and logistic regression predicting incident depression (defined as a new onset of CESD score ≥23 over 2 years of follow up). Predictors in both models included sociodemographic characteristics, traditional risk factors (CV event, heart disease, hypertension, hypercholesterolemia, diabetes, obesity, family history, current or past smoking), and SLE-specific risk factors (renal involvement, history of clot, disease duration, disease activity).

Results: Mean age was 50±12, 60% were at least college educated, 74% were Caucasian, and 11% were living below poverty. In multivariate linear regression, living in poverty, history of CV event, traditional CV risk factors and disease activity were significant

predictors of concurrent depression symptom severity, accounting for 34% of the variance (p<.0001). Over the course of the study there were 163 new 'cases' of incident depression. In multivariate logistic regression, predictors of incident depression included poverty status, history of myocardial infarction or stroke, and disease activity (Table 1). The interaction of CV event and poverty neared significance (p=.09). Descriptive analyses suggested that 80% of persons living below poverty with a history of a CV event developed depression during the study period.

Conclusion: Traditional and SLE-specific CV risk factors are associated with concurrent and incident depression. Participants at greatest risk for the development of depression are described by the confluence of sociodemographic and biological risk factors. Importantly, a number of CV risk factors are modifiable, highlighting the potential of both medical and social interventions to prevent the development of depression and/or to reduce the morbidity associated with depression in SLE.

Table 1. Logistic regression analyses predicting "incident depression".

				OR	CI (95%)	Sig.
Step 1: Demographics						
Female				.54	.23-1.25	.15
College degree				1.15	.68-1.96	.61
Age				.98	.96-1.01	.14
Below poverty				3.26	1.23-8.24	**.01**
Caucasian				.72	.40-1.29	.27
Step 2: Traditional CV risk						
MI or stroke				2.00	1.01-3.96	**.05**
CV risk factor sum				.99	.83-1.20	.94
Step 3: SLE-specific CV risk						
History of clot				.92	.50-1.72	.80
Renal involvement				1.02	.61-1.71	.94
Disease activity				1.12	1.07-1.16	**<.0001**
Disease duration				1.01	.98-1.04	.51
Step 4:						
Interaction: CV event x poverty				6.31	.73-54.2	.09

Disclosure: L. J. Julian, None; **P. P. Katz**, None; **J. Yazdany**, None; **A. O. Hersh**, None; **L. Trupin**, None; **A. Galvin**, None; **L. A. Criswell**, None; **E. H. Yelin**, None.

1984

Depression Is a Risk Factor for Subclinical Atherosclerosis in SLE. Carol M. Greco[1], Tracy Li[2], Abdus Sattar[1], Amy H. Kao[1] and Susan Manzi[1], [1]University of Pittsburgh, Pittsburgh, PA, [2]Bristol-Myers Squibb, Princeton, NJ

Purpose: Women with SLE have increased rates of subclinical atherosclerosis compared to controls, as measured by coronary artery calcium (CAC) and carotid plaque. Women with SLE also exhibit higher prevalence of depression and depressive symptoms than controls. Although depression and other psychological factors have been linked to atherosclerosis in healthy women, the associations between psychological factors and vascular disease in SLE remain largely unexplored. The purpose of this study was to evaluate biological and psychological risk factors associated with subclinical atherosclerosis in women with SLE, as defined by presence of coronary artery calcium and/or carotid plaque.

Method: In this cross-sectional study, 161 women with SLE without prior history of cardiac events completed comprehensive cardiovascular risk factor assessments, SLE disease activity assessments, and the Center for Epidemiologic Studies Depression scale (CES-D). Participants also completed an electron-beam computed tomography scan of the coronary arteries to determine the presence of CAC, and carotid artery ultrasound to detect presence of plaque. For this study, subclinical atherosclerosis was defined as having either or both of these vascular indicators. In unadjusted logistic regression analyses, risk factors associated with atherosclerosis at $p<0.15$ were evaluated for inclusion in multivariable models. The final model was selected based on Akaike's Information Criteria (AIC).

Results: The mean age of the participants was 50 years, and 88% were Caucasian. Mean SLE duration was 16 years. Most (68%) had taken corticosteroids, with median duration of 10 years of use. The mean CES-D score was 11.6 (SD= 9), with 27% of the participants scoring ≥ 16, a score consistent with clinically meaningful depressive symptoms. One hundred and one (63%) met criteria for subclinical atherosclerosis. Using multivariable logistic regression, SLE women with depression were at nearly four-fold risk for having subclinical atherosclerosis (OR= 3.85, 95% CI =1.37, 10.87) after adjustment for several traditional cardiovascular risk factors (age, hypertension, years of education), C-reactive protein (CRP), and waist-to-hip ratio.

Conclusion: Depression is associated with subclinical atherosclerosis in women with SLE, independent of age, education, hypertension, CRP and adiposity. This is important in that mental health factors are modifiable. Interventions that reduce depressive symptoms may impact cardiovascular disease in SLE.

Multivariable logistic regression analysis of risk factors for atherosclerosis in women with SLE (N=161).

Variable	**OR**	**95% CI**	**P value**
Age	1.11	(1.06-1.17)	0.000
Years of Education	.82	(.68-.99)	0.037
Hypertension	2.50	(1.10-5.66)	0.028
Waist-Hip ratio*			
2nd quartile: 0.77 - <0.814	1.11	(.32-3.94)	0.867
3rd quartile: 0.814 - <.868	2.60	(.73-9.36)	0.142
4th quartile: ≥ 0.868	4.03	(1.12-14.49)	0.032
CRP	1.12	(1.01-1.23)	0.029
Depression	3.85	(1.37-10.87)	0.011

*Reference Group is the first quartile of waist-hip ratio.

Disclosure: C. M. Greco, Bristol-Myers Squibb, 2, National Institutes of Health, 2 ; **T. Li**, Bristol-Myers Squibb, 3 ; **A. Sattar**, Bristol-Myers Squibb, 2 ; **A. H. Kao**, NIH, 2 ; **S. Manzi**, Amgen, 2, Aspreva, 2, Genelabs Technologies, Inc., 2, Genentech Inc., 2, Human Genome Sciences, Inc., 2, Immunomedics, Inc., 2, Bristol-Myers Squibb Company, 2, Cellatope Corporation, 5, La Jolla Pharmaceutical, 5, MedImmune, Inc., 5, Genelabs Inc., 5, Genentech Inc., 5, Bristol-Myers Squibb, 5, Human Genome Sciences, 5, Centocor, Inc., 5, Cephalon, 5 .

1985

Cardiovascular Disease (CVD) Prevention Counseling Program for Systemic Lupus Erythematosus (SLE) and/or Antiphospholipid Antibody (aPL) Positive Patients. Virginia F. Haiduc, Monica Richey, Sotiria Tzakas, Josephine Park, Lisa Konstantellis, Julie A. Pollino-Tanner and Doruk Erkan, Hospital for Special Surgery, New York, NY

Background: SLE patients have high-risk CVD profiles as they have increased prevalence of both traditional CVD- and other lupus-related thrombosis risk factors. APL-positive patients with or without SLE are at increased risk for arterial and venous thrombosis.

Purpose: To determine the satisfaction of SLE and/or aPL-positive patients who participate in a counseling program that has been developed to increase the awareness of CVD risk factors as well as thrombosis prevention strategies.

Methods: A free-of-charge counseling program, which is partially supported by the New York Community Trust, has been developed to provide a basic *assessment* of and *education* about the CVD and thrombosis risk factors in SLE and/or aPL-positive patients. The *assessment* phase (chart review by the program MD and patient interview/examination by the program nurse) includes the evaluation of blood pressure, blood glucose, cholesterol profile, waist circumference, body mass index, family history of CVD, diet and exercise habits, smoking status, homocysteine and high-sensitivity C-reactive protein (hs-CRP) levels (if available), Framingham 10-year CVD risk calculation, aPL-profile, and medications. The *education* phase includes detailed discussion of the above risk factors as well as CVD and thrombosis prevention strategies. At the end of the counseling, patients: a) receive tailored lifestyle recommendations; b) are referred to the nutrition and physical therapy departments as needed; and c) complete an anonymous survey to evaluate the program. Patients are followed every 3-6 months with official re- assessment of the CVD risk-profiles. We report the results of patients' initial visit satisfaction surveys (Likert Scale; 1: best to 5: worst).

Results: Since the launch of the program in March 2009, 27 patients have received counseling and 25/27 (93%) completed the satisfaction survey. 52% of the participants reported that they were not aware of the CVD risk in lupus patients, 24% had some but limited knowledge; and 24% were aware of the risk. The mean (± SD) scores for the answers were: a) quality of the counseling: 1.2 ± 0.4; b) quality of the educational materials: 1.4 ± 0.9; c) likelihood of recommending the counseling program to others: 1.4 ± 0.8; d) improvement in patient's knowledge about CVD risk factors: 1.8 ± 1.0; e) likelihood of the counseling program improving patients' diet: 1.7 ± 0.9; and f) likelihood of the counseling program improving patients' exercise pattern: 1.8 ± 0.8.

Conclusion: Our preliminary survey demonstrates that lupus and/or aPL-positive patients are well satisfied with a free CVD prevention counseling program. The three-year longitudinal analysis of patients included in the counseling program will determine the true effectiveness of the program with respect to decreasing the prevalence of cardiovascular disease risk factors.

Disclosure: V. F. Haiduc, None; **M. Richey**, None; **S. Tzakas**, None; **J. Park**, None; **L. Konstantellis**, None; **J. A. Pollino-Tanner**, None; **D. Erkan**, None.

ACR Concurrent Abstract Sessions

B-Cell Biology and Targets in Autoimmune Disease

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

1986

The Importance of APRIL in SLE Disease Activity and Treatment. Kelly T. McNallan, Richard Bram, Cynthia S. Crowson, Kevin G. Moder and Ann M. Reed, Mayo Clinic, Rochester, MN

Purpose: Systemic Lupus Erythematosus is a complex chronic disorder with variable clinical features, treatment response and unpredictable flares of inflammation. Current treatments impact the symptoms, but do not address the underlying mechanisms.

This study targets the underlying abnormal immune responses of myeloid, B and T cell signaling in SLE. Recently, mouse models have expanded the specific functions of APRIL including disease improvement resulting from an APRIL decoy receptor. Others did not find a significant difference in serum levels of APRIL protein in SLE patients, compared to controls. We hypothesized that serum APRIL levels may not truly reflect the extent of its biological actions, because the majority of the protein is typically bound to cell surface proteoglycans. To explore this possibility, we investigated APRIL mRNA levels, as a more accurate predictor of APRIL production than serum protein

levels. We quantitated mRNA expression of B cell receptors BAFFR, TACI and BCMA and their ligands Full Length BAFF (FL BAFF), ΔBAFF, an alternative transcript that inhibits FL BAFF and APRIL in correlation with SLE disease activity, clinical features and medications.

Methods: Total RNA was extracted from Ficoll-Paque enriched PBMCs from 38 SLE patients and 21 healthy controls. Real-Time PCR was performed to assess FL BAFF, ΔBAFF, APRIL, BCMA, TACI, BAFFR and CD20 expression levels and comparisons were performed using Wilcoxon rank sum tests. Correlations with clinical data were performed using Spearmann correlation analyses.

Results: A total of 38 patients with SLE (mean age 43.9 years, 90% female, mean SLAM: 5.4) were studied. Increased SLAM disease index scores correlated with increased APRIL/CD20 (p=.011) and FL BAFF/CD20 (p=.011) levels. Decreased levels of BCMA (p=.039), APRIL (p=.015), FL BAFF (p=.003), ΔBAFF (p=.003) were found in SLE patients taking Hydroxychloroquine (HCQ) therapy. Increased FL BAFF (p=.04), BCMA/CD20 (p=.036) and CD20 (p=.04) were seen in patients with autoantibodies (anti-SSA, SSB, RNP, Smith, dsDNA). In addition, increased APRIL expression was seen in the SLE patients with headaches and seizures (p=.012)

Conclusion: This is the first report showing a positive correlation between APRIL mRNA expression and SLE disease activity and a correlation between a decrease in myeloid derived cytokines APRIL, FL BAFF and ΔBAFF with HCQ treated SLE patients. The use of HCQ in SLE needs to be investigated in a larger cohort to gain a cohesive understanding of its effects. Although we did not find an overall difference in APRIL expression between controls and SLE patients we hypothesize APRIL may be a more potent cytokine due to its increased avidity for TACI and BCMA causing prolonged survival and autoantibody production and T cell activation dependence similar to findings in mouse models. This study implicates APRIL in the disease processes that occur in SLE, and indicates the need for further studies of APRIL's role in a larger sample size.

Disclosure: K. T. McNallan, None; **R. Bram**, St. Jude Children's Hospital, 9 ; **C. S. Crowson**, None; **K. G. Moder**, None; **A. M. Reed**, Kaiser Permenente, 5
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1987

Reactivity with Dichotomous Determinants of Ro60 Stratifies Autoantibody Responses in Lupus and Primary Sjogren's Syndrome.
Joanne H. Reed[1], Nadine L. Dudek[2], Shannon E. Osborne[1], Kenneth M. Kaufman[3], Michael W. Jackson[1], Anthony W. Purcell[2] and Thomas P. Gordon[1], [1]Flinders Medical Centre, Bedford Park, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Oklahoma Medical Research Foundation, OK, OK

Purpose: Flow cytometric-based analysis of B-cell epitopes of Ro60 exposed on the surface of apoptotic cells (apotopes) and intracellular epitopes provides insight into the structural forms of Ro60 that break immune tolerance. The aim of this study was to fine map a Ro60 apotope that is specific for a subset of systemic lupus erythematosus (SLE) and determine whether differentially expressed forms of this determinant stratify anti-Ro60 responses in SLE and primary Sjögren's syndrome (SS).

Method: Ro60 apotopes were mapped by multi-parameter flow cytometry on early apoptotic cells by inhibition experiments using soluble recombinant fragments of Ro60. Anti-Ro60 IgG from patients with SLE (n=32) and primary SS (n=26) were also assessed for reactivity with the immobilised Ro60 fragments by ELISA or immunoblot. Anti-Ro60 IgG was eluted from early apoptotic cells or recombinant Ro60 immobilised on nitrocellulose and binding to membrane-bound and intracellular forms of Ro60 quantitated by flow cytometry. Three-dimensional modelling of immunoreactive domains was based on the crystal structure of *Xenopus laevis* Ro60.

Results: A homology model was constructed using the crystal structure of *X. laevis* Ro60 and the apotope mapped to a prominent helix-loop-helix region or peg-like region on the surface of human Ro60. This immunodominant structure was recognised by patients with SLE and isolated anti-Ro. Immobilisation of the same domain to a solid phase revealed a second determinant (epitope) that was specific for linked anti-Ro and anti-La-responses. Virtually all patients recognising the Ro60 apotope were negative on the epitope and vice versa. Affinity-purification experiments revealed that the apotope and epitope were expressed in a mutually exclusive fashion on membrane-bound and intracellular forms of the autoantigen, respectively.

Conclusion: Dichotomous determinant recognition within a single domain of Ro60 stratifies anti-Ro60 responses in SLE and primary SS and supports a model of anti-Ro60 autoimmunity in which tolerance is broken by different immunogenic forms of the autoantigen.

Disclosure: J. H. Reed, None; **N. L. Dudek**, None; **S. E. Osborne**, None; **K. M. Kaufman**, None; **M. W. Jackson**, None; **A. W. Purcell**, None; **T. P. Gordon**, None.

1988

Pituitary Tumor-Transforming 1 Interacting Protein (PTTG1IP) Is a Novel Target for Autoantibodies in RA. Hanna Maciejewska Rodrigues, Emmanuel Karouzakis, Hossein Hemmatazad, Renate E. Gay, Beat A. Michel, Michel Neidhart, Steffen Gay and Astrid Jüngel, Ctr Exp Rheum, Univ Hosp Zurich / Zurich Ctr Integr Hum Physiol (ZIHP), Zurich, Switzerland

Purpose: The identification of novel autoantigens in RA is important for a better understanding of specific disease mechanisms as well as for diagnostic purposes. Pituitary tumor-transforming 1 interacting protein (PTTG1IP) is a co-activator of transcription and is regulated by Runx2, the major regulator of bone morphogenesis.

Method: A modified serological analysis of recombinant cDNA expression libraries (SEREX) using cDNA derived from RA synovium was used for the identification of novel autoantigens. For screening of peptides reactive with autoantibodies synovial fluid from a RA patient was used. An ELISA was established and used to assess the levels of the identified anti-PTTG1IP autoantibodies in synovial fluids and sera from RA (n=30 and 33) and osteoarthritis (OA) (n=14 and 38) patients and in the sera of healthy individuals (n=37). The expression of PTTG1IP was analysed in RA (n=5) and OA (n=4) synovial tissues by Western blot and immunohistochemistry.

Results: PTTG1IP was detected among 18 other novel autoantigenes by the SEREX method. The levels of PTTG1IP reactive autoantibodies were present in 53% (AU range 0-275, mean ± SEM 43 ± 8) of synovial fluids from RA patients and differed significantly from OA patients ($p<0.05$). Only 7% of synovial fluids from OA patients were positive for anti-PTTG1IP autoantibodies (AU range 0-18, mean 2 ± 1). Most interestingly, anti-PTTG1IP autoantibodies were detected in 43% of synovial fluids from rheumatoid factor (RF) negative RA patients (AU range 0-35, mean 12 ± 5) and in 40% of anti-citrulinated antibodies (anti-CCP) negative RA patients (AU range 0-35, mean 12 ± 6). The levels of anti-PTTG1IP autoantibodies in sera of RA patients were significantly higher compared to OA (324 ± 49 vs 80 ± 17, $p<0.01$) while did not differ significantly from the healthy controls (235 ± 33). PTTG1IP protein was expressed to a similar extent in both RA and OA synovial tissues as assessed by Western blot (RA 125 ± 20 AU vs OA 100 ± 40 AU) and confirmed by immunohistochemistry.

Conclusion: Anti-PTTG1IP autoantibodies are also present in the RF- as well as anti-CCP-negative synovial fluids, and therefore, represent a novel promising candidate for defining a specific subset of RA patients. Since PTTG1IP has been suggested to play a role in osteoblast differentiation, and autoantibodies against PTTG1IP were detected at increased levels in RA patients, it might be speculated that these autoantibodies may interfere with osteoblast differentiation and attempted repair processes in the affected joints.

Disclosure: H. Maciejewska Rodrigues, None; **E. Karouzakis**, None; **H. Hemmatazad**, SNF - 32-119892 / EU Autocure FP6, 2 ; **R. E. Gay**, None; **B. A. Michel**, None; **M. Neidhart**, None; **S. Gay**, None; **A. Jüngel**, None.

1989

Activation of Interferon and Ubiquitin Pathways in Lupus Memory B Cells. Mikhail Olferiev and Mary K. Crow, Hospital for Special Surgery, New York, NY

Purpose: Memory B cells from patients with systemic lupus erythematosus (SLE) represent an important cell population that is associated with disease activity and contributes to production of pathogenic IgG autoantibodies. To gain further insight into the mechanisms of altered B cell function in SLE, we investigated the molecular pathways activated in SLE and healthy donor (HD) memory B cells using gene expression profiling.

Method: Seven adult female patients with established SLE (100% ANA positive; SLEDAI score >4 and <12) and seven HD participated in the study. B cells were first enriched from peripheral blood and the $CD19^+CD27^+$ memory B cell subset separated from naïve B cells ($CD19^+CD27^-$) on a FACS Vantage cell sorter. Microarray analysis of mRNA derived from SLE and HD samples was performed using the Affymetrix Human U133 2.0 chip. Gene expression analysis was carried out using GeneSpring GX 10 software. Samples were per-chip normalized and transformed to the baseline median level. Student T-test was performed to determine differentially expressed genes between the two groups.

Results: 1183 genes were found to be differentially expressed between SLE and HD $CD19^+CD27^+$ cells [Fold Change (FC) >1.5, $p<0.05$]. Among those, 30 genes showed strong significance for differential expression (FC>1.5, $p<0.01$). Unsupervised cluster analysis clearly

discriminated patients with SLE from HD. Functional analysis revealed enrichment of genes related to Ig synthesis, interferon (IFN) signature, B cell signaling and the ubiquitin pathway. Genes with likely relevance to autoimmunity were significantly overexpressed in SLE memory B cells, including AICDA and GCET2 ($p<0.01$). Increased expression of TLR7 and IRF7 and of type I IFN-inducible genes (STAT1, IFI27, IFIT1, IFITM1, OAS2/3/L) identified lupus memory B cells as active participants in type I IFN production and response, and the expression of CD72 and CD22 inhibitory receptors was low. Expression of several ubiquitin conjugating enzymes and ubiquitin ligases was increased in memory B cells from SLE patients, including TRIM25, an E3 ubiquitin ligase responsible for ubiquitylation of RIGI, a mediator of TLR-independent type I IFN production.

Conclusion: mRNA expression was dysregulated in SLE memory B cells, consistent with an important contribution of those cells to the immunoregulatory disturbances that result in autoimmunity and disease. In addition to patterns characteristic of active Ig synthesis and an IFN signature, we identified activation of the ubiquitin machinery, including a participant in TLR-independent IFN production, in lupus memory B cells, pointing to an additional pathway that may be important in lupus pathogenesis.

Disclosure: M. Olferiev, S.L.E. Lupus Foundation, 2 ; **M. K. Crow**, Biogen Idec, 5, Bristol-Myers Squibb, 5, Idera, 5, MedImmune, 5, Roche Pharmaceuticals, 5, Merck Serono, 5, Novo Nordisk, 5 .

1990

The Aortic Adventitia of Coronary Bypass Patients with Rheumatoid Arthritis Provides a Survival Niche, and Antigen Depot, for B Cells. Ammad Ahmed[1], Ivana Hollan[2], Knut Mikkelsen[3], Oystein T. Forre[4], Iain B. McInnes[1] and Carl S. Goodyear[1], [1]University of Glasgow, Glasgow, United Kingdom, [2]1. Feiring Heart Clinic, Feiring, 2. Hospital for Rheumatic Diseases, Lillehammer,, 1. Feiring. 2. Lillehammer, Norway, [3]Lillehammer Hospital for Rheumatic Diseases, Norway, [4]University of Oslo, Oslo

Purpose: Rheumatoid arthritis (RA) is associated with an increase in cardiovascular morbidity and mortality but how the vascular environment affects the immune component of RA is currently unknown. It has previously been shown that inflammatory rheumatic disease patients undergoing coronary artery bypass graft (CABG) have more pronounced chronic inflammatory infiltration in the media and inner adventitia of the aorta. It should also be appreciated that the internal mammary artery (IMA) is protected from atherosclerosis. In this study, we have examined the aortic adventitia of patients with coronary artery disease, in the absence or presence of RA co-morbidity. We assessed the occurrence of B cell infiltrates; expression of B cell survival factors; and the presence of citrullinated protein (CP), an RA-associated antigen.

Methods: Aortic and IMA specimens routinely removed during CABG surgery in 20 RA and 20 non-RA patients were examined by light microscopy for the presence of B cells, BAFF, APRIL and CP. Fisher's exact test and Mann-Whitney U test were used to identify differences between the two groups. Spearman correlation was used to assess the relationships between variables.

Results: B cells, BAFF, APRIL and CP were detectable and significantly increased in the aortic adventitia (AA) of both RA and non-RA patients compared to their matched IMA. Specifically, B cells were detectable in 72% of AA vs 0% of IMA ($p < 0.0001$, odds ratio [OR] 161), BAFF in 97% of AA vs 27% of IMA ($p < 0.0001$, OR 85), APRIL in 68% of AA vs 6.5% of IMA ($p < 0.0001$, OR 30.5), CP in 100% of AA vs 27% of IMA ($p < 0.0001$, OR 173). However, the number/proportion of B cells, BAFF or APRIL in the AA were not significantly different between the RA and non-RA patients. Interestingly, CP was significantly increased ($p = 0.02$) in RA samples compared to non-RA samples. In addition, we also observed a significant correlation between B cells and APRIL ($r2 = 0.49$; $p = 0.002$), B cells and CP ($r2 = 0.56$; $p = 0.02$), and APRIL and CP ($r2 = 0.29$; $p = 0.05$) in RA patients. No association with smoking was found, however, this could be due to small sample size.

Conclusion: The presence of B cell infiltration in the aortic adventitia of RA and non-RA patients indicates that this may be an important pathological mechanism that could contribute to vascular damage/disease. In addition, this study suggest that the aortic adventitia of RA patients, with coronary artery disease, is associated with an environment that is conducive to B cell survival, and harbors a known RA-associated self antigen. Importantly, these inflammatory niches outside of the joint could provide a mechanism for the perpetuation of B cell auto-reactivity and may be amenable to therapeutic intervention.

This study was conducted in association with the Feiring Heart Biopsy Study Group.

Disclosure: A. Ahmed, None; **I. Hollan**, None; **K. Mikkelsen**, None; **O. T. Forre**, None; **I. B. McInnes**, None; **C. S. Goodyear**, None.

ACR Concurrent Abstract Session

Fibromyalgia and Soft Tissue Disorders II - Central Nervous System

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

1991

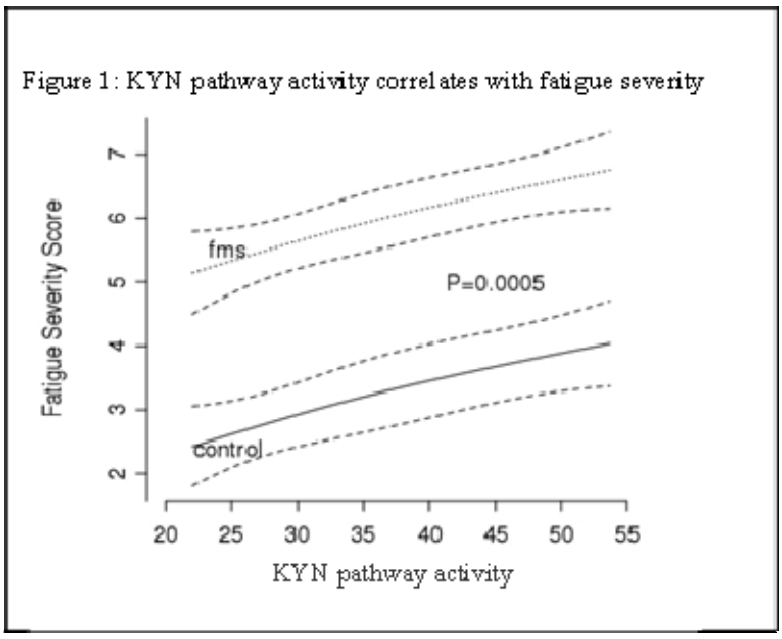
Kynurenine Pathway Activity Linked to Fibromyalgia Fatigue. Chad S. Boomershine[1], Dina Titova[2], Chongbin Zhu[1], Annette M. Oeser[1], M. Wade Calcutt[1], Aihua Bian[1], Tebeb Gebretsadik[1], Raymond Johnson[1] and C. Michael Stein[1], [1]Vanderbilt University, Nashville, TN, [2]FMG, Fox Island, WA

Purpose: Fatigue is often the most disabling fibromyalgia (FM) symptom, but its cause is unknown and therapies are limited. FM is linked to decreased levels of serotonin (5-HT) and its precursor tryptophan (TRP), but 5-HT reuptake inhibition does not treat FM fatigue. The kynurenine pathway (KYN-p) decreases 5-HT and TRP by converting TRP to neurotoxins that cause affective symptoms. Since indoleamine 2,3-dioxygenase (IDO) is the rate-limiting KYN-p enzyme, KYN-p activity can be estimated from the KYN/TRP ratio. We hypothesized increased KYN-p activity caused FM fatigue. KYN-p activity and fatigue levels were studied in human FM patients and a mouse FM model.

Method: 48 FM patients and 32 controls ≥18 years were studied. FM diagnosis was confirmed by ACR classification criteria. Fatigue severity in humans was quantified using the fatigue severity scale (FSS). In wild-type (wt) and syngeneic IDO knockout (IDOko) mice, FM was induced by 300mg/kg p-chlorophenylalanine (PCPA) treatment daily for 1 week. Fatigue severity in mice was assessed by meters (m) traveled in 30 minute open field testing (OFT). KYN and TRP levels were measured by stable isotope dilution and ultra-high pressure liquid chromatography (UHPLC) with tandem mass spectrometry in fasting plasma samples. HPLC with electrodetection was used to determine brain 5-HT, norepinephrine (NE) and dopamine (DA) levels. The relationship of disease status with KYN-p activity and FSS scores was assessed using multivariable linear regressions adjusted for age and race. In mouse studies, two-tailed, Mann-Whitney U tests were used to compare measures. Data are reported as median (interquartile range).

Results: KYN-p activity correlated with fatigue severity in all human subjects ($p = 0.0005$) and in FM patients ($p<0.0001$) (Figure 1). PCPA treatment of wt mice increased KYN-p activity [10.7 (8.6-11.7) to 12.2 (11.4-14.9), $p=0.04$] and induced fatigue in OFT [30.8m (27.7-36.9) to 15.7m (13.8-21.6), $p=0.008$]. IDOko mice had lower KYN-p activity than wt at baseline [5.6 (4.7-6.4) vs. 10.7 (8.6-11.7), $p<0.0001$] and after PCPA treatment [4.2 (3.6-4.6) vs. 12.2 (11.4-14.9), $p=0.0002$]. IDOko and wt mice had similar baseline OFT activity levels [38.1m (35.4-47.7) vs. 30.8m (27.7-36.9), $p=0.1$]. IDOko mice were protected from PCPA-induced fatigue, as they had similar OFT activity levels to baseline levels in wt mice [34.3m (19.4-35) vs. 30.8m (27.7-36.9), $p=0.6$]. No differences were found in levels of 5-HT, NE or DA between PCPA-treated wt and IDOko mice in midbrain or frontal cortex regions (data not shown).

Conclusion: Increased KYN-p activity is associated with FM fatigue in humans and a murine model. IDO enzyme inhibition may be a novel method for treating FM fatigue.



Disclosure: C. S. Boomershine, Pfizer Inc, 2, Cypress Biosciences, Inc., 8, Forest Laboratories, 8, Eli Lilly and Company, 8, Pfizer Inc, 8, NIH, 2, NIH, 2 ; **D. Titova**, None; **C. Zhu**, NIH, 2 ; **A. M. Oeser**, None; **M. W. Calcutt**, NIH, 2 ; **A. Bian**, None; **T. Gebretsadik**, None; **R. Johnson**, NIH, 2 ; **C. M. Stein**, NIH, 2 .

1992

WITHDRAWN

1993

Glutamate in the Anterior Insula Is Associated with Working Memory Performance in Fibromyalgia (FM). Paloma Barjola[1], Jennifer Glass[2], Pia Sundgren[2], Steven E. Harte[2], David A. Williams[2], Daniel Clauw[3] and Richard Harris[2], [1]Rey Juan Carlos, Madrid, Spain, [2]U. Michigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI

Purpose: Glutamate (Glu) is an excitatory neurotransmitter whose concentration within the posterior insula has been shown to be related to pain processing in fibromyalgia (FM) (Harris et al. 2008). The role of Glu in the anterior insula in FM is less understood. Since FM is also associated with multiple cognitive impairments such as reduced working memory (WM), and insular structures have been previously shown to be involved in different aspects of memory function, we hypothesized that anterior insular Glu may be related to WM performance.

Method: 19 FM patients (age 45.2 (15) yrs) participated in a session of H-MRS and single-voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms, TE 30 ms, 90° flip angle, NEX 8, FOV 16cm, and VOI of 2x2x3cm. Two separate SVS sequences were performed, one with the VOI placed in the right anterior insula and another in the right posterior insula. Patients were at rest during the session. Values for Glu were calculated as absolute concentration using water signal as an internal reference, and expressed in arbitrary institutional units (AIU). Raw data were analyzed with LCModel software. WM performance was assessed with the Letter-Number span test (Wechsler Memory Scale). Additionally, reported pain was assessed with the McGill Pain Questionnaire (MPQ). Data were analyzed with SPSS v17.

Results: Concentrations of Glu in the right anterior insula were positively correlated with WM performance ($r=0.626$; $p=0.004$). The sensory subscale, but not the affective subscale, of MPQ was negatively correlated with the scores in WM ($r=-0.495$; $p=0.037$). A stepwise linear regression model with WM performance as a dependent variable was carried out. In the first step pain showed significance as a predictor ($p=0.037$) of WM (worse pain was associated with worse WM). When both pain and Glu levels were entered as simultaneous predictors, the

effect of Glu was significant (p=0.014) and pain displayed a trend towards significance (p=0.104). No such relationships were detected for the right posterior insula.

Conclusion: Consistent with previous literature, the anterior and posterior regions of the insula appear to be functionally distinct. This study suggests that anterior insula Glu may be involved in WM whereas previous studies suggest that the posterior insula is involved in pain processing. Future studies are needed to understand the mechanisms underlying these relationships which may be relevant to other chronic pain populations.

Disclosure: P. Barjola, None; **J. Glass**, Pfizer Inc, 2, Forest Laboratories, 2 ; **P. Sundgren**, None; **S. E. Harte**, None; **D. A. Williams**, None; **D. Clauw**, Pfizer Inc, 2, Forest Laboratories , 2, Cypress Biosciences Inc, 5, Lilly , 5, Pfizer Inc, 5, Forest Laboratories, 5, UCB, 5, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **R. Harris**, Pfizer Inc, 2 .

1994

Bilateral Anterior Insular Glutamate (Glu) Is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls. Richard Harris[1], Pia Sundgren[1], James Hubbard[1], A.D. (Bud) Craig[2] and Daniel Clauw[3], [1]U. Michigan, Ann Arbor, MI, [2]Atkinson Research Laboratory, Barrow Neurological Institute, Phoenix, AZ, [3]University of Michigan, Ann Arbor, MI

Purpose: The insula is involved in processing both sensory and affective aspects of pain. It has been suggested that there is an asymmetric distribution in function within this structure, with the right anterior insula being responsive to pain stimuli and the left playing more of a pain inhibiting role. Using proton magnetic resonance spectroscopy (H-MRS), we examined the relative levels of glutamate (Glu), an excitatory neurotransmitter, within the right and left anterior insula of individuals with fibromyalgia (FM) and pain-free controls (HC). We hypothesized that greater levels of Glu in the right anterior insula as compared to the left, would be associated with more pain sensitivity.

Methods: Subjects from an ongoing acupuncture trial in FM, with complete bilateral insula H-MRS data were studied. 11 patients (ages 47+/-18 yrs) and 14 controls (ages 46+/-11 yrs) underwent single voxel spectroscopy (SVS) using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Four separate SVS sequences were performed in the insula: 1. right anterior, 2. right posterior, 3. left anterior and 4. left posterior. Participants were at rest during the scanning session. Spectra were analyzed offline with LCModel. Values for Glu were expressed in arbitrary institutional units (AIU) using water as an internal standard. The ratio of right anterior insula Glu divided by left anterior insula Glu was calculated and entered into SPSS v.17. Analogous calculations were performed with the right and left posterior insula. Experimental pressure pain testing was performed prior to H-MRS. Data were analyzed with SPSS v.17.

Results: The ratio of right anterior insula Glu versus left anterior insula Glu was significantly correlated with pressure pain sensitivity when both groups were combined (medium pain: r=-0.56, p=0.004; high pain: r=-0.50, p<0.01), and when groups were analyzed separately (HC medium pain: r=-0.57, p=0.04; FM medium pain: r=-0.54; p=0.09). Individuals with greater Glu in the right anterior insula, as compared to the left, displayed lower pressure thresholds. This result was not obtained for the bilateral posterior insula Glu ratio (medium pain: r=-0.36, p>0.05; high pain: r=-0.28, p>0.1).

Conclusion: There appears to be an asymmetric distribution of Glu function in the anterior insulae. Greater excitatory neural activity in the right anterior insula, as compared to the left, is associated with more pain sensitivity. This relationship may represent a general aspect of pain processing.

Disclosure: R. Harris, None; **P. Sundgren**, None; **J. Hubbard**, None; **A. D. (. Craig**, None; **D. Clauw**, Cypress Biosciences, Inc, 5, Forest Laboratories, 5, Lilley, 5, Pfizer Inc, 5, Wyeth Pharmaceuticals, 5 .

1995

Fatigue Enhances the Response to Pain through NMDA Receptors in Nucleus Raphe Obscurus. Luis FS daSilva, Lynn A. Rasmussen and Kathleen A. Sluka, University of Iowa, Iowa City, IA, IA

Purpose: Since many people with chronic fatigue present with pain and many people with chronic pain present with fatigue, we tested if fatigue would enhance the response to pain in male and female mice; and if this fatigue-enhancement of pain behaviors was centrally mediated.

Method: We used a mouse-model of fatigue combined with a mouse-model of chronic widespread pain to examine the interactions between pain and fatigue. To model fatigue, whole-body fatigue was induced by having mice spontaneously run in running wheel for 2h. To model chronic widespread pain, two injections of pH 5.0 were injected into the gastrocnemius muscle; the fatigue task was performed for either 30 min or 2h before the second intramuscular injection of acid. The mechanical sensitivity of the paw (von Frey filaments), muscle (tweezers), and grip force were assessed before and 24h after the second injection of pH 5.0. In a separate group of animals, we tested the role of the NMDA receptors in nucleus raphe obscurus (NRO) in this fatigue-enhancement of pain. Brain cannulae were implanted in the NRO for microinjection of AP5 (1nmol) just prior to the fatigue task. In this group pain behaviors were measured before 1st and 2nd injection of acidic saline, and 24h after the second intramuscular injection of acid.

Results: Both male and female mice that performed the fatigue task, before the second intramuscular injection of acid, showed an enhanced mechanical sensitivity of the paw. There was no change in the non-running control mice, or the muscle hyperalgesia in the running mice when compared to the non-running mice. There was also no change in grip force suggesting that mice had no deficit in motor performance induced by the acid. Microinjection of AP5 into the NRO just prior to the fatigue task, prevented the onset of hyperalgesia 24h later to the fatigue-enhanced response to pH 5.0.

Conclusion: We conclude that fatigue enhances pain through central mechanisms that involve NMDA receptors in the NRO.

Disclosure: L. F. daSilva, None; **L. A. Rasmussen**, None; **K. A. Sluka**, None.

1996

Neurocortical Representation of Locus of Control in Individuals with Fibromyalgia. David A. Williams[1], Richard Harris[1], Rupal Bhavsar[1], Daniel Clauw[2], Jon Kar Zubieta[1] and Richard Gracely[3], [1]U. Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]U, North Carolina, Chapel Hill, NC

Purpose: Cognitive modulation of pain is thought to involve dorsolateral, ventrolateral, and medial prefrontal cortical regions (PFC) – regions that have been associated with placebo responsively, expectations for pain relief, and perceived control over pain. The perception of pain control associated with PFC activity is thought to initiate downstream modulation of the pain matrix and ultimately brain-stem mediated analgesic responses. One cognitive factor, internal locus of pain control (I-loc), defines a belief in pain as being modifiable via personal effort. This study sought to identify neurocortical regions experiencing greater changes in activity as I-loc increases in individuals with FM exposed to evoked pain stimuli.

Method: 57 females satisfying ACR criteria for FM and participating in non-pharmacological treatment (i.e. exercise and relaxation training) aimed at improving (I-loc) also underwent standardized evoked pressure pain testing (EPP) in the context of fMRI neuroimaging both at baseline and the 12-week endpoint. During 10 minute fMRI sessions, pressures of 2kg were applied to the left thumb by a 1 cm diameter probe. fMRI data were acquired by a GE 3 Tesla scanner at 2.5s intervals and analysis of the BOLD signal was performed using Medx. I-loc was assessed using the Beliefs in Pain Control Questionnaire (BPCQ). Responders to treatment were defined as individuals demonstrating a minimal clinically important difference on I-loc (i.e. improving >=0.5 SD). The assessment of change in BOLD tied to improvement in I-loc used ANCOVA as the analytic approach with baseline BOLD values serving as covariates for specific regions of interest (ROIs).

Results: Significant increases in BOLD activation were observed in I-loc responders (but not non-responders) in left IPL BA40 ($F_{(1,54)}$=6.0, p<.02) and in the left medial pre-frontal cortex (MPFC) ($F_{(1,54)}$=7.19, p<.01). Improvement in I-loc was not associated with BOLD changes in other prefrontal regions.

Conclusion: These data support the hypothesis that perceived control over pain is associated with PFC activation and with semantic regions related to but differentiated from the pain matrix. Non-pharmacological interventions appear to modify perceptions of pain control which in turn influence neurocortical regions important to pain perception and modulation.

Disclosure: D. A. Williams, NIAMS-NIH, 2 ; **R. Harris**, Pfizer Inc, 2 ; **R. Bhavsar**, None; **D. Clauw**, UCB, 5, Forest Laboratories, 5, Pfizer Inc, 5, Lilly , 5, Cypress Biosciences Inc, 5, Forest Laboratories , 2, Pfizer Inc, 2, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **J. K. Zubieta**, None; **R. Gracely**, None.

ACR Concurrent Abstract Sessions

Imaging - New Frontiers

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

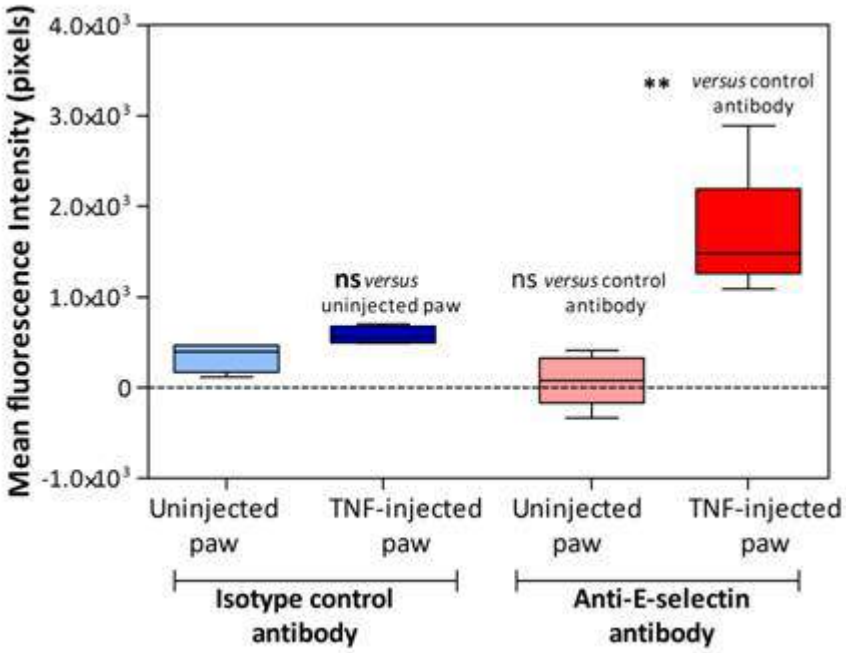
1997

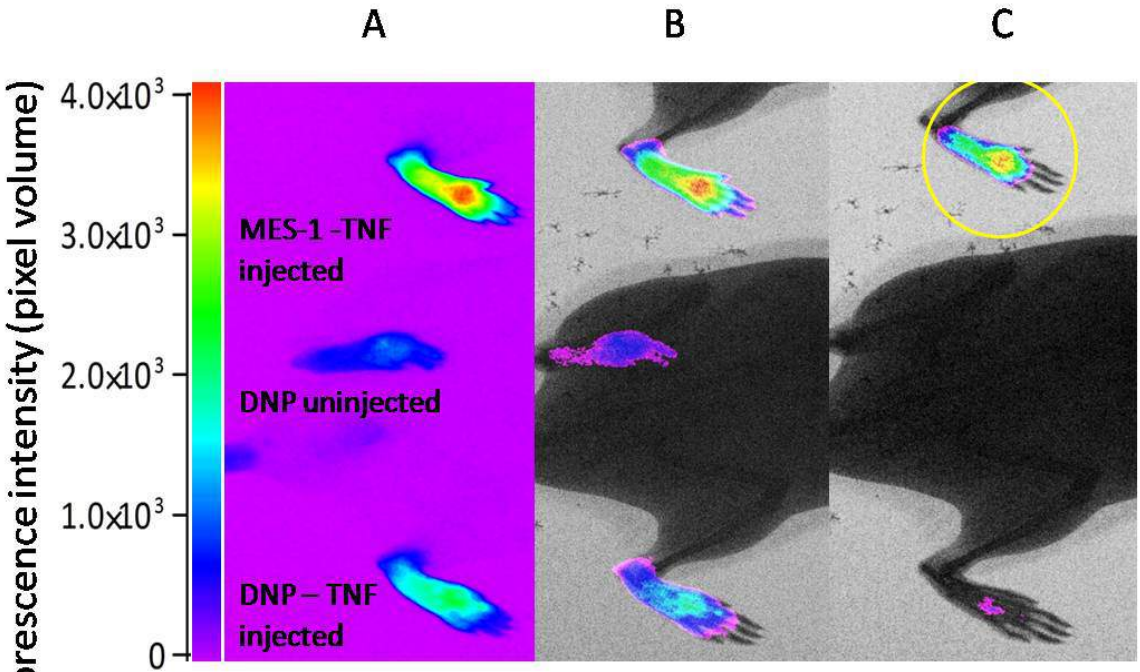
In Vivo Fluorescence Imaging of TNF-Induced Endothelial Inflammation by Targeting E-Selectin. Luke L. Gompels[1], Julia Inglis[1], Tonia Vincent[1], Leigh Madden[1], Kay McNamee[1], Ellen McConnell[2], Dorian O. Haskard[2] and Ewa M. Paleolog[1], [1]London, United Kingdom, [2]Imperial College, London

Purpose: Understanding of the genetic and molecular basis of inflammatory arthritis has advanced rapidly, but non-invasive visualization of specific molecular targets and therapeutic effects *in vivo* remains a challenge. E-selectin is a validated marker of activated endothelium in rheumatoid arthritis. We examined the use of *in vivo* fluorescence imaging, targeting E-selectin expression in mouse TNFα induced paw edema.

Method: Monoclonal anti-murine E-selectin and isotype control antibodies were labeled with a near infrared fluorescent DyLight 750 probe (excitation 752nm, emission 778nm) to maximize probe intensity and signal-to-noise ratio through live tissue. Antibody was injected immediately prior to intraplantar injection of 50ng mouse TNFα, and mice were imaged using the Kodak FX Pro *in vivo* imaging system.

Results: Kinetics of E-selectin expression *in vivo* were used to delineate the sensitivity of optical imaging for differentiating target antibody compared to background/autofluorescence levels, and the specificity of target *versus* control antibody. *In vivo* fluorescent imaging demonstrated specific localization of E-selectin antibody in inflamed joints, with maximal differential effect at 8 hours following TNFα injection, correlating with maximal levels of paw inflammation/edema.





Panel A: Demonstrates fluorescent signal in a representative control (DNP) and MES-1 injected animal at the 8 hr time point
Panels B and C demonstrate X-ray co-registration:
Panel B: Background and auto fluorescence subtracted
Panel C: Average signal intensity from the DNP injected animal inflamed paw subtracted to leave the specific signal from the MES-1 inflamed paw (circled).

Conclusion:

In vivo optical imaging of E-selectin is a sensitive, specific and non invasive method of measuring endothelial activation in inflammation.

The novel use of fluorescently labeled biomarkers has significant potential for visualization of disease states such as inflammatory arthritis. This will facilitate *in vivo* interrogation of molecular pathways and assessment of both local and systemic effects of therapies.

Disclosure: L. L. Gompels, None; **J. Inglis**, None; **T. Vincent**, None; **L. Madden**, None; **K. McNamee**, None; **E. McConnell**, None; **D. O. Haskard**, None; **E. M. Paleolog**, None.

1998

Objective Disease Activity Assessment for Rheumatoid Arthritis Using Optical Monitoring. A.J.L. Meier[1], W.H.J. Rensen[2] and R.N.J. de Nijs[1], [1]Regional Rheumatology Centre (RRC) ZO-Brabant, Eindhoven, Netherlands, [2]Philips, Eindhoven, Netherlands

Purpose: There is a need for an objective, reproducible, fast, quantitative and accurate disease activity monitor for disease progression monitoring in patients with rheumatoid arthritis (RA). Optical spectral transmission is a promising solution, since optical contrast can be related to physiological parameters in the body, such as blood concentration and oxygenation. At relevant wavelengths and intensities, optical radiation is completely harmless. Additionally, the cost of optical methods is low compared to other modalities. Due to the highly scattering nature of tissue, non-invasive optical methods for medical imaging are limited to the extremities of the human body. For application in joint diseases, this is acceptable, because imaging of hands and wrists can provide sufficient clinical information. This study aims to assess feasibility of disease activity monitoring by optical methods.

Method: A device has been developed for optical spectral transmission measurements positioned at the proximal interphalangeal (PIP) joint and at the intermediate phalanx as a reference in a standardized setup. A cross-sectional, non-randomized observational study was performed with this device. In the study, 82 PIP joint measurements in 67 subjects have been performed. Inflammation of these PIP joints was also assessed by a rheumatologist with a score varying from one (not inflamed) to five (severe inflamed), the DAS28-score was used as a reference.

Results: Out of 82 measurements, 30 were performed in moderate or strongly inflamed PIP joints. Correlation between the clinical assessment and a single optical measurement parameter showed $r = 0.59$ ($p < 0.0001$), figure 1. The same optical parameter leads to a ROC curve (AUC= 0.76) that shows that a relative good specificity compared to the sensitivity. Other optical parameters also showed significant differences between inflamed and non-inflamed joints ($p < 0.0001$). Unsurprisingly, both clinical assessment and optical measurements of single joints show a poor correlation with the multi-joint DAS28 score.

Conclusion: Optical spectral transmission measurements correlate with clinical assessment of joint inflammation, and therefore might be useful in monitoring disease activity of RA patients. Further study using a multi-joint device is necessary to demonstrate the usability of optical measurements in clinical practice.

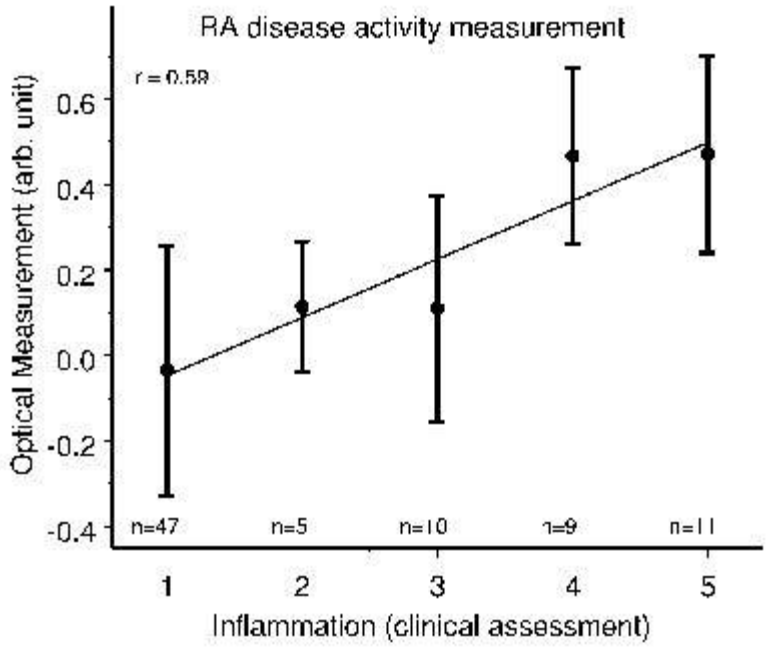


Figure 1 Correlation between the clinical assessment and a single optical measurement parameter

Disclosure: A. J. L. Meier, None; **W. H. J. Rensen**, Philips Research Europe, 3 ; **R. N. J. de Nijs**, None.

1999

Macrophage PET Imaging as Biomarker for Very Early Rheumatoid Arthritis. Ernst H. Elzinga[1], Alexandre E. Voskuyl[1], Nikie J., Hoetjes[1], Emile FI Comans[1], Dirkjan van Schaardenburg[2], Otto S. Hoekstra[1], Adriaan A. Lammertsma[1], Ben A.C. Dijkmans[1] and Conny J. van der Laken[1], [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Institute, Amsterdam, Netherlands

Purpose: Rheumatoid arthritis (RA) is preceded by subclinical disease activity before development of clinical symptoms of arthritis. Visualization of subclinical disease activity may enable initiation of early treatment. However, visualization of subclinical synovitis requires sensitive advanced imaging methods. Our group has demonstrated the value of positron emission tomography (PET) using [^{11}C]-(R)-PK11195 in visualizing (subclinical) synovitis. The purpose of the current study was to investigate whether subclinical synovitis can be visualized using [^{11}C]-(R)-PK11195-PET in arthralgia patients with presence of anti-CCP antibodies, without clinical symptoms of arthritis. The second purpose was to determine whether the presence of PET abnormalities may predict the development of clinical arthritis.

Method: Patients with anti-CCP positive arthralgia without synovial swelling (n = 28) and the presence of anti-CCP antibodies were included. High-resolution [^{11}C]-(R)-PK11195 PET scans of the hands and wrists were performed. All metacarpophalangeal, proximal interphalangeal and wrist joints (i.e. a total of 22 visualized joints per patient) were scored for positivity. Uptake on PET images was scored semi-quantitatively on a scale of 0 to 3 (minimal- high). Follow-up during one year was performed to detect the presence of clinical joint swelling.

Results: At patients level, at least one PET positive joint (score ≥ 1) was found in 7 of 28 patients, with a maximum of 5 PET positive joints per patient. After one year of clinical follow-up 9 patients had developed arthritis: 6 patients had developed arthritis in hands/wrists, 3 patients only in other joints. At least one evident PET positive joint (score 2 to 3) was found in 3 out of 9 patients developing arthritis. None of the patients who did not develop arthritis within a year showed evident enhanced [^{11}C]-(R)-PK11195 uptake (table 1). At joint level, 19/616 were scored PET positive. Clinical arthritis developed in 7 joints after 1 year of clinicalfollow-up.

Conclusion: A positive [^{11}C]-(R)-PK11195-PET signal was found in 25% of all included anti-CCP positive arthralgia patients. High PET-uptake was found in a subgroup of patients, all of these developed clinical arthritis. These findings suggest that high joint-uptake of [^{11}C]-(R)-PK11195 may aid to predict the development of arthritis in patients at risk of RA.

	PET score 0-1	PET score 2-3
Arthritis	6	3
No arthritis	19	0

table 1: PET score versus clinical follow-up after one year

Disclosure: E. H. Elzinga, None; **A. E. Voskuyl**, None; **N. J. ,. Hoetjes**, None; **E. F. Comans**, None; **D. van Schaardenburg**, None; **O. S. Hoekstra**, None; **A. A. Lammertsma**, None; **B. A. C. Dijkmans**, None; **C. J. van der Laken**, None.

2000

Lentiviral-Based Bioluminescent Imaging of Synovial Inflammatory Subtypes in Experimental Arthritis and Human Synovial Fibroblasts. Jeroen Geurts[1], Eline A. Vermeij[1], Onno J. Arntz[1], Raimund W. Kinne[2], Wim B. van den Berg[1] and Fons A. van de Loo[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University Hospital Jena, Eisenberg, Germany

Purpose: Chronic synovial inflammation is a hallmark of rheumatoid arthritis and gene expression analyses of RA synovial tissues have revealed molecularly distinct, high and low inflammatory subtypes. We evaluated the applicability of lentiviral-based (LV) promoter-luciferase reporters for assessing differential inflammation subtypes in experimental arthritis and primary OA and RA synovial fibroblasts (SF).

Methods: Murine promoters of *Saa3* and *Cxcl1* genes, which are strongly regulated in experimental arthritis, were cloned upstream of the luciferase (Luc) cDNA in LV vectors. Murine synovium was transduced *in vivo* and two consecutive flares of acute arthritis were induced by intra-articular injection with streptococcal cell wall (SCW) material. Kinetics of synovial inflammation were assessed using *ex vivo*

luciferase assays and ^{99m}Technetium (Tc) uptake. Classification of SF (*n*=12) inflammatory subtypes was accomplished using hierarchical clustering of gene expression profiles. SF subtypes were transduced with LV-*Saa3*/*Cxcl1*-Luc and stimulated with IL-1b, TNFa or toll-like receptor (TLR) 2/4 agonists. Promoter activity was measured using luciferase assays.

Results: Luciferase expression was strongly upregulated (50-100 fold) during the first flare and *Saa3*, but not *Cxcl1* promoter activity correlated (*P*<0.0005, Pearson *r* 0.82) with inflammation as measured by ^{99m}Tc uptake. While the *Saa3* promoter could be reactivated in a second flare (500 fold), the *Cxcl1* promoter remained stably activated. Interestingly, using lower SCW dosages the bioluminescent reporters, but not ^{99m}Tc measurements were able to assess synovial activation, which indicated a superior sensitivity of our novel method. Hierarchical clustering of SF gene expression profiles discriminated between two subtypes. The high inflammatory subtype was characterized by predominantly increased expression of chemokines (*IL8*, *MCP1*) and matrix-degrading enzymes (*MMP1/3*). Relative *Saa3* promoter responses to cytokines and a TLR4 agonist were significantly (*P*<0.001) increased in OA/RA SF from the high inflammatory subtype (*n*=5) compared to the low inflammatory subtype (*n*=3). Relative *Cxcl1* promoter responses did not discriminate between inflammatory subtypes.

Conclusion: *Saa3* promoter activity is a more sensitive read-out for synovial inflammation than ^{99m}Tc uptake in experimental arthritis. The *Saa3* promoter response in stimulated primary OA/RA SF can distinguish between molecularly distinct high or low inflammatory subtypes. These results demonstrate the sensitivity and versatility of genetic bioluminescent reporters for quantitative imaging of heterogeneous synovial inflammation.

Disclosure: J. Geurts, None; **E. A. Vermeij**, None; **O. J. Arntz**, None; **R. W. Kinne**, None; **W. B. van den Berg**, None; **F. A. van de Loo**, None.

2001

Near Infrared Lymphatic Imaging and Quantification of Lymphatic Draining Function in a Murine Model of Inflammatory Arthritis. Q. Zhou, R. Wood, E.M. Schwarz, B. Boyce and L. Xing, University of Rochester, Rochester, NY

Purpose: The lymphatic system may play a functional role to limit inflammation in affected joints in rheumatoid arthritis (RA). However, approaches to non-invasively measure lymphatic draining function in murine models of RA are lacking. We have developed a near infrared (NIR) fluorescence lymphatic imaging technique and used it to examine lymphatic flow from affected joints to draining lymph nodes (LNs) of arthritic mice.

Method: We used NIR lymphatic imaging based on published literature and our past experience with large animals and human subjects. Indocyanine green (ICG), a NIR tracer, was injected intra-dermally into mouse footpads and changes in the intensity and distribution of the ICG signal over the entire leg region was visualized under an NIR laser and recorded. NIR imaging was repeated 24 hrs after ICG injection. Regions of interest defining draining popliteal lymph nodes (PLNs) and the injection site were identified, yielding 3 outcome measures of lymphatic function: 1) T-initial (Ti), the time it takes for the ICG to reach the PLN; 2) S-max, the maximum ICG signal intensity in the PLN; 3) T-max, the time it takes for a PLN to achieve maximal ICG signal. K/BxN arthritic mice and non-arthritic littermate controls (N=4-6/group) received NIR-ICG at 1 and 3 months of age. Joint inflammation severity was measured by clinical scoring. Lymphangiogenesis in PLNs was determined using immunohistochemistry (IHC) and a LYVE-1 antibody.

Results: NIR-ICG imaging demonstrated dynamic changes in lymphatic drainage from affected paws to PLNs during the development of joint inflammation. Joint lymphatic flow was significantly increased in 1-month-old K/BxN mice with severe joint inflammation compared to control mice (Ti: 1±0 vs 14±2 min; Tmax: 31±19 vs 51±17min; Smax: 98±56 vs 12±4). Arthritic mice had extensively dilated and irregular lymphatic vessels in their feet and increased numbers of LYVE-1+ lymphatic sinuses with narrow lumens in their PLNs compared with control mice. At 3 months, K/BxN mice had 2-3 fold slower lymphatic flow than 1-month-old mice and they had a network of numerous small lymphatic vessels in their inflamed feet. Clinical scoring showed that they had decreased joint swelling compared with 1-month-old mice (3.3±0.2 vs 4.5±0.5 mm^2) and the number of LYVE-1+ lymphatic sinuses in their PLNs was significantly increased, the majority having extensive, dilated lumens.

Conclusion: NIR-ICG imaging is a powerful new tool to monitor dynamic changes in lymphatic draining function of inflamed joint tissue in mice. In the acute phase of joint inflammation, increased lymphatic flow exceeds lymphatic draining capacity, associated with severe joint swelling. Later enhanced lymphatic drainage from joints and PLNs reduces the degree of joint swelling. This technique could be used to assess the efficacy of intervention therapy to improve lymphatic draining function in models of RA.

Disclosure: Q. Zhou, None; **R. Wood**, None; **E. M. Schwarz**, None; **B. Boyce**, None; **L. Xing**, None.

2002

Monocyte Scintigraphy in Rheumatoid Arthritis, Dynamics of Monocyte Migration in Immune-Mediated Inflammatory Disease.
Rogier M. Thurlings[1], Carla A. Wijbrandts[2], Roel Bennink[2], Serge Dohmen[3], Elena Izmailova[4], Danielle M. Gerlag[1], Berthe van Eck-Smit[2] and Paul P. Tak[5], [1]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Sanquin Research, Amsterdam, Netherlands, [4]Millennium Pharmaceuticals, Cambridge, MA, [5]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Macrophages are principal drivers of synovial inflammation in rheumatoid arthritis (RA), a prototype immune-mediated inflammatory disease. Conceivably, synovial macrophages are continuously replaced by circulating monocytes in RA. Animal studies from the 1960s suggested that macrophage replacement by monocytes is a slow process in chronic inflammatory lesions. Translation of these data into the human condition has been hampered by the lack of available techniques to analyze monocyte migration in man. We developed a technique that enabled us to analyze the migration of labelled autologous monocytes in RA patients using single photon emission computer tomography (SPECT).

Method: Peripheral blood was drawn from 8 patients with active RA. CD14+ monocytes were isolated using CliniMACS and labeled with technetium-99m (^{99m}Tc-HMPAO). Monocytes were re-infused into the same patient. Scintigraphy was performed at 1, 2, 3, and 20 hours after re-infusion. The number of positive joints was counted and the exact signal intensity of a large joint was measured selecting a region of interest (ROI).

Results: Scintigraphic scans showed distinct uptake of labeled monocytes in inflamed joints in all patients. Using SPECT we calculated that a very small but specific fraction of 3.4×10^{-3} ($0.95\text{-}5.1 \times 10^{-3}$) % of re-infused monocytes migrated to the inflamed joints, being detectable within one hour after re-infusion.

Conclusion: The results indicate monocytes migrate continuously into the inflamed synovial tissue of RA patients, but at a slow macrophage-replacement rate. This suggests that the rapid decrease in synovial macrophages that occurs after antirheumatic treatment might rather be explained by an alteration in macrophage retention than in monocyte influx and that RA might be particularly sensitive to treatments targeting inflammatory cell retention.

Disclosure: R. M. Thurlings, None; **C. A. Wijbrandts**, None; **R. Bennink**, None; **S. Dohmen**, None; **E. Izmailova**, Millennium Pharmaceuticals , 3 ; **D. M. Gerlag**, None; **B. van Eck-Smit**, None; **P. P. Tak**, None.

ACR Concurrent Abstract Sessions

Pediatric Rheumatology – Pathogenesis and Outcomes

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

2003

Children with Persistent Oligoarticular Juvenile Idiopathic Arthritis (OJIA) Resistant to Standard Therapy: An Under-Recognized Population.
Alisa C. Gotte[1] and Marilynn G. Punaro[2], [1]Univ of Texas Southwestern, Dallas, TX, [2]Texas Scottish Rite Hospital for Children, Dallas, TX

Purpose: Persistent OJIA is the most common subtype of JIA, accounting for a significant proportion of children managed by pediatric rheumatologists. Although often considered benign, inadequate response to therapy can result in joint deformity and disability. Persistent OJIA is primarily treated with non-steroidal anti-inflammatories (NSAIDs) and/or intra-articular corticosteroid injections (IACI); however, the optimal treatment is unknown. Little is known about the frequency of children with persistent OJIA who fail standard therapy or about features associated with resistance to standard therapy.

Method: The records of all children seen at Texas Scottish Rite Hospital for Children (TSRHC) from 2000-2008 who met International League of Associations of Rheumatologists (ILAR) criteria for OJIA and had at least six months of follow-up were reviewed.

Results: 341 children were seen at TSRHC from 2000-2008 who met ILAR criteria for OJIA. 56 (16%) of these children developed extended OJIA, the remaining 285 (84%) children were classified as persistent OJIA. 106 children with persistent OJIA were treated with IACI with or without concomitant NSAID use. 75 (71%) of children treated with IACI +/- NSAIDs had resolution of all signs and symptoms of arthritis in the treated joint for at least six months, and were defined as IACI-responsive. 31 children (29%) had active arthritis despite IACI, and were defined as IACI-resistant. IACI-resistant children failed a mean of 1.97 injections (range 1-7) before declared IACI-resistant. All but 2 of the IACI-resistant children were then treated with DMARD therapy (usually methotrexate); 18 of the 29 children treated with a DMARD had resolution of arthritis, 11 children had continued arthritis despite DMARD therapy. 9 children who failed DMARDs were treated with anti-TNF agents, all of whom experienced sustained remission of disease activity.

IACI-resistant children were more likely to be of Hispanic ethnicity (IACI-resistant group 32% Hispanic vs. IACI-responsive group 8% Hispanic, p=0.008), had a higher ESR at the time of presentation (37.9 mm/hr vs. 22.6, p=0.012), had more joints involved at initial presentation (1.9 joints vs. 1.3, p=0.022), and were more likely to have involvement of an upper extremity (35% with upper extremity joint involvement vs. 8%, p=0.004) than IACI-responsive children.

Conclusion: Almost one-third of children with persistent OJIA were resistant to standard therapy, suggesting that resistance to standard therapy is more frequent than previously appreciated. Hispanic children with persistent OJIA, an unreported population affected by OJIA, were at particular risk for failure of standard therapy. IACI-resistant OJIA may be responsive to DMARD and anti-TNF therapy, and more aggressive therapy should be considered in children with persistent OJIA resistant to standard therapy.

Disclosure: A. C. Gotte, None; **M. G. Punaro**, None.

2004

Optimization of the Provisional Criteria for Clinically Inactive Disease for Select Categories of Juvenile Idiopathic Arthritis. Carol A. Wallace[1], Edward H. Giannini[2] and N. Ruperto[3], [1]Seattle Children's Hospital, Seattle, WA, [2]Children's Hospital Medical Center, Cincinnati, OH, [3]Pediatria-II PRINTO, IRCCS G. Gaslini, Genova, Italy

Purpose: To optimize and begin prospective validation of the provisional classification criteria for *inactive disease* (ID) in patients with select categories of JIA.

Methods: Data from 1096 patient-visits from the Phase III randomized controlled trial of infliximab in polyarticular JIA without systemic features were used to develop 60 patient-profiles. Profiles were selected that either met or came close to meeting the provisional criteria for ID, and contained 7 clinical and 4 laboratory variables. Profiles were supplied via an online-survey to 40 pediatric rheumatologists in 27 countries. Physicians were asked to rate each patient-profile as being in a state of *ID*, *active disease* (AD), or *unable to determine*. To assess intra-physician reliability, a second survey containing 20 of the original 60 profiles was sent to the same physicians 2 months after receipt of results from the first survey. Multivariate statistical approaches were used to identify models that showed the highest area under the ROC curve when physician ratings of patient status were cross tabulated with status as determined by the provisional criteria. The best fit model was then applied to the remaining 1036 profiles from the RCT. A third online-survey containing the modified criteria was sent to 60 pediatric rheumatologists to calculate the quantitative content validity index (CVI) of the criteria set overall, and the face validity index (FVI) of each criterion and its respective critical value. The resulting set of variables is referred to as the optimized provisional criteria set.

Results: All 40 physicians scored all 60 patient-profiles (2400 evaluations) and 37 (92.5%; 740 evaluations) replied to the second e-survey. The best fitting model produced an area under the ROC of .942, indicating excellent sensitivity and specificity. Intra-observer reliability kappa score was 0.7 (95% CI: .63 -.77), indicating *substantial* agreement. 41 of the 60 physicians (68%) replied to the third online-survey. Data from the model development analyses and final survey necessitated three changes to the provisional criteria. The *physician's global assessment of disease activity* (PGA) was modified to read *'PGA of disease activity score of ≤ 0.5 cm on a 10 cm VAS or ≤ 0.5 on an ordinal scale'*. The *ESR* was modified to read *'within normal limits in the laboratory where tested or, if elevated, not attributable to JIA'*. *Duration of morning stiffness* (DMS) was added to the criteria set and reads, *'DMS ≤ 15 minutes'*. The modified criteria have a CVI of 95%. The FVI of each criterion ranged from 93% to 100%.

Conclusion: The provisional criteria for *ID* (now referred to as *clinically inactive disease* (CID) in extended oligo, polyarticular RF + or (-) or systemic JIA without systemic features can be said to have excellent feasibility, face, content, criterion, and discriminant validity. Intra-physician reliability is substantial. The predictive validities of a classification of *CID*, *clinical remission on medication*, and *clinical remission* off medication are yet to be determined.

Disclosure: C. A. Wallace, Centocor, Inc., 2 ; **E. H. Giannini**, Centocor, Inc., 2 ; **N. Ruperto**, None.

2005

Candidate Urinary Biomarkers May Predict Histological Features On Lupus Nephritis (LN) Biopsy. Lena Das[1], Michiko Suzuki[1], Prasad Devarajan[1], Brad H. Rovin[2], Jun Ying[3] and Hermine Brunner[1], [1]Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [2]Ohio State University Medical Center, Columbus, OH, [3]University of Cincinnati, Cincinnati, OH

Purpose: Current non-invasive blood and urine tests do not reliably reflect renal histology in LN. Thus invasive kidney biopsies are needed to establish the diagnosis of and support treatment decisions for LN. The objective of this study was to assess whether recently identified novel LN urinary biomarkers [lipocalin-like prostaglandin-D synthetase (L-PGDS), α1-acid-glycoprotein (AGP), transferrin (Tf), ceruloplasmin (Cp) and neutrophil-gelatinase associated lipocalin (NGAL)] differentiate between certain LN histological features.

Methods: Concentrations of the LN biomarkers by nephelometry or ELISA were measured in the urine samples of patients with LN (n=40), collected within 60 days of a kidney biopsy. The following histological features of LN activity and chronicity as reported in the biopsy reports (present/absent) were considered: mesangial expansion, capillary proliferation, crescent formation, necrosis, wire loops, fibrosis, interstitial cell infiltrate, tubular atrophy and acute tubular necrosis (ATN). Biomarker levels were standardized by urinary creatinine and compared by nonparametric statistics for significant differences with histological features.

Results: As is shown in the table below, levels of biomarkers often significantly differed with certain histological features. Most importantly, features that are highly related to LN activity; crescents were associated with increased levels of CP and AGP (both $p<0.03$), while NGAL and L-PGDS were associated with wire loops (both $p<0.05$). Other features of activity like necrosis correlated with higher levels of TF and AGP ($p < 0.025$). In addition, increases of CP and NGAL were seen with glomerular endocapillary proliferation ($p<0.005$).

None of the biomarkers differentiated between the presence or absence of fibrosis or tubular atrophy. Additional analyses in larger cohorts are in process to assess whether combinations of the biomarkers can more accurately predict histological features of LN.

Conclusion: This pilot study suggests that urinary levels of AGP, NGAL, CP, TF and L-PGDS may predict histological changes and thus activity and chronicity on kidney biopsy with LN. If supported in future studies the above biomarkers may be part of a biomarker panel that will ultimately make invasive renal biopsies redundant.

Table : Ratio of mean urinary biomarker concentrations for presence versus absence (p/a) of each histological characteristic

Histology	N (p/a)	TF	CP	AGP	L-PGDS	NGAL
Mesangial expansion	25/15	0.74	0.56	0.71	**0.40****	**0.21****
Capillary proliferation	12/28	1.88	**4.09****	1.72	1.60	**4.53****
Crescents	26/14	1.78	**2.65***	**2.22***	1.50	2.20
Necrosis	31/9	**3.42***	1.86	**2.50***	1.50	2.06
Wire loops	34/6	2.50	2.18	1.60	**2.50***	**6.42****
Cellular infiltrate	13/27	0.96	0.96	1.25	1.60	3.24*
Acute tubular necrosis	30/10	1.42	2.16	2.00	**3.60****	**4.95****
$*p < 0.05$, $** p < 0.005$						

Disclosure: L. Das, None; **M. Suzuki**, None; **P. Devarajan**, DoD, ALR, TRI, NIAMS, 2 ; **B. H. Rovin**, None; **J. Ying**, None; **H. Brunner**, DoD, ALR, TRI, NIAMS, 2 .

2006

The EULAR/PRINTO/PRES Criteria for Childhood Vasculitides. Ankara 2008. Introduction and Methods. Nicola Ruperto[1], Seza Ozen[2], Angela Pistorio[1], Pavla Dolezalova[2], Paul Brogan[2], Ruben Cuttica[2], David Cabral[2], Raju Khubchandani[2], Daniel J. Lovell[2], Kathleen O'Neil[2], Pierre Quartier[2], Angelo Ravelli[3], Silvia M. Iusan[2], Giovanni Filocamo[1], Claudia Saad Magalhães[2] and Alberto Martini[1], [1]Pediatria-II PRINTO, IRCCS G. Gaslini, Genova, Italy, [2]PRINTO, Genova, Italy, [3]IRCCS G. Gaslini, Genova, Italy

Purpose: To validate classification criteria for Henoch-Schönlein purpura (HSP), childhood (c-) polyarteritis nodosa (c-PAN), c-Wegener granulomatosis (c-WG), and c-Takayasu arteritis (c-TA).

Methods: The preliminary Vienna 2005 consensus conference, which proposed preliminary criteria for paediatric vasculitides, was followed by a EULAR/PRINTO/PRES supported validation project divided into 3 main steps. Step 1: retrospective/prospective web-data collection for clinical characterisation of HSP, c-PAN, c-WG and c-TA, with age at diagnosis ≤ 18 years. Step 2: blinded classification by consensus panel of difficult cases enabling expert diagnostic verification. Step 3: Ankara 2008 consensus conference and statistical evaluation (sensitivity, specificity, k-agreement) using as gold standard the final disease attribution of the patients after step 2 (consensus classification or original treating physician diagnosis).

Results: A total of 1,183/1,398 (85%) of the samples collected were available for the analysis: 827 HSP, 150 c-PAN, 60 c-WG, 87 c-TA and 59 c-other. Prevalence, signs/symptoms, laboratory, biopsy and imaging reports were consistent with the clinical picture of the 4 c-vasculitides. A subgroup of 280/1,183 (20%) patients was blinded to the treating physician diagnosis and classified by a consensus panel with a k agreement of 1 (HSP and c-TA), 0.95 (c-WG) and 0.92 (c-PAN) (overall k 0.88 with 95% CI 0.82-0.94). The final definitions showed sensitivity/specificity/k agreement with the consensus classification/original diagnosis of 100%/87%/0.9 for HSP, 73%/100%/0.81 for c-PAN, 97%/98%/0.92 for c-WG and 100%/99%/0.99 for c-TA.

Conclusion: EULAR/PRINTO/PRES propose validated classification criteria for HSP, c-PAN, c-WG and c-TA, with high sensitivity/specificity and almost perfect agreement with the final patient disease attribution.

Disclosure: N. Ruperto, None; **S. Ozen**, None; **A. Pistorio**, None; **P. Dolezalova**, None; **P. Brogan**, None; **R. Cuttica**, None; **D. Cabral**, None; **R. Khubchandani**, None; **D. J. Lovell**, None; **K. O'Neil**, None; **P. Quartier**, None; **A. Ravelli**, None; **S. M. Iusan**, None; **G. Filocamo**, None; **C. Saad Magalhães**, None; **A. Martini**, None.

2007

Genetics, Clinical Features, and Treatment in a Well-Defined Cohort with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA). Sivia Lapidus[1], Puja Chitkara[1], Henry Feder[2], Balu H. Athreya[3], Ivona Aksentijevich[1], Beverly K. Barham[1], Michael M. Ward[1], Karyl S. Barron[4], Daniel L. Kastner[1] and Silvia Stojanov[1], [1]NIAMS/NIH, Bethesda, MD, [2]University of Connecticut Health Sciences Center/Connecticut Children's Medical Center, Hartford, CT, [3]duPont Hospital for Children/Thomas Jefferson University, Wilmington, DE, [4]NIAID/NIH, Bethesda, MD

Purpose: To elucidate the clinical features of PFAPA that may distinguish this condition from the known Mendelian periodic fever syndromes.

Method: Children who fulfilled inclusion criteria of recurrent fever in addition to two of the three defining clinical features of PFAPA (aphthous stomatitis, pharyngitis, and/or cervical adenopathy) were recruited prospectively and had longitudinal follow-up. We analyzed clinical symptoms, response to medications, and hereditability. Patients included in the study had genetic testing to exclude mutations in the known genes associated with hereditary periodic fever syndromes and cyclic neutropenia.

Results: Of forty-nine patients who met inclusion criteria, genetic testing revealed variants in 9 children (18%) in the *MVK* (V377I/I268T, V377I), *MEFV* (G304R, E148Q, K695R/V726A), *TNFRSF1A* (3 with R92Q), and *ELA2* (P257L) genes. Patients with negative genetic testing were included in the clinical analysis. All three defining features of PFAPA were present in the majority of patients. Atypical characteristics of attacks in over half of the PFAPA patients included loss of appetite, headache, myalgia, and abdominal pain. Oral

corticosteroids aborted fevers in all 30 patients treated, with 53% of patients experiencing subsequently shortened intervals between attacks. Three of 12 patients (25%) treated with cimetidine had decreased intensity of fevers and increased intervals between attacks. Seven of 10 patients (70%) who had tonsillectomies went into remission. Eight patients (20%) had affected family members who fulfilled the diagnostic criteria for PFAPA or had recurrent fevers as children.

Conclusion: Three important new findings are shown in this cohort: (1) the high number of genetically positive patients, who resemble PFAPA clinically, emphasizes the importance of excluding hereditary periodic fever syndromes genetically; (2) the familial predilection suggests a genetic etiology of this disease; (3) the data imply a broader clinical spectrum in PFAPA.

Disclosure: S. Lapidus, None; **P. Chitkara**, None; **H. Feder**, None; **B. H. Athreya**, None; **I. Aksentijevich**, None; **B. K. Barham**, None; **M. M. Ward**, None; **K. S. Barron**, None; **D. L. Kastner**, None; **S. Stojanov**, None.

2008

Characterization of Osteoclastogenesis in Interleukin-1 Receptor Antagonist Deficiency. Sreelatha Reddy[1] and James W. Verbsky[2], [1]Medical College of Wisconsin, Milwaukee, WI, [2]Medical College of WI, Milwaukee, WI

Purpose: We recently described a case of Interleukin-1 receptor antagonist deficiency (IRAD), a novel autoinflammatory disease characterized by marked systemic inflammation, pustular rash, severe osteopenia, and lytic bone lesions. This infant had a homozygous deletion of six IL-1 family members: *IL-1F5*, *IL-1F6*, *IL-1F8*, *IL-1F9*, *IL-1F10* and IL-1 receptor antagonist. Treatment with anakinra completely resolved all symptoms and lesions. Studies were performed to characterize the aberrant osteoclastogenesis in this patient.

Method: Peripheral blood mononuclear cells(PBMCs) were stimulated with LPS for 4 hours and microarray analysis was performed. Inflammatory cytokine expression was determined by a commercially available bead array. CD14 positive monocytes were isolated with magnetic beads and used to generate osteoclasts by treatment with M-CSF and RANKL. Osteoclasts were detected by staining for multinucleated tartarate-resistant acid phosphatase (TRAP) positive cells.

Results: PBMCs from the IRAD patient spontaneously produced IL-1b, IL-6, and TNF-a. LPS or IL-1b further induced the production of these cytokines that was blocked by the addition of IL-1 receptor antagonist. Microarray gene expression data demonstrated the upregulation of several genes (PTGS2, IL-6, TFPI2, MMP1, CXCL1, CXCL5) with suspected roles in osteoclastogenesis. In addition, this patient demonstrated high levels of serum cytokines all of which are known to promote osteoclast formation and bone resorption. The IRAD patient did not show any spontaneous production of osteoclasts indicating no intrinsic predisposition for the formation of osteoclasts. MCSF/RANKL although induced similar levels of TRAP activity in this patient compared with controls, the IRAD patient demonstrated a significantly higher number of TRAP positive cells displaying greater than 6 nuclei compared with controls . We observed that IL-1b by itself, in the absence of RANKL, was able to significantly drive TRAP activity which could in part contribute to the abnormal bone resorption

Conclusion: IRAD is an autoinflammatory disease characterized by high levels of circulating inflammatory cytokines with the potential to promote osteoclastogenesis. This patient exhibited increased size and hypernucleation of osteoclasts which are hallmarks of bone resorption disorders. We are further investigating the role of deleted genes (*IL-1F5*, *IL-1F6*, *IL-1F8*, *IL-1F9*, and IL-1F10) in formation and function of osteoclasts is being examined.

Disclosure: S. Reddy, None; **J. W. Verbsky**, None.

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Therapy: Treatment Strategies

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

2009

Combination Therapy of Leflunomide with Biologics (COLEBI) in Rheumatoid Arthritis: An Observational Study. Jaap Fransen[1], Pauline Knapen[1], Dan Nordstrom[2], Dimitrios Boumpas[3], Ulrich Von Hinueber[4], Georg Schett[5], Zoltan Szekanecz[6], Karel Pavelka[7], Tore K. Kvien[8] and Piet Van Riel[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Helsinki University Central Hospital, Helsinki, Finland, [3]University of Crete, Heraklion, Greece, [4]Rheumatologische Gemeinschaftspraxis, Hildesheim, Germany, [5]University of Erlangen-Nuremberg, Erlangen, Germany, [6]University of Debrecen medical and Health Sciences Center, Debrecen, Hungary, [7]Institute of Rheumatology, Prague, Czech Republic, [8]Diakonhjemmet Hospital, Oslo, Norway

Purpose: Leflunomide (LEF) is an effective agent for the treatment of RA and may be an alternative for Methotrexate (MTX) in the combination with biologicals, if MTX cannot be used. The objective was to determine effectiveness of LEF and anti-TNF compared with MTX and anti-TNF in RA, in a comparative observational study.

Methods: These are preliminary data from an international multi-centre retrospective study, for which already collected data from several biologics databases were combined. A cohort of RA patients exposed to Leflunomide in combination with anti-TNF was compared with a cohort of RA using MTX and anti-TNF. LEF users were selected by complete ascertainment, MTX users were matched by centre on disease duration (+/- 3 years) and calendre year. Effectiveness was determined using drug survival with Cox proportional hazard models and using DAS28 changes after 12 months using linear regression models, both including confounder correction.

Results: There were n=244 LEF users and n=288 MTX users included. There were no differences in age (mean SD), gender (n %) and disease duration (median (P25-P75). LEF users had more severe disease regarding RF positivity (63% versus 57%, p=0.19), erosions (67% versus 49%, p<0.001), nodules (28% versus 20%, p=0.11), median number of previous DMARDs (2 versus 1, p<0.001). Mean (SD) baseline DAS28 was similar in both groups: 5.5 (1.3) versus 5.4 (1.5), p=0.55, as was the median (P25-P75) HAQ: 1.0 (0.5-1.6) versus 1.0 (0.5-1.4), p=0.23.

Mean anti-TNF survival time was 4.3 years for LEF users and 5.8 years for MTX users, with a Hazard Ratio (95%CI) of 1.4 (0.8-2.3) (p=0.20) after correction for RF, erosions, and number of previous DMARDs. DAS28 (0-12 months) reduced with mean (SD) -1.4 (1.4) in the MTX group and -1.6 (1.5) in the LEF group (p=0.34).

Conclusion: Long-time survival of anti-TNF and decrease in DAS28 at 12 months were quite similar for the combination with leflunomide or methotrexate. Worse prognosis at anti-TNF start partly explained a tendency for less anti-TNF survival in leflunomide users.

Disclosure: J. Fransen, Sanofi Aventis, 2 ; **P. Knapen**, None; **D. Nordstrom**, Sanofi Aventis, 5 ; **D. Boumpas**, Sanofi Aventis, 5 ; **U. Von Hinueber**, Sanofi Aventis, 5 ; **G. Schett**, None; **Z. Szekanecz**, Sanofi Aventis, 5 ; **K. Pavelka**, Sanofi Aventis, 5 ; **T. K. Kvien**, Sanofi Aventis, 5 ; **P. Van Riel**, Sanofi Aventis, 5 .

2010

Efficacy of Initial Methotrexate Monotherapy Versus Combination Therapy with a Biologic Agent in Early Rheumatoid Arthritis: A Meta-Analysis of Clinical and Radiographic Remission. Bindee Kuriya[1], Elizabeth V. Arkema[1], Vivian P. Bykerk[2] and Edward C. Keystone[3], [1]Harvard School of Public Health, Boston, USA, Boston, MA, [2]Mt Sinai Hospital, Toronto, [3]Professor of Medicine/University of Toronto, Toronto, ON

Purpose: A prime objective of treating early rheumatoid arthritis (ERA) is to induce remission and halt radiographic progression. The aim of this meta-analysis was to compare the ability to achieve clinical remission and/or radiographic non-progression in patients with ERA, who have been unexposed or minimally exposed to methotrexate (MTX), and are initially treated with MTX monotherapy or combination therapy (MTX + biologic agent) in randomized controlled trials (RCTs).

Method: A systematic literature search was performed for RCTs published to April 2009 in Medline, Embase, Cochrane Controlled Trials Register and ACR/EULAR abstracts of 2007-2008. Trials reporting at least one remission outcome among ERA patients with no or minimal MTX exposure (</= 4 weeks), randomized to initial monotherapy or combination therapy for > 12 weeks duration were included using predefined in/exclusion criteria. Relative risk (RR) estimates were calculated and a random effects model was used to pool the RR for clinical and radiological outcome at 52-56 weeks of follow-up.

Results: Seven studies involving 2763 ERA subjects, 1152 randomized to MTX alone and 1611 to combination therapy with infliximab, adalimumab, etanercept or abatacept were included. The proportion of patients with prior corticosteroid or MTX exposure was comparable between groups, as was the mean dose of MTX at average follow-up of 1 year. One study reported clinical remission using the ACR remission criteria while the remaining 6 studies defined remission as a DAS28 score </= 2.6. Radiographic non-progression, defined as a modified Total sharp score (TSS) change of < 0.5 units, was reported in 4 trials. All trials demonstrated risk estimates in favor of combination therapy and the pooled RR for clinical remission was 1.74 (95% CI 1.54 to 1.98). The RR for radiographic non-progression was 1.30 (95% CI 1.01 to 1.68). Significant heterogeneity among studies for this outcome was detected ($p < 0.001$) but reasons were not explored due to lack of statistical power.

Conclusion: Current RCT evidence indicates that the efficacy of combination therapy with a biologic agent is greater than for MTX monotherapy for the outcome of clinical remission at 1 year. Data are too heterogeneous to draw firm conclusions about the efficacy on radiographic non-progression. Uniform definitions of remission/non-progression are needed in trials of drug therapy to allow comparison of within and between studies. Furthermore, the proportion of subjects who achieve the combined endpoint of clinical and radiographic remission should be considered as a clinically meaningful outcome in future studies of ERA.

Figure 1. Forest plot of the risk ratios for clinical remission using combination therapy vs. MTX monotherapy at the end of follow-up.

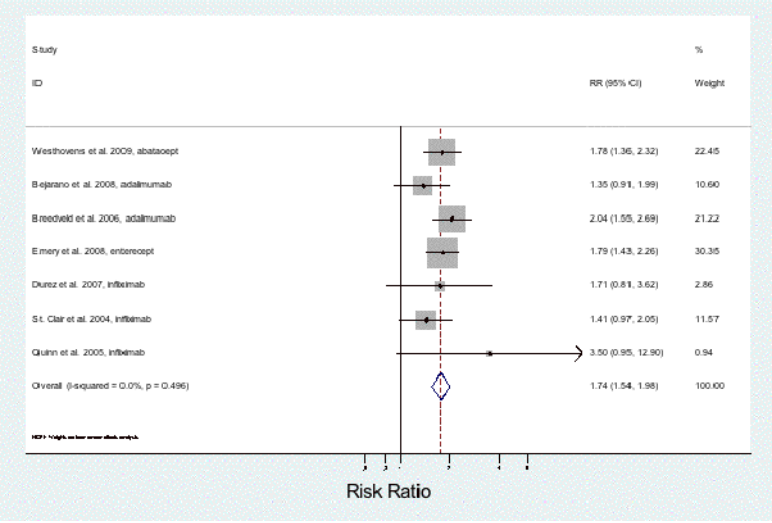
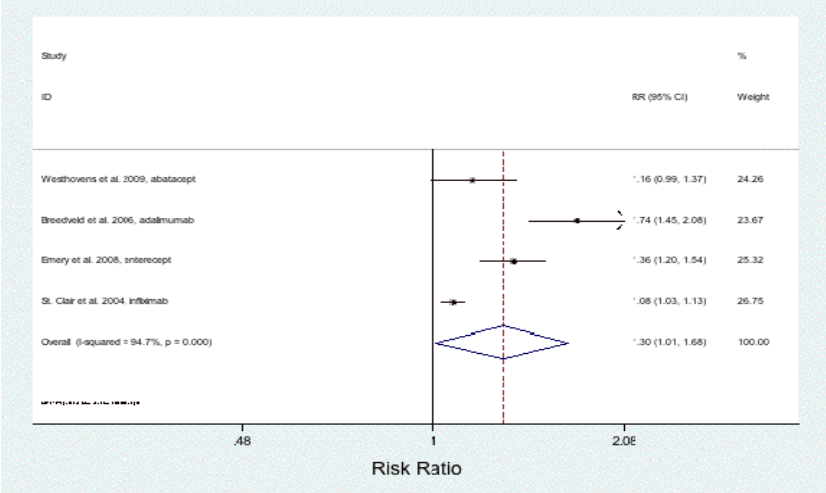


Figure 2. Forest plot of the risk ratios for radiographic non-progression with combination therapy vs. MTX monotherapy at the end of follow-up.



Disclosure: B. Kuriya, None; **E. V. Arkema**, None; **V. P. Bykerk**, Genzyme Corporation, 3, Amgen Wyeth, 2, Amgen, Abbott, Wyeth, Bristol Meyers Squibb, Hoffman La Roche, , 5, Amgen, Abbott, Wyeth, Bristol Meyers Squibb, Hoffman La Roche, , 8, Canadian Rheumatology Research Consortium; Canadian Rheumatology Association, 6 ; **E. C. Keystone**, Abbott Laboratories, Amgen, AstraZeneca, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc, Novartis Pharmaceutical Corporation, Schering-Plough, UCB, Wyeth Pharmaceuticals, 2, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Research and Development, Inc, Hoffmann-La Roche, Inc., Genentech, Inc., GlaxoSmithKline, Schering-Plough, UCB, Wyeth Pharmaceuticals, 5, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Centocor Reserch and Development, Inc., Hoffmann-La Roche, Inc., Genentech, Inc., Schering-Plough, Wyeth Pharmaceuticals, 8 .

2011

Etanercept (ETN) Plus Methotrexate (MTX) Combination Therapy Resulted in Better Clinical and Radiographic Outcomes Than ETN Monotherapy Even in Patients with Active Rheumatoid Arthritis Despite MTX Treatment: 52-Week Results From the JESMR Study. Hideto Kameda[1], Katsuaki Kanbe[2], Eri Sato[2], Yukitaka Ueki[3], Kazuyoshi Saito[4], Shouhei Nagaoka[5], Toshihiko Hidaka[6], Tatsuya Atsumi[7], Michishi Tsukano[8], Tsuyoshi Kasama[9], Shunichi Shiozawa[10], Yoshiya Tanaka[11], Hisashi Yamanaka[12], Tsutomu Takeuchi[13] and JBASIC study goup, [1]Saitama Medical Ctr, Kawagoe, Japan, [2]Tokyo Women's Medical University Medical Center, Tokyo, Japan, [3]Sasebo Chuo Hospital, Sasebo, Japan, [4]University of Occupational and Environmental Health, Japan, KItakyushu, Japan, [5]Yokohama Minami Kyosai Hospital, Yokohama, Japan, [6]Zenjinkai Shimin-No-Mori-Hospital, MIyazaki, Japan, [7]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [8]Kumamoto Hospital, Kumamoto, Japan, [9]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [10]Kobe Univ School of Med, Kobe, Japan, [11]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [12]Tokyo Women's Medical University, Tokyo, Japan, [13]Keio University School of Medicine, Tokyo, Japan

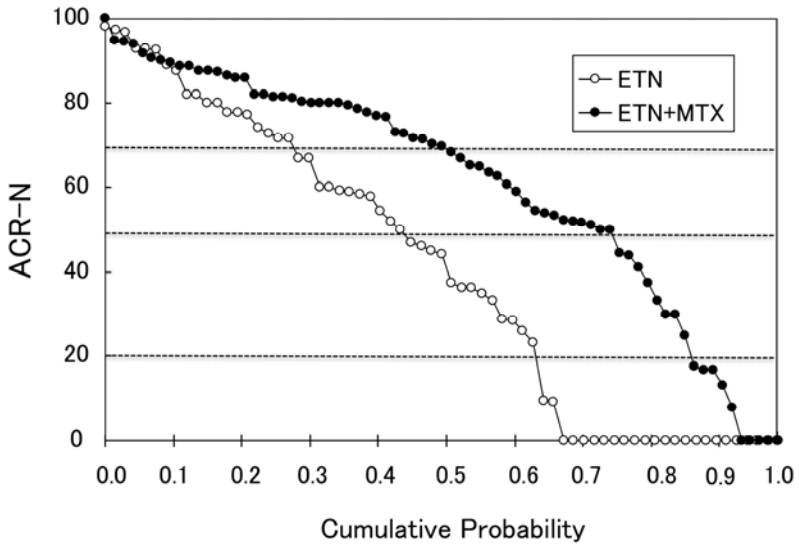
Purpose: The superiority of the continuation of methotrexate (MTX) to its discontinuation at the commencement of etanercept (ETN) in patients with active rheumatoid arthritis (RA) despite MTX therapy has not been clarified on a long-term follow-up. Therefore, the aim of the JESMR study is to compare the efficacy and safety of continuation versus discontinuation of MTX at the commencement of ETN for two years in patients with active RA despite MTX therapy.

Methods: In total, 151 patients with active RA despite treatment with MTX were randomized to either ETN 25 mg twice a week with 6-8 mg/week of MTX (the E+M group), or ETN alone (the E group). Co-primary endpoints included the radiographic progression assessed by van der Heijde-modified Sharp score at week 52.

Results: Demographic and clinical features between groups at baseline were similar. The cumulative probability plot of ACR-N at week 52 clearly demonstrated the superior response in the E+M group to that in the E group. The ACR 20, 50 and 70 response rates at week 52 were 86.3%, 76.7% and 50.7%, respectively, in the E+M group, all of which were significantly greater than 63.8% ($p=0.003$), 43.5% ($p<0.0001$) and 29.0% ($p=0.01$), respectively, in the E group. The mean health assessment questionnaire (HAQ) score decreased from 1.2 at baseline to 0.6 at week 52 in the E+M group which was significantly better than 0.9 at week 52 in the E group ($p=0.03$). The mean progression of the

erosion score was negative at weeks 24 and 52 only in the E+M group, and a significant difference was observed versus the E group at week 52 (-0.2 versus 1.8, respectively, p=0.02). The mean progression in total score tended to be smaller in the E+M group than in the E group (0.8 versus 3.6, p=0.06), and a significant difference was observed in the radiographic progression between at weeks 24 and 52 (0.3 versus 2.5, respectively, p=0.03).

Conclusion: MTX should be continued at the commencement of ETN therapy even in RA patients who had shown an inappropriate response to MTX.



Disclosure: H. Kameda, Wyeth Pharmaceuticals, 8 ; **K. Kanbe**, None; **E. Sato**, None; **Y. Ueki**, None; **K. Saito**, None; **S. Nagaoka**, Wyeth Pharmaceuticals, 2 ; **T. Hidaka**, Wyeth Pharmaceuticals, 8 ; **T. Atsumi**, Wyeth Pharmaceuticals, 8 ; **M. Tsukano**, Wyeth Pharmaceuticals, 2 ; **T. Kasama**, Wyeth Pharmaceuticals, 2 ; **S. Shiozawa**, Wyeth Pharmaceuticals, 2 ; **Y. Tanaka**, Wyeth Pharmaceuticals, 8 ; **H. Yamanaka**, Wyeth Pharmaceuticals, 2 ; **T. Takeuchi**, Wyeth Pharmaceuticals, 2 .

2012

Discontinuation of Infliximab After Attaining Low Disease Activity in Patients with Rheumatoid Arthritis: An Interim Report On RRR (remission induction by remicade in RA) Study. Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Tsuneyo Mimori[3], Nobuyuki Miyasaka[4], Takao Koike[5] and RRR study group, [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Saitama Medical Center/Univ, Kawagoe, [3]Kyoto Univ Grad Schl of Med, Kyoto, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: TNF inhibitors have enabled high clinical remission rate when used for treatment of RA, which has made us approach to biologic-free remission. Discontinuation of TNF inhibitors after acquisition of remission is an important issue from the viewpoints of safety and economy. However, reports published to date on this topic are confined to those from BeSt study and TNF20 study involving only patients with early stage of RA. The present multicenter study was undertaken to seek the possibility of discontinuing infliximab therapy after acquiring low disease activity of RA and to evaluate progression of articular destruction during infliximab discontinuation.

Method: The study involved 114 RA patients who have received infliximab therapy, whose DAS28 (ESR) remained less than 3.2 (low disease activity, LDA) for 24 weeks and who consented to discontinuation of infliximab treatment. The average disease duration was 6 years and mean DAS28 was 5.5 among all patients. Patients receiving steroid over 5 mg/day were excluded. DAS28 was evaluated, and total Sharp score (TSS) was analyzed in 41 patients for whom articular X-ray records at the start and discontinuation of infliximab therapy and after 1 year of discontinuation were available.

Results: After keeping LDA for more than 24 weeks by infliximab therapy, infliximab was discontinued in 114 cases and DAS28 in 102 cases could be evaluated at year 1. Of them, 29 cases restarted infliximab after 7 months (mean) because of the relapse of symptoms and in 17 cases DAS28 was more than 3.2 at year 1, and thereby 46 cases (45%, mean duration of disease: 7.9 years) failed RRR at year 1. The remaining 56 cases (55%, mean duration of disease: 4.9 years) have kept DAS28<3.2 (LDA) and remained off infliximab and 44 cases (43%) reached DAS<2.6 (remission) for more than 1 year after discontinuation of infliximab. By multivariable logistic analysis, disease duration was shorter in a RRR-achieved group than that in a RRR-failed group. Also, DAS28 at RRR-entry was lower in a RRR-achieved group than that in a RRR-failed one. By logistic regression analysis, the estimated DAS28 at RRR-entry was 2.22 to attain DAS28<3.2 at endpoint in 50% of enrolled patients, suggesting that deep remission may be required to keep LDA for 1 year without infliximab. The mean TSS was 64.5 and the estimated yearly progression of TSS before was 12.6 at the study entry. The yearly progressions of TSS were 0.3 and 1.6, in RRR-achieved group and RRR-failed group, respectively, during RRR study period, implying that articular destruction did not progressed during the discontinuation.

Conclusion: After reduction of disease activity of RA by infliximab treatment, about 55% of the 102 patients could discontinue infliximab for more than 1 year without radiologic progression of articular destruction.

Disclosure: Y. Tanaka, Mitsubishi-Tanabe Pharma, 5, Pfizer Inc, 5, Mitsubishi-Tanabe Pharma, 8, Takeda Pharmaceutical Co Ltd, 8, Abbott Immunology Pharmaceuticals, 8, Eisai Pharma, 8, Chugai Pharma, 8 ; **T. Takeuchi**, Wyeth Pharmaceuticals, 5, Tanabe-Mitsubishi Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5, Chugai, 5, Bristol-Myers Squibb, 5, Astellas, 5, Pfizer Inc, 5, AstraZeneca, 5 ; **T. Mimori**, Mitsubishi-Tanabe Pharma, 5, Wyeth Japan, 5, Abbott Immunology Pharmaceuticals, 5, Chugai Pharma, 5, Mitsubishi-Tanabe Pharma, 8, Wyeth Japan, 8, Chugai Pharma, 8, Astellas Pharma, 8, Bristol-Myers-Squibb, 5 ; **N. Miyasaka**, Mitsubishi-Tanabe Pharma, 5, Abbott, 5, Eisai Pharma, 5, Janssen Pharma, 5, Chugai Pharma, 5, Bristol-Myers-Squibb, 5, Mitsubishi-Tanabe Pharma, 8, Takeda Pharmaceutical Co Ltd, 8, Wyeth Japan, 8, Abbott Immunology Pharmaceuticals, 8, Eisai Pharma, 8, Chugai Pharma, 8 ; **T. Koike**, Bristol-Myers-Squibb, 5, Abbott Immunology Pharmaceuticals, 5, Mitsubishi-Tanabe Pharma, 8, Takeda Pharmaceutical Co Ltd, 8, Wyeth Japan, 8, Abbott, 8, Eisai Pharma, 8, Chugai Pharma, 8 .

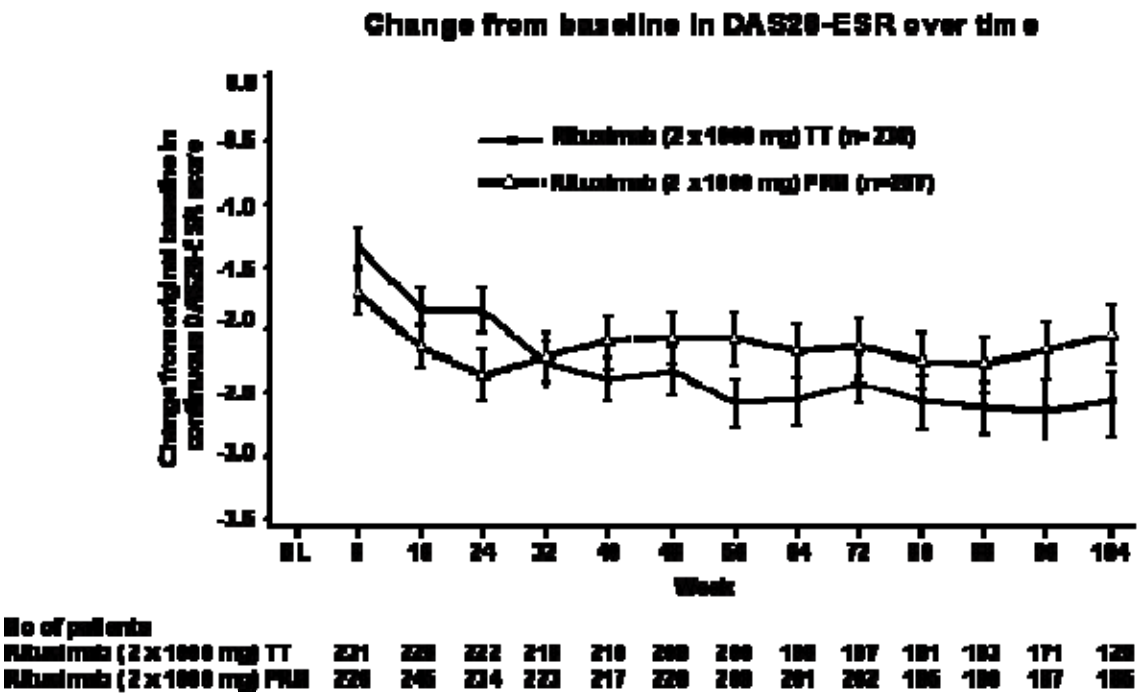
2013

Retreatment with Rituximab (RTX) Based On a Treatment to Target (TT) Approach Provides Better Disease Control Than Treatment as Needed (PRN) in Patients (pts) with Rheumatoid Arthritis (RA). Paul Emery[1], Philip J. Mease[2], Andrea Rubbert-Roth[3], Jeffrey R. Curtis[4], Ulf Müller-Ladner[5], Norman B. Gaylis[6], Gillian K. Armstrong[7], Lachy McLean[8], Mark Reynard[7] and Helen Tyrrell[7], [1]Leeds General Infirmary, Leeds, United Kingdom, [2]Seattle Rheumatology Association, Seattle, WA, [3]University of Cologne, Cologne, Germany, [4]University of Alabama, Birmingham, AL, [5]Kerckhoff Clinic, Bad Nauheim, Germany, [6]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [7]Roche Products Ltd, Welwyn Garden City, United Kingdom, [8]Genentech Inc., South San Francisco, CA

Purpose: Two treatment (tx) strategies have been employed in clinical trials of RTX in RA. Assessing differences in efficacy and safety profiles may be useful in determining an optimal tx regimen.

Methods: RA pts with an inadequate response to methotrexate (MTX) recruited into Phase II or III studies with RTX were permitted to receive further courses of open-label RTX based on 2 approaches: a) TT whereby pts were assessed at 24 weeks (wks) following each course. Those with DAS28≥2.6 were retreated, those with DAS28<2.6 were retreated if and when DAS28 increased to ≥2.6; b) PRN whereby pts were retreated at the physician's discretion after a minimum period of 16 wks if both swollen and tender joint counts were 8. Regardless of tx strategy, study visits were at least every 8 wks with unscheduled visits at any time if required. All courses consisted of RTX (2 x 1000mg) given as IV infusions 2 wks apart in combination with MTX. Observed data were pooled and analyzed according to tx strategy. Clinical outcomes including ACRn, DAS28-ESR and HAQ-DI responses were determined over time. Safety data were compared.

Results: Over multiple courses of RTX, responses were maintained or improved irrespective of tx strategy. However, compared with PRN, TT provided tighter control of disease activity as indicated by greater improvements in DAS28-ESR (Figure), lower HAQ-DI and higher ACRn. PRN resulted in the recurrence of disease symptoms between courses as evidenced by DAS28-ESR scores returning close to pre-RTX treatment levels, together with higher rates of withdrawals due to RA flare. TT also resulted in more pts achieving major clinical response (ACR70 ≥ 6 months) compared with PRN (12.3% vs. 5.9%). TT resulted in more frequent retreatment with a median time between courses of approx. 25 wks compared with approx. 62 weeks for PRN. Despite this, the safety profiles of the regimens were comparable. Importantly, TT was associated with a reduced incidence of RA flare (19 vs 42%) with no increase in the rate of serious infection (2.2 vs 3.5 per 100 pt-yrs), serious adverse events (12.0 vs 16.2 per 100 pt-yrs) or proportion of pts with Ig below normal compared with PRN.



Conclusion: Repeat treatment to a target of DAS28 remission with RTX led to tighter control of disease activity compared with PRN treatment.

Disclosure: P. Emery, Roche Pharmaceuticals, 5, Abbott Laboratories, 2, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 9 ; **P. J. Mease**, Genentech and Biogen IDEC Inc., 9, Genentech and Biogen IDEC Inc., 9 ; **A. Rubbert-Roth**, Roche Pharmaceuticals, 5, Wyeth, 5, Abbott Laboratories, 5, UCB, 5, Essex, 5, Bristol-Myers Squibb, 5, Chugai, 5 ; **J. R. Curtis**, Roche Pharmaceuticals, 5, UCB, 5, Procter & Gamble, 5, Amgen, 5, Centocor, Inc., 5, Corrona, 5, Novartis Pharmaceutical Corporation, 2, Amgen, 2, Merck Pharmaceuticals, 2, Procter & Gamble, 2, Eli Lilly and Company, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Corrona, 5, Novartis Pharmaceutical Corporation, 8, Procter & Gamble, 8, Eli Lilly and Company, 8, Roche Pharmaceuticals, 8, Merck, 8 ; **U. Müller-Ladner**, Abbott Laboratories, 5, Wyeth Pharmaceuticals, 5, UCB, 5, Roche Pharmaceuticals, 5, Chugai, 5, Essex, 5, Medac, 5 ; **N. B. Gaylis**, None; **G. K. Armstrong**, Roche , 3 ; **L. McLean**, Genentech and Biogen IDEC Inc., 3, Amgen, 1, AstraZeneca, 1, Elan, 1, GlaxoSmithKline, 1, Merck Pharmaceuticals, 1, Rigel Pharma, 1, Roche Pharmaceuticals, 3 ; **M. Reynard**, Roche Pharmaceuticals, 1, GlaxoSmithKline, 1, Roche Pharmaceuticals, 3 ; **H. Tyrrell**, Roche Pharmaceuticals, 3 .

2014

An Algorithm Using Genome-Wide SNP Analysis for Prediction of Responders and Non-Responders, and Adverse Events in Tocilizumab-Treated RA Patients. Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], Sayumi Toriyama[3], Kunihiko Nakahara[3], Takafumi Hagiwara[1], Takako Miura[1], Kosuke Okuda[1], Akira Sagawa[4], Takeo Sakurai[5], Hiroaki Matsuno[6], Tomomaro Izumihara[7] and Eisuke Shono[8], [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]HuBit genomix, Inc., Tokyo, Japan, [4]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [5]Inoue Hospital, Takasaki, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [8]Shono Rheumatology Clinic, Fukuoka, Japan

Purpose: Tocilizumab, a human anti-IL-6 receptor antibody, is an efficient biologic agent for inflammatory diseases such as RA. However, there is no method for prediction of responders, non-responders, and adverse events which can occur during the treatment. We established an SNP algorithm for prediction of responders or non-responders, and adverse events among tocilizumab-treated RA patients.

Methods and Patients: One hundred RA patients treated with tocilizumab were included in this study. The efficacy was determined by Clinical Disease Activity Index (CDAI) within 24-30 weeks after the initial treatment. The efficacy of tocilizumab was judged by the scores of CDAI (remission and low disease activity group- 'responders', moderate and high disease activity group- 'nonresponders'). Adverse events such as leukopenia, high total cholesterol, fever, and skin manifestations were documented. Genome-wide SNP genotyping was performed by Illumina HumanHap300K chip technology. Case-control analyses between 285,548 SNPs and CDAI were examined by chi-square tests. We selected 10 SNPs strongly associated with tocilizumab-responsiveness, or adverse events ($p < 0.001$).

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for responsiveness of tocilizumab ranged 92-97%. For adverse events, accuracy, specificity and sensitivity of the algorithm ranged 90-97%. It is, therefore, suggested that the SNP algorithm predict responders and adverse events prior to the initiation of treatment with this biologic agent.

Conclusion: The highly accurate algorithm using SNP analysis may be useful in the prediction of responsiveness and adverse events before treatment of tocilizumab, and in this way can contribute to future tailor-made treatment with biologic agents.

Disclosure: T. Matsubara, None; **S. Koyano**, None; **K. Funahashi**, None; **S. Toriyama**, None; **K. Nakahara**, None; **T. Hagiwara**, None; **T. Miura**, None; **K. Okuda**, None; **A. Sagawa**, None; **T. Sakurai**, None; **H. Matsuno**, None; **T. Izumihara**, None; **E. Shono**, None.

ACR Concurrent Abstract Sessions

SLE - Animal Models

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

2015

Anti-PD-1 Antibody Reduces CD4+PD-1+ T Cells and Relieves the Lupus-Like Nephritis of NZB/W F1 Mice. Shimpei Kasagi[1], Seiji Kawano[2], Taku Okazaki[3], Tasuku Honjo[4], Akio Morinobu[2], Saori Hatachi[5], Kenichiro Shimatani[4], Yoshimasa Tanaka[4], Nagahiro Minato[4] and Shunichi Kumagai[2], [1]Kobe University Graduate School of Medicine,, Kobe, Japan, [2]Kobe University Graduate School of Medicine, Kobe, Japan, [3]Institute for Genome Research, University of Tokushima, Tokushima, Japan, [4]Kyoto University Graduate School of Medicine, Kyoto, Japan, [5]Kitano Hospital, Osaka, Japan

Purpose: Programmed cell death 1 (PD-1) is an immunosuppressive receptor that transduces an inhibitory signal into activated T cells. Although a single nucleotide polymorphism in the gene for PD-1 is associated with susceptibility to systemic lupus erythematosus (SLE), PD-1's role in SLE is still not well understood. we used NZB/W F1 mice, a model of lupus-like nephritis, to examine the function of PD-1 and its ligands.

Method: Immunohistochemistry, Intracellular cytokine assay, Antibody treatment using anti-PD-1 and anti-PD-L1 mAb, and CDC assay.

Results: PD-1 was predominantly expressed on $CD4^+$ T cells that infiltrated the kidney, and $CD4^+PD\text{-}1^{high}$ T cells produced higher levels of IFN-γ than $CD4^+PD\text{-}1^{low}$ or $CD4^+PD\text{-}1^-$ T cells. Stimulation with PMA/ionomycin caused splenic $CD4^+PD\text{-}1^+$ T cells to secrete high levels of IFN-γ and IL-10, low levels of TNFα, and no IL-2, IL-4, or IL-17. *In vivo* anti-PD-1-mAb treatment reduced the number of $CD4^+PD\text{-}1^+$ T cells in the kidney of NZB/W F1 mice and significantly reduced their mortality rate ($p=0.03$). Conversely, blocking PD-L1 using an anti-PD-L1 mAb increased the number of $CD4^+PD\text{-}1^+$ T cells in the kidney, enhanced serum IFN-γ, IL-10, and IgG2a ds-DNA-Ab levels, accelerated the nephritis, and increased the mortality rate.

Conclusion: $CD4^+PD\text{-}1^{high}$ T cells are dysregulated IFN-γ-producing, proinflammatory cells in NZB/W F1 mice.

Disclosure: S. Kasagi, None; **S. Kawano**, None; **T. Okazaki**, None; **T. Honjo**, None; **A. Morinobu**, None; **S. Hatachi**, None; **K. Shimatani**, None; **Y. Tanaka**, None; **N. Minato**, None; **S. Kumagai**, None.

2016

Activation of the Nitric Oxide-Mitochondrial Hyperpolarization-mTOR-Rab4 Signaling Pathway Before Disease Development in Lupus-Prone Mice. David Fernandez[1], Tiffany Telarico[1], Ram Raj Singh[2] and Andras Perl[1], [1]Upstate Medical Univ, Syracuse, NY, [2]UCLA, Los Angeles, CA

Purpose: Nitric oxide (NO) dependent persistent mitochondrial hyperpolarization (MHP) and enhanced calcium fluxing underlie aberrant T-cell activation and death pathway selection in patients with systemic lupus erythematosus. Activity of the mammalian target of rapamycin (mTOR), which is a sensor of the mitochondrial transmembrane potential, is increased in lupus T cells which in turn promotes expression of HRES-1/Rab4, a small GTPase that regulates recycling and lysosomal degradation of CD4 surface receptors and TCR . Here, we investigated the activity of the NO-MHP-mTOR-Rab4 signaling pathway in lupus-prone mice.

Method: NZB/NZW(F1) and MRL/lpr lupus-prone female mice and age-matched Balb/c/NZW, C57BL/6, MRL, C57BL/6/lpr female control mice were investigated prior to disease manifestations. NO production, mitochondrial transmembrane potential, and recycling of surface receptors were measured by flow cytometry. Expression and phosphorylation of proteins were studied by western blot.

Results: Increased NO production and MHP as well as over-expression of Rab4 and diminished endocytic recycling of CD4 and CD3 were detected at 4-month of age, while the loss of TCR was observed 7-month of age in NZB/NZW(F1) mice. MRL/lpr mice exhibited increased expression of the mitochondrial voltage-dependent anion channel 1(VDAC1) protein and transaldolase (TAL) and Rab4 but not Rab5 as well as increased mTOR activity at 2 months of age. Rab4 expression was also increased in MRL mice.

Conclusion: T cells from lupus-prone mice exhibit mitochondrial dysfunction characterized by increased NO production, MHP, elevated expression of VDAC1 and TAL, as well as increased mTOR activity. Diminished recycling of CD4 and CD3 were associated with elevated expression of Rab4. The results suggest that mitochondrial and endocytic recycling gene expression signatures and activation of the NO-MHP-mTOR-Rab4 signaling pathway are detectable and precede disease development in lupus-prone mice.

Disclosure: D. Fernandez, None; **T. Telarico**, None; **R. R. Singh**, None; **A. Perl**, None.

2017

Interferon Regulatory Factor 5 Regulates Murine Lupus Independently of Type-I Interferons. Christophe Richez[1], Kei Yasuda[1], Ramon G. Bonegio[1], Amanda A. Watkins[1], Tamar Aprahamian[1], Patricia Busto[1], Rocco J. Richards[1], Chih Long Liu[2], Regina Cheung[2], Paul J. Utz[2], Ann Marshak-Rothstein[1] and Ian R. Rifkin[1], [1]Boston Univ Schl of Med, Boston, MA, [2]Stanford Univ Schl of Med, Stanford, CA

Purpose: Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated with an increased risk of SLE. To examine the biological role of IRF5 in lupus pathogenesis, and its potential functions beyond regulation of type I interferon (IFN) expression, we compared the impact of deficiency of IRF5 and the type I IFN receptor IFNAR1 in the C57BL/6 *FcγRIIB* $^{-/-}$ *Yaa* (RII.*Yaa*) model of SLE.

Method: We intercrossed IRF5-deficient mice with *FcγRIIB* $^{-/-}$ *Yaa* mice to generate the following experimental groups: *Irf5* $^{+/+}$ RII.*Yaa* (n=12); *Irf5* $^{+/-}$ RII.*Yaa* (n=12); and *Irf5* $^{-/-}$ RII.*Yaa* (n=14). We intercrossed *IFNAR1*-deficient mice with *FcγRIIB -/- Yaa* mice to generate the *IFNAR1* $^{+/+}$ RII.*Yaa* (n=10) and *IFNAR1* $^{-/-}$ RII.*Yaa* (n=11) experimental groups. At 5 months of age, we compared disease manifestations in these cohorts, using age- and sex-matched C57BL/6 wildtype (WT) mice as controls.

Results: *Irf5* $^{+/+}$ RII.*Yaa* mice developed marked lymphadenopathy and splenomegaly whereas lymph node and spleen size in *Irf5* $^{-/-}$ RII.*Yaa* mice was no different from WT controls. *Irf5* $^{+/+}$ RII.*Yaa* mice produced very high titers of anti-nuclear autoantibodies (ANA) including anti-ribonucleoprotein (SmRNP) and anti-double-stranded DNA antibodies, while ANA were almost totally absent from the sera of *Irf5* $^{-/-}$ RII.*Yaa* mice. As expected, the *Irf5* $^{+/+}$ RII.*Yaa* mice developed a severe proliferative glomerulonephritis. In contrast, *Irf5* $^{-/-}$ RII.*Yaa* mice exhibited a renal phenotype indistinguishable from that of WT mice. *Irf5* $^{+/+}$ RII.*Yaa* mice had a median survival of 27 weeks, while more than 90% of mice in the *Irf5* -/- cohort were alive at 40 weeks of age ($p < 0.0001$, test logrank). Remarkably, *Irf5* $^{+/-}$ heterozygous RII.*Yaa* mice had a phenotype similar to *Irf5* $^{-/-}$ RII.*Yaa* mice. One function of IRF5 is to promote the production of IFN-α, a cytokine linked to lupus pathogenesis. In order to determine if the phenotype observed in *IRF5* $^{-/-}$ mice was mediated only by inhibition of type I IFN production, we compared the phenotype of *Irf5* $^{-/-}$ RII.*Yaa* mice with that of *Ifnar1* $^{-/-}$ RII.*Yaa* mice. In contrast to the *Irf5* $^{-/-}$ mice, there were no significant

differences in ANA levels between *Ifnar1* $^{+/+}$ and *Ifnar1* $^{-/-}$ RII.*Yaa* mice. Furthermore, substantial splenomegaly and renal disease remained in the *Ifnar1* $^{-/-}$ RII.*Yaa* mice, and *Ifnar1* $^{-/-}$ RII.*Yaa* mice had decreased survival compared to either the *Irf5* $^{+/+}$ or *Irf5* $^{+/-}$ RII.*Yaa* cohorts.

Conclusion: IRF5 plays an essential role in pathogenesis in a mouse lupus model and this is mediated through pathways beyond that of type I IFN production. The fact that even IRF5 heterozygous mice developed minimal disease manifestations indicates that a certain threshold level of IRF5 is required for disease development. Thus, IRF5 might be a key therapeutic target in lupus, particularly since a partial reduction in the level of IRF5 could have a meaningful effect on disease severity.

Disclosure: C. Richez, None; **K. Yasuda**, None; **R. G. Bonegio**, None; **A. A. Watkins**, None; **T. Aprahamian**, None; **P. Busto**, None; **R. J. Richards**, None; **C. L. Liu**, None; **R. Cheung**, None; **P. J. Utz**, Bayhill Therapeutics, 1, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5 ; **A. Marshak-Rothstein**, None; **I. R. Rifkin**, None.

2018

IL-23/IL-17 Contributes to the Expression of Lupus Nephritis. Vasileios C. Kyttaris, Zheng Zhang and George C. Tsokos, Beth Israel Deaconess Med Ctr, Boston, MA

IL-17/IL-23 contribute to the expression of lupus nephritis

Purpose: T cells that express IL-17 (Th17) infiltrate the kidneys of patients with systemic lupus erythematosus. A significant proportion of these cells are CD3+CD4-CD8- double negative T cells (DNT). The mechanisms underlying this phenomenon and its contribution to the expression of kidney pathology is unclear. DNT cells are expanded and form the majority of the T cell population in the well-described murine lupus models MRL/lpr and B6/lpr. We therefore hypothesized that DNT cells expressing IL-17 contribute to the development of disease and in particular nephritis in these mice. Furthermore, we hypothesized that IL-23, a cytokine that is important for the maintenance of Th17 cells, plays a role in sustaining this abnormal autoimmune response.

Method: MRL/lpr and B6/lpr as well as their respective control (MRL/MPJ and B6) mice were used for these experiments. Rag-1-/- mice were used in the adoptive transfer experiments. IL-17 was measured by intracellular cytokine staining. IL-23 receptor (IL-23R) levels were measured by PCR. Kidney pathology was assessed using H&E staining and immunofluorescence.

Results: T cells from MRL/lpr mice expressed significantly higher than control mice levels of IL-17. The majority of these cells were DNT cells. As the mice aged and their disease worsened, the expression of IL-17 as well as that of the IL-23R in lymphocytes increased. IL-17+ T cells were found infiltrating the tubulo-interstitial area of the kidneys in lupus-prone but not the control mice. In order to evaluate the role of IL-17+ cells in the induction of lupus nephritis, lymph node cells from lupus prone–mice and control mice were transferred in non-autoimmune, lymphocyte-deficient Rag-1-/- mice. Surprisingly only lymph node cells from lupus-prone but not control mice, which were pre-treated in vitro with IL-23, induced nephritis in the recipient mice. Lymph node cells not treated with IL-23 did not cause nephritis. Kidney specimens from the recipient mice with nephritis showed significant immunoglobulin and complement deposition. In addition, we found that IL-23 acted as a trophic factor for DNT cells, increasing their percentage among the lymph node cells.

Conclusion: These data indicate that an aberrantly active IL-23/IL-17 axis contributes to the development of nephritis in lupus-prone mice. IL-23 acts as a trophic cytokine for the expansion of DNT cells. These cells in turn exhibit characteristics of Th17 pro-inflammatory cells, able to induce nephritis when transferred to non-autoimmune mice.

Disclosure: V. C. Kyttaris, Jazz Pharmaceuticals, 5 ; **Z. Zhang**, None; **G. C. Tsokos**, None.

2019

Pathogenesis of Proliferative Lupus Nephritis: Different Genetic Control for Acute and Chronic Glomerulonephritis and New Insight Into the Mechanism of Immune Complex Mediated Nephritis. Yan Ge, Chao Jiang, Felicia Gaskin, Sun-Sang J. Sung, Harini Bagavant and Shu Man Fu, University of Virginia, Charlottesville, VA

Purpose: Previously, we have mapped a genetic region on chromosome 1 (chr.1) which controls susceptibility to acute GN (aGN) and chronic GN (cGN) in a mouse model NZM2328. The NZM2328.C57Lc1 (Lc1) congenic line was generated by introgressing a segment of chr.1 from C57L/J to NZM2328. Lc1 females have markedly reduced incidences of GN and ANA. An intrachromosomal recombinant line

NZM2328.Lc1R27 (R27) was generated. In R27, an 8Mb chr.1 segment of C57L/J covering the *Cgnz1* locus which is linked to cGN was introgressed to NZM2328. In this study, pathogenesis and genetics of lupus nephritis were studied using R27 and additional intrachromosomal recombinant lines.

Method: A cohort of R27 female mice was followed to 12 months of age. Urine protein, ANA, anti-dsDNA antibodies, immune complex deposits, and kidney histology were examined. The ultrastructure of R27 kidney was studied by electron microscopy. Additional chr.1 recombinant congenic lines were generated and characterized. Real-time PCR was used to compare gene expression between R27 and NZM2328 mice.

Results: R27 females had aGN and mild to moderate proteinuria without impairment of renal function and markedly reduced incidence of ANA. The affected mice had immune complex deposits of all Ig isotypes, and subclasses of IgG and C3. No progression to cGN was observed in this cohort. Morphological studies of R27 kidneys by immunofluorescence and EM suggest recycling of immune complexes and deposition of these complexes in subendothelial and mesangial regions of glomeruli. Thus, immune complex deposition with complement activation is not sufficient to induce irreversible renal damage in R27 mice. Further studies involving additional intrachromosomal recombinant lines identified a 1.27Mb region controlling cGN, and this region is located within the *Sle1b* locus that was previously identified by Wakeland and Mohan et al. This region also appears to control ANA and anti-dsDNA autoantibodies. By real-time PCR, two candidate genes preferentially transcribed by kidney cells were identified to be genes controlling end organ damage, while the third gene Ly108 preferentially expressed in B cells may be relevant to B cell activation and production of autoantibodies to nucleosome and related antigens.

Conclusion: Our observations support our hypotheses that aGN and cGN are under separate genetic control and that aGN need not progress to cGN leading to end stage renal failure. They also show that normal kidney has significant reserve to repair immune complex induced renal lesions. Factors in addition to immune complex deposition and complement fixation are needed for the progression to renal failure.

Disclosure: Y. Ge, None; **C. Jiang**, None; **F. Gaskin**, None; **S. S. J. Sung**, None; **H. Bagavant**, None; **S. M. Fu**, None.

2020

Epistatic Interactions Between Lupus Susceptibility Loci On New Zealand Black Chromosomes 1 and 13 Lead to Marked Expansion of Dendritic Cell Populations but Have Little Effect On Autoimmunity. Yui Ho Cheung[1], Evelyn Pau[1], Christina Loh[1], Ginette Lajoie[2] and J. E. Wither[3], [1]University of Toronto, Toronto, ON, [2]Department of Pathology, William Osler Health Centre,, Brampton, ON, [3]U of Toronto, Toronto Western Hospital, Toronto, ON

Purpose: In previous work we have shown that mice with an introgressed homozygous NZB chromosome 1 interval (63.1 to 192.1 Mb; B6.NZBc1) or chromosome 13 interval (48 to 113 Mb; B6.NZBc13) have high titer IgG anti-nuclear antibodies (Ab) and develop glomerulonephritis (GN). In this study we have produced bicongenic mice with both NZB intervals, to determine whether interactions between these loci lead to exacerbation of the autoimmune phenotype.

Method: Splenic cellular populations were examined by flow cytometry. Serum levels of autoAb were measured by ELISA and the presence of GN determined by light microscopy. BAFF and IFN-α mRNA level in the spleen was examined using real time PCR. Splenic TLR responses were assessed by measurement of cytokine production.

Results: B6.NZBc1c13 mice at 8 mo of age had significantly increased spleen weights and numbers of splenocytes when compared with B6, B6.NZBc1, and B6.NZBc13 mice. Although the proportions of various splenic B and T cell populations and their activation was similar in bicongenic mice to that seen in single congenic mice, bicongenic mice had a 2-3 fold expansion in the absolute number of splenic $CD11c^+$ dendritic cells (DC) as compared to single congenic mouse strains (B6.NZBc1, $p = 0.0004$; B6.NZBc13, $p = 0.0007$). Increases in both the plasmacytoid DC population ($B220^+CD11c^+NK1.1^-$) and myeloid DC population ($CD11b^+CD11c^+$) contributed to this increase. Despite these cellular changes, the levels of IgM and IgG autoAb, and severity of GN in bicongenic mice were similar to single congenic mice. Interestingly, bicongenic mice had significantly elevated levels of total IgA and IgA anti-chromatin, -ssDNA and -dsDNA Ab when compared with single congenic mouse strains. Consistent with the increased IgA production, bicongenic mice had markedly increased levels of BAFF mRNA and BAFF-producing myeloid DC in their spleens. In contrast, mRNA levels of Type I IFN and IFN-inducible genes were reduced in the spleens of 8 mo old bicongenic mice. At 8 mo of age bicongenic splenocytes produced reduced amounts of IFN-α in response to CpG stimulation as compared to B6 controls. This appeared to result from inhibition of IFN-α secretion in older mice, since the splenocytes of 8 wk old bicongenic mice produced normal amounts of IFN-α following CpG stimulation.

Conclusion: Epistatic interactions between the lupus susceptibility loci on NZB chromosomes 1 and 13 lead to marked expansion of DC populations and high levels of BAFF production. Despite this clinical autoimmune disease was not exacerbated, possibly due to the lack of IFN-α secretion.

Disclosure: Y. H. Cheung, None; **E. Pau**, None; **C. Loh**, None; **G. Lajoie**, None; **J. E. Wither**, None.

ACR Concurrent Abstract Sessions

Spondyloarthropathies: Early Diagnosis and Outcome Measures
Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

2021

Screening for Ankylosing Spondylitis and Other Axial Spondyloarthritides-Are Established Criteria for Inflammatory Back Pain Useful in Primary Care? Annalina Braun[1], Ertan Saracbasi[1], Joachim Grifka[2], Jörg Schnitker[3], Franziska Klein[4] and Jürgen Braun[1], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Asklepios Kliniken, Bad Abbach, Germany, [3]Institut für angewandte Statistik, Bielefeld, Germany, [4]Abbott GmbH & Co. KG, Wiesbaden, Germany

Purpose: The early diagnosis of ankylosing spondylitis and early axial spondyloarthritis (SpA) has proven difficult. The value of the leading symptom, inflammatory back pain (IBP), is unclear- partly because of different definitions. This study analyzes different items and criteria associated with IBP in a large cohort of patients presenting to primary care physicians.

Method: 1012 consecutive patients with back pain > 2 months who were < 45 years old and who presented to orthopaedic surgeons in private practice (n=139) were randomized on the basis of a questionnaire with 4 primary and 4 secondary key questions on IBP for referral to rheumatologists (n=31) after having given informed consent. The randomization was done by an independent statistical institute on the basis of an optimal distribution of the number of positive answers to questions related to IBP and SpA. The vast majoritiy of patients (>80%) was seen within 6 weeks after referral.

Results: Altogether, 303 patients who were representative of the whole cohort were referred to rheumatologists to receive a diagnosis based on the expert's opinion. The mean age of patients was 36 years, the male/female ratio was approximately 1, and the mean duration of back pain was 30 months. AS was diagnosed in 44 patients (14.6%), uSpA in 46 (15.1%) and other SpA in 9 patients (3%). Thus, almost one third of all patients screened was diagnosed with SpA. Almost half (48.5%) of the patients had a relatively short disease duration (≤ 2 years chronic back pain). Of all patients seen by rheumatologists, 64% reported improvement by exercise, not rest, 48% told wakening up in the 2nd half of the night, 34% had morning stiffness >30 minutes, and 56% improvement when treated with NSAIDs (even 77% who really took the medication). No single item was differentiating very well between SpA and other causes of back pain (96% vs 90%), but when more than 2 items were combined , the difference was useful: 73% vs. 29% ($p<0.0001$). This worked better in AS than in other SpA (data not shown).

Conclusion: This study confirms that it is possible to identify SpA patients relatively early on the basis of a systematic referral pattern. Many orthopaedic surgeons were trained by this approach and referred more SpA patients than expected. Our study shows that in this early phase mainly the combination of three and more items helped to differentiate SpA patients from those with other causes of back pain.

Disclosure: A. Braun, None; **E. Saracbasi**, None; **J. Grifka**, None; **J. Schnitker**, None; **F. Klein**, None; **J. Braun**, None.

2022

Achieving Minimal Disease Activity (MDA) Criteria with Anti-TNF Therapy in Psoriatic Arthritis Can Prevent Progressive Joint Damage. Laura C. Coates and Philip S. Helliwell, University of Leeds, Leeds, United Kingdom

Purpose: Minimal disease activity (MDA) is defined by OMERACT as "that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations" and criteria for MDA in psoriatic arthritis (PsA) have been developed. The aim was to investigate if achieving MDA can improve radiological outcome.

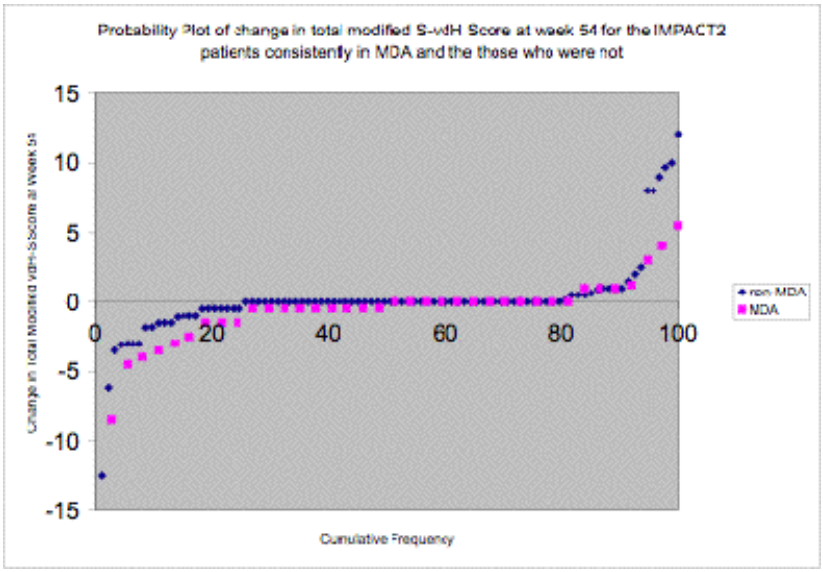
Methods: The study was an analysis of most patients in the phase III infliximab studies. In both, patients with active PsA (>5 tender & swollen joints) who failed standard therapy (NSAIDs or DMARDs) were treated with infliximab 5mg/kg or placebo. In IMPACT1, patients were given double blind therapy for 16 weeks and open label treatment to week 94. In IMPACT2, patients were given double blind therapy for 24 weeks followed by open label treatment. Early escape was possible at week 16 for non-response.

Patients were classified as MDA if they fulfilled 5 of 7 from: tender joint count²1; swollen joint count²1; psoriasis activity and severity index²1 or body surface area²3; patient pain visual analogue score(VAS)²15; patient global disease activity VAS²20; health assessment questionnaire²0.5; tender entheseal points²1. Radiological progression was assessed using modified PsA Sharp-van der Heijde (S-vdH) scores for the hands and feet. All analysis is on an intention-to-treat basis.

Results: In IMPACT1 full data were available for 63 patients. Of those receiving infliximab, 48% (15/31) achieved MDA at week 16 compared to 3% (1/32) on placebo ($p<0.0001$). At week 50, when all patients were treated with infliximab, 42% were in MDA. At week 50, 96% of those patients who achieved MDA showed no progression of radiological disease (increase in S-vdH score of ²0), compared to 67% of those who did not achieve MDA ($p=0.012$). At week 98, 12/37 (30%) were in MDA. All patients who achieved MDA at week 98 showed no radiological progression, compared to 58% of those who did not achieve MDA ($p=0.03$).

In IMPACT2 data were available for 157 patients. Of those receiving infliximab, 52% (40/77) achieved MDA at week 24 compared to 21% (17/80) on placebo ($p<0.001$). At week 54, when all patients were on infliximab, 63 of 157 (40%) were in MDA. At week 54, 78% of those patients who achieved MDA showed no radiological progression, compared to 57% of those who did not achieve MDA ($p=0.009$). Cumulative probability plots of changes in S-vdH score through week 54 are shown. The curve for IMPACT2 patients consistently in MDA (at week 24 and 52) lies to the right of the control curve indicating less proportion of patients with radiographic progression and a smaller average amount of radiographic progression in MDA patients.

Conclusion: Achieving MDA in PsA using effective therapy reduces ongoing radiological joint damage, even in a DMARD resistant cohort. The new MDA criteria could provide an objective target for treatment in trials and clinical practice.



Disclosure: L. C. Coates, None; **P. S. Helliwell**, None.

2023

Is There Subclinical Joint Disease in Early Psoriatic Arthritis? A Clinical Comparison with Power Doppler Ultrasound. Jane E. Freeston, Laura C. Coates, Philip S. Helliwell, Elizabeth M. A. Hensor, Richard J. Wakefield, Paul Emery and Philip G. Conaghan, University of Leeds, Leeds, United Kingdom

Purpose: In line with rheumatoid arthritis (RA), the emphasis in psoriatic arthritis (PsA) is to treat early to minimise damage and functional disability. Traditionally, clinical examination (CE) in the form of tender (TJC) and swollen joint (SJC) counts has been used to assess disease activity. In RA, multiple studies have shown sub-clinical disease using ultrasound (US) assessment of disease activity. The aim of this study was to compare CE and US findings in an early PsA cohort.

Method: 40 patients with new onset PsA, according to the CASPAR criteria, were recruited. They were all DMARD naïve and had a median disease duration of 10 months. All patients underwent grey scale (GS) and power doppler (PD) US as well as TJC and SJC of the most symptomatic hand and wrist (9 joints per patient) and additional target joints that the patients identified as symptomatic. The digits of the 4 fingers on this hand were also scanned for flexor tenosynovitis (FT – defined as presence of GS and/or PD) and clinically assessed for dactylitis. GS and PD were scored separately on a 0-3 semi-quantitative scale for each joint imaged. A GS score of ≥2 and/or a PD score ≥1 were used to identify US active joints.

Results: When considering each joint individually, a total of 431 joints were assessed. Of these joints, 68% had imaging findings consistent with CE. A substantial correlation (rho 0.510, p=0.001) was identified between clinical assessment of activity (tender and/or swollen) and imaging assessment of activity. CE rarely over-estimated activity, particularly the swollen joint count where 95/100 swollen joints showed imaging activity. However, 93 clinically inactive joints scanned showed significant imaging findings.

A total of 160 digits were examined for clinical dactylitis and FT on US. Of these, 88% had consistent findings (2 digits were clinically dactylitic with FT on US). FT was found in an additional 20 digits (13%) that were not clinically considered to be dactylitic.

Conclusion: There was substantial correlation seen between clinical and imaging findings in early PsA. However, CE can underestimate joint activity in over 20% of joints. Likewise, when assessing digits for dactylitis and FT, the majority show consistent findings, but a proportion of digits have FT without clinical dactylitis. These preliminary data confirm the presence of sub-clinical disease in early PsA and have implications for both research and clinical practice, particularly in terms of the classification of PsA patients with either oligoarticular or polyarticular disease.

Table – Comparison of clinical and ultrasound assessment of disease activity by individual joint.

Type of assessment	US active	US inactive	Total
CE active	101 (23%)	41 (10%)	142
CE inactive	93 (22%)	196 (45%)	289
Total	194	237	431

Disclosure: J. E. Freeston, None; **L. C. Coates**, None; **P. S. Helliwell**, None; **E. M. A. Hensor**, None; **R. J. Wakefield**, None; **P. Emery**, None; **P. G. Conaghan**, None.

2024

The Diagnostic Utility of MRI in Early Spondyloarthritis: An International Multicentre Evaluation of 187 Subjects (The MORPHO Study). Walter P. Maksymowych[1], Ulrich Weber[2], Mikkel Ostergaard[3], Juerg Hodler[2] and Robert GW Lambert[1], [1]University of Alberta, Edmonton, AB, [2]University Clinic Balgrist, Zurich, Switzerland, [3]Copenhagen University Hospitals, Copenhagen, Denmark

Purpose: Although there is widespread acceptance that MRI constitutes a major diagnostic tool for the assessment of spondyloarthritis (SpA), its utility in early disease is limited to small studies with limited control data and diverse approaches to the evaluation of the sacroiliac joints (SIJ). Summation of this data has provided an estimated likelihood ratio (LR) of 9 for the diagnostic utility of MRI in SpA. We aimed to systematically assess the diagnostic utility of MRI in early SpA using a standardized approach to the evaluation of the SIJ.

Method: Five experienced readers (3 rheumatologists, 2 radiologists) from 3 international centres, blinded to patient and diagnosis, independently assessed MRI scans (T1-weighted and short tau inversion recovery sequences) from the following subjects: 77 patients with AS and symptom duration < 10 years; 26 patients with mechanical causes of low back pain (mLBP) <45 years of age and symptom duration < 10 years; 25 patients with inflammatory back pain (mean (range) symptom duration 26 (4-96) months) who did not meet radiographic criteria for AS; and 59 healthy controls (HC) < 45 years of age. Semi-coronal slices through the SIJ were read systematically as described in a standardized online training module developed by the Spondyloarthritis Research Consortium of Canada (SPARCC). We recorded bone marrow edema, marrow fat replacement, joint erosions, and ankylosis according to standardized definitions using an online data entry system. Readers also answered the following question dichotomously (yes/no) and according to a 0-10 rating for level of confidence: This SIJ scan confirms the presence of SpA? Sensitivity, specificity, and likelihood ratios were calculated according to clinical diagnosis.

Results: Diagnostic utility of MRI was very high for all 5 readers for both early AS and pre-radiographic SpA and much higher than previously recorded. Mean concordance (%) amongst all possible reader pairs (n = 10) for diagnosis by MRI of early AS was 82.2% and only 14.4% were discrepant. For pre-radiographic SpA only 5.6% were discrepant for diagnosis by MRI.

Table. Mean (range) sensitivities, specificities and likelihood ratios for 5 readers.

Comparison groups	**Sensitivity**	**Specificity**	**LR+**	**LR-**
AS vs mLBP+HC	89.3 (81.8-97.4)	97.4 (94.7-98.9)	34.6 (17.8-79.1)	0.11(0.03-0.18)
AS vs mLBP	89.3 (81.8-97.4)	96.9 (92.3-100)	nc (12.3-nc)	0.11 (0.03-0.18)
AS vs HC	89.3 (81.8-97.4)	97.7 (95.7-98.6)	48.3 (22.0-69.6)	0.11(0.03-0.18)
IBP vs mLBP + HC	50.4 (48.0-52.0)	97.4 (94.7-98.9)	28.5 (9.8-47.3)	0.51 (0.49-0.54)
IBP vs mLBP	50.4 (48.0-52.0)	96.9 (92.3-100)	nc (6.7-nc)	0.51 (0.48-0.54)
IBP vs HC	89.3 (81.8-97.4)	97.7 (95.7-98.6)	48.3 (22.0-69.6)	0.11 (0.03-0.18)

LR+/LR-: Positive and negative likelihood ratios, nc not calculable (specificity 100% for at least one reader)

Conclusion: The adoption of a systematic and standardized approach to the assessment of SIJ showed that MRI has much greater diagnostic utility than documented previously.

Disclosure: W. P. Maksymowych, None; **U. Weber**, None; **M. Ostergaard**, None; **J. Hodler**, None; **R. G. Lambert**, None.

2025

Frequent Detection of Sacroiliac Joint Abnormalities On MRI in Healthy Subjects and Patients with Non-Specific Back Pain. Ulrich Weber[1], Mikkel Ostergaard[2], Juerg Hodler[1], Robert GW Lambert[3] and Walter P. Maksymowych[3], [1]University Clinic Balgrist, Zurich, Switzerland, [2]Copenhagen University Hospitals at Hvidovre and Gentofte, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB

Purpose: MRI of the sacroiliac joints (SIJ) is increasingly used to diagnose spondyloarthritis (SpA) and definitions have been proposed for active and chronic abnormalities. However, no systematic study of these findings in young healthy subjects or those with non-specific back pain has determined their frequency or potential for eliciting diagnostic confusion. We aimed to assess the frequency of active and chronic abnormalities of the SIJ in young healthy subjects and those with non-specific causes of back pain.

Method: Five experienced readers (3 rheumatologists, 2 radiologists) from 3 international centres independently assessed T1 and STIR MRI sequences from 187 subjects blinded to patient and diagnosis. These included 77 patients with AS and 26 patients with non-specific causes of low back pain (NSBP) that were <45 years of age and had symptom duration < 10 years, 25 patients with inflammatory back pain but who did not meet radiographic criteria for AS, and 59 healthy volunteers <45 years of age (HV). Semi-coronal slices through the synovial portion of the SIJ were read systematically as described in a standardized online training module developed by the Spondyloarthritis Research Consortium of Canada (SPARCC). We recorded bone marrow edema, marrow fat replacement, joint erosions, and ankylosis according to standardized definitions using an online data entry system which allowed the scoring of active and chronic findings in each quadrant of each

coronal slice on a dichotomous basis (yes = 1, no = 0). Readers also answered the following question: This SIJ scan confirms the presence of SpA? (yes/no). Data was analyzed descriptively.

Results: Bone edema, erosion, and fat replacement were each recorded in a third of NSBP and healthy subjects by at least one reader. More than 1 SIJ quadrant was identified by the presence of bone edema by at least 1 reader in 5 (8.5%) HV and 5 (19.2%) NSBP subjects, by the presence of erosion in 2 (3.4%) HV and 2 (2.9%) NSBP subjects, and by the presence of fat replacement in 12 (20.3%) HV and 5 (19.2%) NSBP subjects. Ankylosis was recorded in 2 subjects with NSBP (1 reader per subject) but was not recorded in healthy subjects. Two (7.7%) patients with NSBP were each recorded by 2 readers as having SpA while 4 (6.8%) Healthy volunteers were recorded as having SpA (one by 3 readers, 2 by 2 readers, 1 by 1 reader).

	Bone edema, No (%)		Erosion, No (%)		Fat replacement, No (%)	
	≤2 readers	>2 readers	≤2 readers	>2 readers	≤2 readers	>2 readers
HV	18 (30.5)	8 (13.6)	17 (28.8)	3 (5.8)	20 (33.9)	7 (11.9)
NSBP	10 (38.5)	5 (19.2)	10 (38.5)	1 (3.8)	10 (38.5)	3 (11.5)

Number (%) of subjects with SIJ abnormalities

Conclusion: Both low-grade active and chronic abnormalities meeting standardized definitions are observed by experienced MRI readers in up to a third of healthy volunteers and subjects with NSBP. The non-specific presence of such SI joint changes should be considered when defining MRI thresholds for the diagnosis of SpA.

Disclosure: U. Weber, None; **M. Ostergaard**, None; **J. Hodler**, None; **R. G. Lambert**, None; **W. P. Maksymowych**, None.

2026

The Prevalence of Inflammatory Back Pain, Spondyloarthritis, and Axial Spondyloarthritis in the Community. Ingris Pelaez-Ballestas[1], Eduardo Navarro-Zarza[1], Bernardo Julian[1], Julio Casasola-Vargas[1], Roxanna Flores-Camacho[1], LH Sanin[2], Armando Lopez[3], Lourdes Rivas[3] and Ruben Burgos-Vargas[1], [1]Hospital General de México, Mexico City, Mexico, [2]UACH-INSP, Mexico, Mexico, [3]ABC Medical Center, Mexico

Purpose: To determine the prevalence of SpA in an urban community by ESSG and ASAS criteria

Method: Community-based door-to-door survey of 9,269 subjects >18 years in a pre-determined district in México City.

1st screening (Scr), 6 trained nurses identified subjects with back pain (BP) using the Community Orientated Program for the Control of Rheumatic Diseases (COPCORD) initial phase approach; 2nd Scr, selection of BP COPCORD positive subjects with BP >6 weeks and onset > 50 years; 3rd Scr, 3 GPs and 2 rheumatologists identified subjects with inflammatory (I) BP (Berlin criteria). Finally, 2 hospital-based rheumatologists double-checked IBP positive subjects and grouped them into those with true IBP (double-positive IBP assessment) and false positive IBP (IBP negative in the 2nd assessment). True positives were considered “cases” and those negatives “controls”. The two groups underwent a SpA oriented study including HLA-B27 typing, sacroiliac joint (SIC) x-ray and magnetic resonance (RM) including the lumbar spine. Clinical evaluations were made independently from HLA-B27, x-ray, and MR results. X-ray and MR interpretations were made by two-blinded observers. Classification criteria included ESSG for SpA and ASAS criteria (sets 1 & 2) for axial SpA.

Results: Scr 1: 4,059/9,269 (43.8%) subjects (2,795 [68.8%] females; 1,264 [31.1%] males; 44.7 ± 17.9 years; married 2,822 [69.5%], jobless 2,582 [63.6%]) accepted the invitation to participate in the study.

Scr 2: 553 (13.6%; 95%CI 12.5, 14.7) had BP. Scr 3: 180 (4.4% IC95% 3.8, 5.1) subjects (112 [68.4%] females; 68 [31.6%] males; 43.8 ± 15.4 years) had BP >6 weeks and onset > 50 years. 87 additional subjects fulfilled either of such two criteria, but were not further analyzed.

Until now, 65/180 with IBP in the first survey have been double-checked; 36 of them were cases and 29 controls. According to ESSG 36/3,944 subjects (0.009 %, 95%CI 0.0063, 0.0125) as well as 39 according to ASAS-1 (0.009%, 95%CI 0.007, 0,013), and 10 to ASAS-2 had SpA (0.002%, 95%CI 0.001, 0.004). Compared with ESSG, ASAS-1 had high sensitivity and low specificity (LR+ 1.75) and ASAS-2 low sensitivity and very high specificity (LR 7.0) in this population.

Conclusion: The prevalence of IBP in this population was 4.4%. The prevalence of SpA according to ESSG and axial SpA according to ASAS-1 is about de same (0.009%), but according to ASAS-2, the prevalence of axial SpA is much lower (0.002%). The use of ASAS criteria to identify axial SpA in subjects with IBP from the community seems feasible, but cost of this approach should be considered.

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Disclosure: I. Pelaez-Ballestas, None; **E. Navarro-Zarza**, None; **B. Julian**, None; **J. Casasola-Vargas**, None; **R. Flores-Camacho**, None; **L. Sanin**, None; **A. Lopez**, None; **L. Rivas**, None; **R. Burgos-Vargas**, Abbott Laboratories, 2 .

ARHP Concurrent Abstract Session

Strategies for Patient Self Management

Wednesday, October 21, 2009, 9:00 AM - 10:30 AM

2027

Crossing the Threshold: Help-Seeking for Early Symptoms in People with Rheumatoid Arthritis. Linda C. Li[1], Anne F. Townsend[1], Paul M. Adam[2], Susan M. Cox[1], Zubin Amarsi[3], Catherine L. Backman[1] and ERAHSE team, [1]University of British Columbia, Vancouver, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Purpose: Recent research suggests that up to 38% of people with rheumatoid arthritis (RA) waited longer than three months to initiate a consult with a family physician for joint symptoms[1]. However, little is known about factors associated with the initiation of medical consults. The current study aims to understand the process of help-seeking for early symptoms in people with RA.

Method: 38 people (37 women, 1 man), who were diagnosed with RA within the past 12 months, were recruited from offices of rheumatologists and family physicians and from newsletters of patient advocacy groups. In-depth face-to-face interviews were organized around three overlapping topics: 1.) onset of symptoms and initial illness actions; 2.) seeking help from health professionals leading to diagnosis; and 3.) post-diagnosis experiences. Follow-up phone calls were made to check and elaborate on data gained at the interviews. Analysis was informed by grounded theory and a narrative approach.

Results: The decision to seek help for early arthritis symptoms was influenced by the complex interplay of disease-related, environmental and personal factors: 1.) severity and nature of symptoms, e.g., mild vs. severe; presence of pain and/or fatigue; 2.) impact of symptoms on function and participation in social roles; 3.) prior experience with medical professionals; and 4.) knowledge about arthritis and other chronic diseases. A key theme to the action of seeking help was the process of 'normalization of symptoms'[2], in which participants attempted to explain away the early signs and symptoms, and only sought medical help when they were no longer able to cope (i.e., crossing the threshold). Initially, some individuals sought care for symptoms which they believed were other debilitating chronic diseases such as osteoarthritis. In some participants, this normalization process led to a delay in seeking help from medical professionals.

Conclusion: Severity of symptoms was only a part of the puzzle in understanding people's decision to seek help. Given the importance of early diagnosis and treatment in RA, multi-faceted interventions may be required to address environmental and personal factors, in addition to improving people's ability to recognize early RA symptoms. Further research should focus on understanding the contribution of these factors to timely help-seeking in RA.

[1]Potter et al. Rheumatology. 2002;41(8):953-955.

[2]Dingwall R. *Aspects of Illness*. 1976.

Disclosure: L. C. Li, None; **A. F. Townsend**, None; **P. M. Adam**, None; **S. M. Cox**, None; **Z. Amarsi**, None; **C. L. Backman**, None.

2028

Engaging Providers to Recommend Community-Based Self Management Programs to Their Patients: Results From a Survey of Primary Care Practices. Teresa J.. Brady[1], S. Price[2], C. Ryan[2], P. Eidson[3] and T. Savage[2], [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Westat, Rockville, MD, [3]Directors of Health Promotion & Education, Atlanta, GA

Purpose: Community-based self management programs are crucial adjuncts to clinical care but previous research suggests physicians have limited awareness of community-based programs. The purpose of this study was to determine how to increase providers' awareness of and willingness to recommend community-based programs to their patients with arthritis.

Methods: Data was collected from a convenience sample of primary care practitioners (PCPs), (e.g.; physicians, nurse practitioners and physician assistants) and practice managers through an on-line survey (N=404). Stratified recruitment of various practitioner type; practice types, sizes, and locations (rural, suburban, urban); and patient demographics assured a mix of perspectives. Descriptive statistics were calculated using SPSS. Open ended questions were thematically coded.

Results: By design, approximately 50% of respondents were physicians, 25% were nurse practitioner/physician assistants, and 25% were office managers. 54% were from family practice offices, 47% were from practices with fewer than 5 clinical staff, 52% were from suburban settings, and 22% indicated that at least half their patient population was racial/ethnic minorities.

60% of respondents recommend a community-based program at least several times per week. Among program features that influence a practice's decision to recommend a program, low cost (X=4.64, 1 = no, 5 = great influence), convenient location and time (X=4.63; X=4.47), led by trained instructors (X=4.49), and programs evidence-based (X=4.43) emerged as the most influential.

80% of respondents indicated that a personal visit by program staff bring information to the practice was somewhat/very effective for getting the practice to consider these programs (X=4.17; 1= not at all; 5 = very effective). Disseminating materials at conferences (X=3.21); through newsletters, e-mail, and journals (X=3.15); and via postal mail (X=3.07) were all considered substantially less effective.

A program fact sheet listing program goals, instructor qualifications, and patient activities was identified as the most useful practitioner-oriented material. More than three quarters (82%) also rated patient handout materials (brochures and flyers) to be useful.

Conclusion: PCPs do recommend community-based programs, but have specific questions and concerns that need to be addressed and prefer a personal introduction to the program. Introducing community-based programs to PCP offices will require in-person visits for the initial introduction and materials that specifically address practitioner questions/concerns about the cost, credibility, and convenience of the programs.

Disclosure: T. J. .. Brady, None; **S. Price**, None; **C. Ryan**, None; **P. Eidson**, None; **T. Savage**, None.

2029

Improving Osteoporosis Knowledge and Health Bone Habits of Rural-Dwelling Older Adults. Terri L. White[1] and Gail C. Davis[2], [1]Texas Woman's University, Dallas, TX, [2]Texas Woman's University, Denton, TX

Purpose: The purpose of this study was to compare three community-based bone health interventions with rural-dwelling older adults (age 65 years and over) by comparing participants' knowledge and osteoporosis-related behaviors. Changes in knowledge and behaviors of those participating in the different interventions were also of interest. The conceptual framework guiding this study was Fleury's Wellness Motivation Theory. Kiresuk, Smith, and Cardillo's Theory of Goal Attainment Scaling provided a methodological guide for the intervention.

Method: The research design was quasi-experimental using four groups. The first group was included as a control and did not receive an intervention (Group 1). The remaining groups received the following specific bone health intervention: (Group 2) bone health educational booklet; (Group 3) bone health educational booklet, 2 educational sessions, and 2 follow-up phone calls; and (Group 4) all components of Group 3 plus an individualized bone health goal-setting session and their results of the Short Food Questionnaire estimates of daily dietary calcium and vitamin D intake. All participants received a calcaneus qualitative ultrasound (QUS), Groups 2, 3, and 4 at the beginning and Group 1 at the end of the study. Seven weeks intervened between the pre- and posttests which assessed osteoporosis-related knowledge, osteoporosis self-management behaviors, and readiness to use positive health behaviors. Participants were recruited from 8 senior centers in rural Central Texas communities; the centers were randomized to study groups. The sample ($N = 85$) included 69 women and 16 men (M_{age} = 78, range 65 – 95). ANOVA and *t*-tests were used to calculate the differences between and among the groups.

Results: Major findings indicated there were significant increases in osteoporosis knowledge from pretest to posttest in Group 3 [t (18) = -4.89, p = <.001] and Group 4 [t (23) = -3.68, p = <.001] with large and medium effect sizes of $\eta 2 = 0.57$ and $\eta 2 = 0.37$, respectively. Group 4 participants significantly increased their performance of healthy bone behaviors [t (23) = -4.15, p = <.001] with a medium effect size of $\eta 2 = 0.43$. The knowledge of Group 3 was significantly different than that of the control group (F (3, 81) = 4.17, p = .008) at posttest. Readiness did not demonstrate a role in the changes.

Conclusion: Increasing osteoporosis knowledge and healthy bone behaviors is more complicated than issuing pre-printed bone health information. The changes that occurred in this study having the greatest likelihood of positively affecting bone heath occurred when participants set individualized bone-health goals. The findings in this study support earlier study findings that osteoporosis knowledge and healthy bone behaviors in older adults can be increased through group educational programs that include goal setting aimed at improving bone health.

Disclosure: T. L. White, Texas Christian University's Beta Alpha Chapter of Sigma Theta Tau, 2 ; **G. C. Davis**, None.

2030

Co-Morbidity Status of People with Arthritis Sways Their Self-Management Education Program Preference. Louise Murphy[1], Teresa J. Brady[1], Kristina A. Theis[1], Julie Bolen[1] and Patience White[2], [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]The George Washington University, Washington, DC

Purpose: To characterize, among people with arthritis, who is most likely to be interested in attending self management education programs (SME), and to describe how presence of co-morbidities influences preferred type of SME among people with arthritis.

Method: We analyzed data from a national U.S. phone survey of white and black adults (n=1002), aged 40-70 years old, who have doctor diagnosed arthritis and "some" or "many" limitations due to arthritis. Participants in this survey were those who responded 'yes' to "Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" Both a generic chronic disease and an arthritis-specific SMP were described to participants, who were queried on their preference and receptivity ("very/somewhat likely" or "not very/not at all likely") to participation in each. We estimated the prevalence of receptivity and preference for each SMP type and examined correlates (e.g., demographics, symptoms, number of comorbidities) in multivariable adjusted logistic regression models with odds ratios (ORs) and 95% confidence intervals (95% CI). Comorbidities examined were cancer, cardiovascular disease, depression, diabetes and high blood pressure.

Results: Nearly 60% of respondents reported being very/somewhat likely to participate in either type of SME. Blacks, women, and those reporting severe pain in the past week, and some physical limitations had the greatest interest in SMEs. The multivariable adjusted regression models showed that respondents who were black (OR=1.9; 95% CI=1.2 - 2.9), retired (OR=1.7; 95% CI= 1.2 - 2.6), or had comorbidities preferred the generic SMP (1 comorbidity: OR=1.7 [95% CI=1.0 - 2.9]; 2 comorbidities: OR=3.3 [95% CI=2.0 - 5.7], and at least 3 comorbidities: 6.7 [95% CI=3.8-11.8]), while respondents who experienced moderate or high levels of pain on a typical day were more likely to prefer the arthritis specific SMP (OR=0.3; 95% CI=0.1 - 0.9).

Conclusion: Among people with arthritis, blacks, women, and those with severe pain in the past week and some physical limitations are most likely to be interested in participating in any type of SMP. People with arthritis and comorbid conditions preferred generic to arthritis-specific SMPs, and this preference for a generic SMP was highest among those with multiple comorbidities. Recognizing the high prevalence of comorbidities among people with arthritis, expanding the availability of generic SMPs, particularly among blacks and women, should improve chronic disease self-management skills and improve quality-of-life for people with arthritis.

Disclosure: L. Murphy, None; **T. J. Brady**, None; **K. A. Theis**, None; **J. Bolen**, None; **P. White**, None.

2031

Self-Management for Osteoarthritis of the Knee; Health Professionals or Lay Leaders? Sophie Coleman[1], Jessica Rose[2], Jean McQuade[2], Graeme Carroll[3], Charles Inderjeeth[4] and N. Kathy Briffa[1], [1]Curtin Health Innovation Research Institute Curtin University of Technology, Bentley, Australia, [2]Arthritis WA, Wembley, Australia, [3]Arthrocare, Mt Lawley, Australia, [4]SCGH, Nedlands, Australia

Purpose: To compare two 6 week self-management (SM) programs for people with OA knee. We have developed a disease specific self-management education program (OAK), for people with OA of the knee[1]. OAK includes specific education and exercise advice- designed for delivery by health professionals (HP's) utilising their knowledge and expertise. We compared this program with the Arthritis Self-Management Program (ASMP)[2]. ASMP is scripted for delivery by lay leaders and is generic in content. There is little evidence to support one approach in preference to the other. We hypothesised that the disease specific OAK would lead to better outcomes than ASMP.

Method: In a registered RCT (ACTRN 12607000031460), 190 people (59 male) of mean age 67 years with OA knee were randomised to either OAK or ASMP. Groups were assessed pre- and post-intervention, and 6 &12 months later. Outcomes measured were health status (WOMAC), quality of life (SF36), balance, mobility, self-efficacy (S-E), and patient global health (PGH). VAS pain was measured each week of the intervention. Differences between groups were examined using an intention to treat analysis with repeated measures ANOVA. P-values are single tail.

Results: Both groups improved over time ($p<0.01$) in WOMAC, balance, mobility, S-E, and SF36 PCS. Improvements were maintained to12mths. There were no between group differences in improvement (group x time $p\geq0.06$) although OAK participants tended to have better improvements in physical outcomes. During the intervention VAS pain decreased more in the OAK group; mean (SE) OAK: 5.5 (0.3) to 4.4 (0.3); ASMP: 5.1 (0.3) to 4.7 (0.3) (group x time $p=0.02$). Neither SF36 MCS or PGH changed significantly (time $p\geq0.08$)

Conclusion: Improvements in health status, function and QOL were comparable between both groups. This information is relevant when planning SM models for use in OA considering the additional costs incurred employing HP's. [1]Coleman S, Briffa K, Conroy H, Prince R, Carroll G, McQuade J: BMC Musc Dis 2008 9:117 [2]Lorig K, Gonzalez V: Hlth Educ & Bhvr 1992 19:355

Table: Mean (SE) health status and quality of life pre- and post-intervention and 6 &12 months

	Pre-		Post-		6month		12month		*Group x Time*
	OAK	ASMP	OAK	ASMP	OAK	ASMP	OAK	ASMP	p-value
WOMAC Pain	7.3(0.37)	7.1(0.37)	6.2(0.37)	6.6 (0.37)	5.8 (0.4)	6.1(0.4)	5.2(0.4)	6.0(0.4)	0.13
Stiffness	3.5(0.2)	3.5(0.2)	3.2(0.2)	3.1(0.2)	3.2(0.2)	3.0(0.2)	2.8(0.2)	3.0(0.2)	0.16
Phys Fn	24.6(1.3)	23.6(1.3)	20.2(1.3)	20.8(1.3)	21.1 (1.5)	20.0(1.5)	18.4(1.4)	20.2(1.4)	0.06
Total	35.5(1.8)	34.1(1.8)	29.6(1.7)	30.5(1.7)	30.2(2.0)	29.0(2.0)	26.8(1.9)	29.2(1.9)	0.07
SF36 PCS	34.3(1.1)	36.6(1.1)	38.6(1.1)	37.9(1.1)	38.7(1.2)	38.5(1.2)	39.0(1.2)	38.7(1.3)	0.08
MCS	50.8(1.3)	51.6(1.4)	52.5(1.2)	53.6(1.3)	51.2(1.4)	53.2(1.4)	51.4(1.3)	54.3(1.3)	0.32

Disclosure: S. Coleman, None; **J. Rose**, None; **J. McQuade**, None; **G. Carroll**, None; **C. Inderjeeth**, None; **N. K. Briffa**, None.

2032

Evaluation of Group and Self-Directed Formats of the Arthritis Foundation's (AF) Walk with Ease (WWE) Program. Leigh F. Callahan[1], Jack Shreffler[1], Mary Altpeter[1], Kathryn Remmes Martin[1], Laura O. Houenou[1] and Jennifer M. Hootman[2], [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Centers for Disease Control and Prevention, Atlanta, GA

Purpose: To evaluate the effect of a revised 6 week walking program for people with arthritis, WWE, in 2 delivery formats, group instruction or self-directed.

Method: A quasi-experimental pretest-posttest evaluation was conducted in 468 individuals with self-reported arthritis from 27 urban and rural communities. Participants selected either instructor-led group (n=192) or self-directed (n=276) format. All participants received the revised WWE workbook. Baseline and post-WWE program assessments were administered, with 93% group and 83% self-directed participant follow-up rates. Arthritis related self-reported outcomes were: Health Assessment Questionnaire (HAQ), pain, fatigue, and stiffness visual analog scales (VAS), the Rheumatology Attitudes Index (RAI), and Arthritis Self-Efficacy (ASE). Performance measures of function included chair stands, 360 degree turns, single leg stands, normal and fast walking pace, and the 2 minute step test (a measure of endurance). Adjusted mean outcome values for the group and self-directed participants posttest were determined using regression models, adjusting for baseline outcome, age, gender, race, and education. Effect sizes (ES) and 95% confidence intervals (CI) were computed.

Results: Group participants were on average 71 yrs old, 86% female 24% black, with 66% having > high school (HS) education. Self-directed were on average 65 yrs old, 89% female, 24% black, with 74% having > HS education. In both delivery formats (group vs self-directed), significant adjusted mean improvements ($p<0.05$) were seen for all of the self-report and performance measures, except for ASE and the 2 min step. There were no significant differences between the delivery formats. Therefore, the groups were combined and ESs were computed for all outcomes. Moderate effects were seen for the HAQ (ES=.21, 95% CI .15-.27), pain (ES=.34, CI .24-.44), fatigue (ES=.26, CI .17-.35), stiffness (ES=.39, CI .29-.49), and RAI (ES=.25, CI .17-.33). The ASE pain and symptom scales had modest improvements (ES =.13, CI .03-.22 and .12, CI .03-.22, respectively). The performance measures, strength (ES=.37, CI .30-.44), balance (ES= .35, CI .28-.41), and walking pace (ES=.22, CI .15-.30) all showed modest to moderate improvements; the 2 min step showed essentially no improvement (ES= .03, CI -.08-.14). No adverse events were reported for either delivery format.

Conclusion: The AF's revised WWE program appears to decrease disability and improve arthritis symptoms, self-efficacy and perceived control, balance, strength, and walking pace in individuals with self-reported arthritis regardless of whether they are taking an instructor-led group class or doing the program on their own as independent self-directed walkers. This is a safe, easy, inexpensive program for community-based physical activity delivery.

Disclosure: L. F. Callahan, None; **J. Shreffler**, None; **M. Altpeter**, None; **K. R. Martin**, None; **L. O. Houenou**, None; **J. M. Hootman**, None.

ACR Concurrent Abstract Sessions

Hyperuricemia and Gout

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

2033

Hyperuricemia as An Early Marker for Type 2 Diabetes Among Young Adults. M. Bennett[1], B. J. Pandya[2], Eswar Krishnan[1], A. Hariri[2], L. Chung[1], Hyon K. Choi[3] and O. Dabbous[2], [1]Stanford University School of Medicine, Palo Alto, CA, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]Boston University School of Medicine, Boston, MA

Purpose: Diabetes mellitus is one of the biggest public health problems in the industrialized world. Early markers that can predict incidence of diabetes would be helpful in instituting preventive strategies. The purpose of this study was to test the hypothesis that hyperuricemia can be used as an early marker of type 2 diabetes mellitus independent of obesity, physical activity, and other known risk factors.

Method: 5,012 diabetes-free men (46%) and women (54%) between ages 18 and 30 at baseline were prospectively followed for 15 years with regular visits every 2 to 3 years. The outcome of interest was incidence of diabetes fulfilling the American Diabetes Association criteria or need for any hypoglycemic medications. The independent variable of interest was serum uric acid level (sUA) at baseline. The relationship between sUA concentration and the risk for subsequent diabetes was studied using logistic regression models adjusted for the

effects of age, gender, ethnicity, body mass index (BMI), diastolic blood pressure, smoking, fasting glucose concentration, family history of diabetes, and a physical activity score.

Results: Half (51%) of subjects were African-American. The mean±SD of age (years), BMI (kg/m^2), diastolic blood pressure (mm Hg), and physical activity score (1 to 5 scale of increasing activity level) were 24.8±3.6, 22.4±4.8, 68.6±9.6, and 3.3±1.1, respectively, at baseline. In multivariable regression models, the highest category of sUA (≥7.0 mg/dL) had statistically higher risk of developing type 2 diabetes, even after excluding patients who met the World Health Organization criteria for metabolic syndrome (Table). When sUA was examined as a continuous variable, each unit increase in sUA was associated with increased overall risk of type 2 diabetes (odds ratio 1.18; 95% confidence interval: 1.04-1.35) and among those without metabolic syndrome (1.22 [1.07-1.38]).

Conclusion: In this study, increased levels of sUA appear to be associated with increased overall risk of type 2 diabetes among our cohort of young adults. These data expand on well-established, cross-sectional associations between hyperuricemia, and the metabolic syndrome and may extend the link to the future risk of type 2 diabetes in young adults.

Serum Uric Acid and the Adjusted Relative Risk for Incidence of Type 2 Diabetes Mellitus

Serum Uric Acid Concentration (mg/dL)	Odds Ratio (95% Confidence Interval)	
	Participants Without Metabolic Syndrome (n=4,752*)	Overall (n=4,762*)
0.4-4.9	1 (referent)	1 (referent)
5.0-6.9	1.26 (0.88-1.81)	1.23 (0.86-1.75)
7.0-13.3	1.99 (1.18-3.36)	1.94 (1.16-3.25)

*Number of individuals included in the regression model; multivariable logistic regressions were adjusted for age, gender, ethnicity, body mass index, diastolic blood pressure, smoking, fasting glucose concentration, family history of diabetes, and a physical activity score.

Disclosure: M. Bennett, None; **B. J. Pandya**, Takeda, 3 ; **E. Krishnan**, Savient, 1, Takeda, 2 ; **A. Hariri**, Takeda, 3 ; **L. Chung**, None; **H. K. Choi**, Centocor, Inc., 9, Savient, 9, Takeda, 9, Takeda, 2 ; **O. Dabbous**, Takeda, 3 .

2034

Incidence of Allopurinol Hypersensitivity Syndrome (AHS) Among Renally Impaired Patients. Dinesh Khanna[1], B. J. Pandya[2], A. O. D'Souza[3], B. L. Meissner[3], R. Kamalakar[2] and V. Harikrishnan[2], [1]UCLA, Los Angeles, CA, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]Xcenda LLC, Palm Harbor, FL

Purpose: It is generally acknowledged that renal impairment is associated with a higher incidence of AHS. However, no study has assessed this in a large population. This study assessed the incidence of AHS among renally impaired patients who are commercially insured through administrative claims data using a clinically validated algorithm.

Methods: This study applied a retrospective cohort design to determine AHS incidence among treatment-naive allopurinol users with and without renal impairment within two large commercial datasets. A 6-month washout period prior to the initial (index) allopurinol prescription was used to define treatment-naive patients. During this washout period, patients were defined as renally impaired based on ICD-9 and HCPCS codes. The presence of AHS was then examined using a multi-step process. First, an uninterrupted allopurinol exposure period was identified. Second, presence of AHS symptoms within the appropriate temporal sequence was applied, and severity of the AHS episode was assessed. Episodes were considered invalid if alternative disease states or medications could account for similar AHS signs and symptoms, or if additional allopurinol exposure periods occurred after the AHS episode. The primary outcome was AHS incidence among the two cohorts (renally impaired vs non–renally impaired) computed as the total number of patients with AHS divided by the total number of allopurinol users within the respective cohort. Logistic regression analyses were conducted to determine statistically significant differences.

Results: A similar proportion in both datasets were found to be renally impaired (10.5% and 12.8%). Overall, renally impaired patients were 2.5 to 4 years older (P<0.001), less likely to be male (P<0.001), more likely to use a diuretic (P<0.001), and had a higher Charlson comorbidity index (P=0.001). Presence of AHS among renally impaired patients ranged from 0.41% (n=24) to 0.72% (n=63). The majority of AHS episodes among renally impaired patients were characterized by acute renal failure (ARF; 20 of 24 and 57 of 63). Unadjusted estimates indicate that the incidence of AHS was 3 to 4 times higher among renally impaired patients compared with non–renally impaired patients (P<0.007). After controlling for age, gender, comorbidity burden, gout diagnosis, and diuretic use, renally impaired patients were significantly more likely to have AHS (OR 2.06; 95% CI 1.21-3.51; P=0.010 and OR 3.29; 95% CI 2.31-4.70; P<0.001).

Conclusion: Similar results were found in both datasets with the incidence of AHS being 2-3 times higher in renally impaired. Also, a majority of AHS episodes were characterized by ARF, suggesting a potential relationship between allopurinol and ARF. Further research is needed to better understand predictors and overall characteristics of patients susceptible to developing AHS, and if there is a causal relationship between allopurinol and ARF.

Disclosure: D. Khanna, UCB, 9, Takeda, 9, Actelion , 5, Fibrogen, 5, Gilead, 5, Savient, 5, Takeda, 5, Actelion , 9, Takeda, 9, Abbott , 9, UCB, 9, Actelion , 9, Gilead, 9 ; **B. J. Pandya**, Takeda, 3 ; **A. O. D'Souza**, Xcenda, 5 ; **B. L. Meissner**, Xcenda, 5 ; **R. Kamalakar**, Takeda, 3 ; **V. Harikrishnan**, Takeda, 3 .

2035

Serum Cholesterol in Young Men and Risk of Incident Gout. Allan C. Gelber[1], Lucy Meoni, Audrey Chu[1] and Michael J. Klag, [1]Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: Cholesterol screening in young adults is a common preventive strategy to assess risk for preclinical coronary heart disease (CHD). Several factors related to incident CHD, including hypertension and obesity, are similarly related to the development of gout. We sought to identify whether serum cholesterol, measured in early adult life, might predict incident gout in men.

Method: Serum cholesterol was measured at a mean age of 22 years among 1040 male medical students who graduated from 1948-1964 and have since been prospectively followed to detect incident disease. Cumulative incidence was estimated using Kaplan-Meier analysis. In addition, the risk of incident gout associated with the highest quintile of serum cholesterol was estimated using Cox proportional hazards analysis, with adjustment for body mass index at age 35 years and time-dependent hypertension.

Results: At cohort entry, mean cholesterol was 189.7 mg/dl (5.84 mmol/L). During a median follow-up of 45 years, a total of 139 men developed gout. Sixty participants reporting incident gout were mailed the ACR Criteria for the Classification of Gout, among whom 42 returned the questionnaire. Within this group, 34 fulfilled the ACR criteria; the other 8 satisfied criteria based on medical record review. Median age at gout onset was 58 years. Overall, the cumulative incidence of gout was 20%, and greater in the highest compared to the lowest 4 combined cholesterol quintiles (p=0.01). The relative risk of incident gout associated with the highest quintile of serum cholesterol, >209 mg/dl, was as follows:

Model for all Gout	Relative Risk	95% confidence interval
Cholesterol, unadjusted	1.7	1.1 – 2.5
Time-dependent hypertension, cholesterol-adjusted	1.9	1.2 – 2.9
Weight at age 35, cholesterol-adjusted	1.1	1.0 – 1.2
Cholesterol, hypertension and weight-adjusted	1.6	1.1 – 2.4
Model for Gout onset prior to 60 years	**Relative Risk**	**95% confidence interval**
Cholesterol, hypertension- weight-adjusted	2.2	1.3 – 3.7

Conclusion: During greater than four decades of follow-up, approximately 20% of the cohort developed gout. Moreover, the highest quintile of serum cholesterol, >209 mg/dl at a mean age of 22 years, was related to a 60% increase in risk of incident gout. This heightened risk was most apparent for gout that occurred prior to the age of 60 years. These findings imply that measurement of serum cholesterol in young adults, obtained during health maintenance screening to identify risk for CHD, is also of value to identify men at heightened risk to develop gout.

Disclosure: A. C. Gelber, None; **L. Meoni**, None; **A. Chu**, None; **M. J. Klag**, None.

2036

Weight Loss and the Risk of Hyperuricemia Among Men with a High Cardiovascular Risk Profile. Yanyan Zhu[1], Y. Zhang[1], Eswar Krishnan[2] and Hyon K. Choi[3], [1]BUSM, Boston, MA, [2]Stanford University School of Medicine, Palo Alto, CA, [3]Boston University School of Medicine, Boston, MA

Purpose: Hyperuricemia is the precursor of gout, which is the most common inflammatory arthritis for adult men. Furthermore, serum uric acid levels are associated with several major conditions, including cardiovascular disorders, renal function decline, the metabolic syndrome, and type 2 diabetes. Adiposity is a major determinant for hyperuricemia, but little is known about the quantitative impact of weight loss on the risk of hyperuricemia. To estimate this impact, we performed a longitudinal analysis of 12,465 men with a high cardiovascular risk profile, who participated in the Multiple Risk Factor Intervention Trial (MRFIT).

Method: We analyzed the relation between weight change and hyperuricemia using data prospectively collected at baseline and annually over a 6-year period (79,112 observations from 12,465 men). Our primary definition of hyperuricemia was 6 mg/dL, a widely accepted therapeutic target. We performed longitudinal analysis using logistic regression with generalized estimating equations to incorporate correlations of repeated observations in a given participant. Our final multivariate model was adjusted for baseline covariates (age, education, weight) and time-varying covariates (alcohol intake, hypertension, serum creatinine level, diuretic use and fructose use).

Results: The mean age was 46 years and mean BMI was 28 kg/m^2. The mean serum uric acid was 6.79 mg/dl and 73% were hyperuricemic at baseline. Consistent with the intent of the risk factor intervention trial, weight loss was observed in 38% of visits (Table). There was a graded relation between weight loss and reduction in the risk of hyperuricemia, and weight loss of 10 kg or more led to a 51% lower risk of hyperuricemia (Table). Overall, weight change of 1kg led to a 5% change in the risk of hyperuricemia (p for trend <0.0001).

Conclusion: This prospective data indicate that weight reduction could substantially help achieve a widely-accepted therapeutic uric acid target level (6mg/dL) among men with a high cardiovascular risk profile. Weight loss of 10 kg or more could lead to a 51% lower risk of hyperuricemia.

Table. Odds Ratios of Hyperuricemia (6mg/dL) According to Weight Change in the MRFIT Study

Weight Change (kg)	Number of Visits (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Loss 10	2844 (3.59)	0.43 (0.39, 0.49)	0.49 (0.43, 0.55)
Loss 5 to 9.9	8524 (10.77)	0.75 (0.70, 0.81)	0.78 (0.73, 0.84)
Loss 1 to 4.9	19089 (24.13)	0.90 (0.86, 0.94)	0.91 (0.86, 0.95)
No Change (-0.9 to 0.9)	25590 (32.35)	1 (Referent)	1 (Referent)
Gain 1 to 4.9	15988 (20.21)	1.16 (1.10, 1.22)	1.15 (1.09, 1.22)
Gain 5 to 9.9	5520 (6.98)	1.61 (1.46, 1.76)	1.57 (1.43, 1.72)
Gain 10	1557 (1.97)	1.65 (1.38, 1.96)	1.55 (1.29, 1.86)
p for trend		<0.0001	<0.0001

Disclosure: Y. Zhu, None; **Y. Zhang**, None; **E. Krishnan**, None; **H. K. Choi**, None.

2037

Risk Factors for Incident Gout Among Women: A Prospective Study. Vidula Bhole[1], Mary De Vera[1], M. Mushfiqur Rahman[1], E. Krishnan[2] and Hyon K. Choi[3], [1]Arthritis Research Centre of Canada, Vancouver, BC, [2]Stanford University School of Medicine, Palo Alto, CA, [3]Boston University School of Medicine, Boston, MA

Purpose: Despite recent doubling of the incidence of gout among women and substantial prevalence particularly in the aging female population, little data are available on the risk factors for gout among women. Given the important gender differences in uric acid metabolism, role of sex hormones, and frequency of gout, the risk factors for gout may vary considerably between genders. We examined the relation between serum uric acid level, purported risk factors and the risk of incident gout among women in the Framingham Heart Study (FHS) cohort.

Methods: Using data from FHS (1950-2002), we prospectively examined the relation between uric acid, purported risk factors and incidence of gout in 2,476 women and 1,951 men. We calculated the incidence rates of gout according to uric acid categories. We used Cox proportional hazards model with time-dependent variables to estimate the relative risk (RR) for incident gout by age, education, obesity, hypertension, diuretic use, alcohol use, glucose and cholesterol level, and menopausal status. We explored potential interaction by gender by testing significance of interaction terms added to our final multivariate models.

Results: At baseline mean age of the cohort was 47 years and 50% women were postmenopausal. Mean baseline uric acid level was 4.5 mg/dL for the cohort; and 4.0 mg/dL for women. The proportion of individuals with obesity, hypertension, diuretic use, and heavy alcohol use were 13%, 13%, 4% and 14% respectively; and for women 14%, 15%, 6%, and 6%, respectively. Over 28 year median follow-up, we documented 304 incident gout cases, 104 in women. Incidence rates of gout for women per 1000 person years for uric acid levels of <5.0, 5.0-5.9, 6.0-6.9, 7.0-7.9 and ≥8.0 mg/dL were 0.8, 2.5, 4.2, 13.1, and 27.3, respectively (p for trend <0.0001). The magnitude of this association was significantly lower than that among men (p for interaction, 0.0002). The associations of purported risk factors and incident gout were similar between genders (**Table**), except for a stronger age effect among women (p for interaction, 0.02)

	Multivariate RR	
	Women	Men
Age, per 5 yr	**1.24 (1.08, 1.43)**	**1.14 (1.03, 1.26)**
BMI, kg/m^2		
<25	1.0	1.0
25-30	1.44 (0.88, 2.37)	**1.76 (1.22, 2.54)**
≥30	**2.74 (1.65, 4.58)**	**2.90 (1.89, 4.44)**
Diuretics		
No	1.0	1.0
Yes	**2.39 (1.53, 3.74)**	**3.41 (2.38, 4.89)**
Alcohol		
Light	1.0	1.0
Moderate	1.30 (0.80, 2.12)	1.44 (0.99, 2.08)
Heavy	**3.10 (1.69, 5.68)**	**2.21 (1.56, 3.14)**
Hypertension		
No	1.0	1.0
Yes	**1.82 (1.06, 3.14)**	**1.59 (1.12, 2.24)**
Glucose, per 10 mg/dL	1.02 (0.98, 1.07)	0.99 (0.95, 1.03)

Cholesterol, per 10 mg/dL	0.99 (0.95, 1.04)	1.03 (0.99, 1.06)
Education, grades		
<12	1.0	1.0
12	1.05 (0.67, 1.66)	0.86 (0.59, 1.24)
>12	0.58 (0.34, 1.02)	1.12 (0.81, 1.56)
Menopause		
No	1.0	-
Yes	3.54 (0.46, 27.15)	-

Conclusion: Higher levels of serum uric acid increase the risk of gout in a graded manner among women, but the rate of increase is lower than that among men. The latter finding appears to provide another reason behind the lower background incident rates of gout among women that goes beyond their lower baseline serum uric acid levels. Age, obesity, hypertension, alcohol consumption, and diuretic use were associated with the risk of incident gout among women.

Disclosure: V. Bhole, None; **M. De Vera**, None; **M. M. Rahman**, None; **E. Krishnan**, Savient, 1, Takeda, 2 ; **H. K. Choi**, None.

2038

Drinking Water Can Reduce the Risk of Recurrent Gout Attacks. T. Neogi[1], C. Chen[1], C. Chaisson[1], D.J. Hunter[2] and Y. Zhang[1], [1]BUSM, Boston, MA, [2]NEBH, Boston, MA

Purpose: Dehydration is thought to be one possible trigger for acute gout attacks. We therefore examined whether water consumption may reduce the risk for recurrent gout attacks.

Methods: We conducted an internet-based case-crossover study to assess a set of putative risk factors thought to trigger recurrent gout attacks. This methodology uses each participant as his/her own control by comparing the frequency of a particular risk factor during periods of gout attacks with that during periods during which they are not having an attack, thereby eliminating between-person confounding. Subjects with gout who had an attack within the past year were recruited online and asked to provide access to medical records pertaining to their gout diagnosis. Data were obtained on the amount of water consumed over the 24-hour period before a gout attack and over the 24-hour period during an intercritical period. We examined the relation of amount of water intake (0-1, 2-4, 5-8, >8 glasses per 24-hours) and the risk of recurrent gout attacks using conditional logistic regression adjusting for diuretic use, alcohol consumption, and purine intake.

Results: 535 participants (78% male, mean age 53) provided information during both times of a gout attack and an intercritical period (median # of attacks/person=2; median # of intercritical period questionnaires/person=2). Increasing water intake was associated with decreased risk for recurrent gout attacks (Table).

Conclusion: Water intake in the prior 24-hours was associated with a significant reduction in risk for recurrent gout attacks. Drinking adequate water may be a simple, safe, and effective way for individuals with gout to prevent recurrent gout attacks, and can easily be recommended to patients with gout by healthcare providers. Future work will examine the effects of other concurrent beverage intake.

Table: Relation of water intake in prior 24-hours to risk for recurrent gout attack

Amount of water intake in prior 24-hours	N case periods	N control periods	Crude OR	*Adjusted OR (95% CI)
0-1 glass	163	159	1.0 (ref)	1.0 (ref)

2-4 glasses	487	579	0.82	0.84 (0.59-1.18)
5-8 glasses	356	441	0.57	0.60 (0.40-0.90)
>8 glasses	116	138	0.52	0.54 (0.32-0.90)
P for linear trend				P=0.02
*adjusted for diuretic use, purine and alcohol intake				

Disclosure: T. Neogi, None; **C. Chen**, None; **C. Chaisson**, None; **D. J. Hunter**, None; **Y. Zhang**, None.

ACR Concurrent Abstract Sessions

Novel Aspects of Intercellular Cytokine Signaling

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

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The Fibronectin III 13-14 Domains Activate Catabolic Pathways in Joint Tissue Via TLR4. Nidhi Sofat[1], Robin Wait[2] and Hideaki Nagase[3], [1]St. George's, University of London, London, United Kingdom, [2]The Kennedy Institute of Rheumatology, London, United Kingdom, [3]Kennedy Institute for Rheumatology, London, United Kingdom

Purpose: Fibronectin is an extracellular matrix (ECM) molecule implicated in a number of processes during physiology and inflammation. Expression of full-length FN is upregulated in chronic conditions such as rheumatoid arthritis and osteoarthritis and fibronectin fragments induce specific biological effects. The aggrecanases (ADAMTSs) and MMPs are believed to be the key enzymes mediating joint damage in arthritis. The C-terminal heparin-binding region of fibronectin has been implicated in regulating aggrecanase activity in vitro, but the activation of aggrecanase activity by this region has not been investigated in experimental models of arthritis.

Methods: The expression of fibronectin and its fragments was investigated in normal and arthritic tissue by Western blotting. Normal porcine articular cartilage was then used to test recombinant fragments of fibronectin, either alone, or in combination with the cytokines IL-1 and TNF, for their ability to induce aggrecanase and MMP activity. Enzyme activity was measured by RT-PCR and neoepitope assays by Western blotting. The ability of recombinant fragments to regulate the production of other proteins in chondrocytes was established by metabolic labelling using cysteine and methionine-free medium and then probing for newly synthesised proteins using one-dimensional gels analysed by mass spectrometry. The receptor for the most active fibronectin fragment was established using cultures from hip explants of TLR-4 knockout mice.

Results: Our data showed that full-length fibronectin and its fragmented forms are highly upregulated in arthritic cartilage from subjects with rheumatoid arthritis and osteoarthritis. Here, we show for the first time, that the fibronectin III 13-14 domains in the C-terminal heparin-binding region are potent inducers of aggrecanase activity at micromolar concentrations in articular cartilage. The FN III 13-14 domains also induced aggrecananase activity in a synergistic manner with the cytokines IL-1 and TNF, which was 5-6 fold higher than each of these molecules alone. We also show that the FN III 13-14 domains induce release of MMP-1, MMP-3, hsp 70, gp 38 and serum amyloid A-like protein in chondrocytes, an effect that was not observed for full-length FN. Furthermore, the III 13-14 domains increased IL-6, IL-8 and PGE2 production in monocytes. In studies using knockout mice, wild-type, but not TLR4 knockout murine cartilage showed the induction of aggrecanase activity by fibronectin domains III 13-14.

Conclusion: Our data describes a new mechanism of activation of TLR4 in articular cartilage which may be a significant activation pathway during joint damage. These findings show how the release of endogenous matrix proteins such as fibronectin maintains the persistence of chronic inflammation by the activation of pro-inflammatory pathways in diseases such as rheumatoid arthritis and osteoarthritis. Targeting pathways involving the imbalance of ECM proteins may provide new therapeutic options for the treatment of arthritis in the future.

Disclosure: N. Sofat, None; **R. Wait**, None; **H. Nagase**, None.

2040

Type-I Interferon Modulates Monocyte Recruitment and Maturation in Chronic Inflammation. Pui Lee, Yi Li, Jason S. Weinstein, Dina Nacionales, Edward Butfiloski, Eric S. Sobel, Minoru Satoh and Westley H. Reeves, University of Florida, Gainesville, FL

Purpose: Chronic inflammation, characterized by the continuous recruitment and activation of immune cells such as monocytes in response to a persistent stimulus, occurs in the rheumatoid synovium and at other sites of autoimmune attack. Although chemokine gradients play a prominent role in monocyte migration, the mechanism(s) responsible for the sustained chemokine production and subsequent influx of monocytes in chronic inflammation are not well defined. Intraperitoneal administration of TMPD (2,6,10,14-tetramethylpentadecane; pristane) in mice potently induces chronic inflammation and potentiates the development of autoimmune manifestations. Influx of monocytes to the peritoneal cavity persists for months after a single injection. Using TMPD-induced chronic peritonitis as a model, we aimed to identify specific mediators and pathways responsible for the persistent recruitment of monocytes.

Method: Wild-type or cytokine-deficient mice were treated (i.p.) with TMPD or thioglycollate. Surface markers on peripheral blood and peritoneal exudate cells were analyzed by flow cytometry. Monocyte labeling and tracking was performed using fluorescent labeled liposomes two weeks after TMPD treatment. Chemokine expression in peritoneal exudate cells was analyzed by quantitative PCR and cytokine production *in vitro* was measured by ELISA.

Result: TMPD treatment resulted in the persistent recruitment of $Ly6C^{hi}$ "inflammatory" monocytes, but not $Ly6C^{lo}$ "residential" monocytes, into the peritoneum for more than two months. Interestingly, this response was abolished in type-I interferon (IFN-I) receptor deficient mice but was unaffected by the absence of IFNγ, TNFα, IL-6 or IL-1. IFN-I signaling stimulated the production of monocyte chemoattractants (CCL2, CCL7, and CCL12), which recruited $Ly6C^{hi}$ monocytes via interactions with the chemokine receptor CCR2. Injection of recombinant IFNα directly induced the migration of $Ly6C^{hi}$ monocytes to the peritoneal cavity. In tracking studies, we found that rapid turnover of inflammatory monocytes in the inflamed peritoneum of wild-type mice was associated with a lack of differentiation into $Ly6C^{lo}$ monocytes, a more mature subset with enhanced phagocytic capacity and diminished secretion of proinflammatory cytokines. Curiously, $Ly6C^{hi}$ monocytes differentiated normally into $Ly6C^{lo}$ cells in IFN-I receptor deficient mice. The effects of IFN-I were specific for monocytes as granulocyte migration was unaffected in the absence of IFN-I signaling.

Conclusion: Our findings reveal a novel role of IFN-I in persistently recruiting inflammatory monocytes through the direct induction of chemokines that interact with monocyte CCR2. The continuous recruitment of monocytes and their inability to terminally differentiate due to the effects of IFN-I sustain the chronic inflammatory response in this model of chronic autoimmune inflammation. This mechanism may be relevant to chronic autoimmune inflammation in rheumatoid arthritis and other disorders.

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2041

IL-21R-Deficiency During Experimental Arthritis Increases Local Expression of Inflammatory Mediators, but Protects against Joint Pathology by Suppressing Th17 Cells. Marije I. Koenders[1], Renoud J. Marijnissen[1], Cheryl Nickerson-Nutter[2] and Wim B. van den Berg[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Wyeth Research, Cambridge, MA

Purpose: One of the cytokines that contributes to the formation of Th17 cells is IL-21, a pleiotropic cytokine produced by Th17 cells themselves. The purpose of this study was to investigate the effect of IL-21R-deficiency on joint pathology in relation to Th17 cells during chronic experimental arthritis.

Method: In IL-21R-/- mice, chronic SCW-arthritis was induced by intraarticular (i.a.) injections of Streptococcal Cell Wall (SCW) fragments at day 0, 7, 14, and 21.

Results: At day 28, histological analysis showed significantly reduced inflammation in IL-21R-/- mice compared to wild-types. Although IL-21R-/- mice demonstrated suppressed levels of IL-6 in the serum, this proinflammatory cytokine tended to be increased in the local patella-washouts.

This increased local activation in IL-21R-/- mice was studied in more detail in the early phase of SCW-arthritis. Before and 4 days after the first i.a. injection with SCW fragments, the expression level of various receptors and regulators was determined by QPCR. No differences were found in the expression of TLR2 and NOD2, the most import receptors for SCW. However, while the WT showed a massive upregulation of SOCS1/3 at day 4 of arthritis, IL-21R-/- mice were significantly less capable in upregulating these genes. This failure to upregulate SOCS expression in the joint might contribute to the increased local expression of inflammation and destruction markers in IL-21R-deficient mice.

Interestingly, despite the increased local activation in the IL-21R-/- mice, detailed histological analysis of the joints at day 28 of the chronic SCW-arthritis demonstrated the IL-21R-deficiency protected against cartilage proteoglycan depletion and chondrocyte death. FACS analysis of synovial cells showed a significant reduction of the percentage IL-17+ T cells. These findings were confirmed in a second model of chronic destructive arthritis, the mBSA antigen-induced arthritis (AIA). Also in this model, IL-21R-deficiency resulted in a significant reduction of joint inflammation and destruction, again in striking contrast to the local increase in cytokine expression, but accompanied by suppressed numbers of Th17 cells.

Conclusion: Despite the local suppressive role of IL-21 via SOCS, IL-21 has a more dominant prodestructive role driving Th17 cells and joint pathology during chronic experimental arthritis.

Disclosure: M. I. Koenders, None; **R. J. Marijnissen**, None; **C. Nickerson-Nutter**, Wyeth Pharmaceuticals, 3 ; **W. B. van den Berg**, None.

2042

Opposing Roles for BAFF and CTLA-4 in the Development of IL-17-Producing or Foxp3+ T Regulatory (Treg) Cells. Xiaohui Zhou[1], Julie Wang[2], William Stohl[3] and Song Guo Zheng[4], [1]University of Southern California, Los Agneles, CA, [2]CA, [3]Univ Southern California, Los Angeles, CA, [4]University of Southern California, Los Angeles, CA

Purpose: Excessive Th17 cell and/or insufficient Foxp3+ Treg cell responses likely contribute to multiple autoimmune and inflammatory diseases, including RA, SLE, and psoriasis. CTLA-4 is not only a potent down-regulator of Th1 and Th2 responses but also mediates Treg activity., Its effects on Th17 responses are largely unknown. BAFF (BLyS), a potent B cell survival and differentiation factor, augments Th1 responses while suppressing Th2 responses. The effects of BAFF on the generation of Th17 and Treg cells are largely unknown.

Method: T cells were isolated from the spleen, thymus, lymph nodes (LN), blood, lungs, liver, and kidneys of congenic B6 wild-type (WT), BAFF knockout (KO), BAFF transgenic (Tg), APRIL KO, CTLA-4 KO, BAFF/CTLA-4 double KO (DKO) and BAFF KO mice in which a BAFF Tg was introduced (BAFF KO/Tg). These cells were analyzed ex vivo for intracellular IL-17, RORgt, IL-4, GATA-3, IFNg, T-bet, and Foxp3 and for surface CD3, CD4, CD8, CD25, and CCR-6. The effect of BAFF on in vitro differentiation of naïve CD4+ T cells into Th17 cells or Foxp3+ Treg cells was assessed through stimulation with anti-CD3/CD28-coated beads in the presence of IL-2 + TGF-b or IL-6 + TGF-b, respectively.

Results: In comparison to WT mice, Th1 and Th17 cells were increased in the spleens, LN, blood, lungs, liver, and kidneys of both BAFF Tg mice and CTLA-4 KO mice. Th2 cells were also increased in CTLA-4 KO mice. Conversely, Th17 cells were decreased in BAFF KO, but not APRIL KO, mice. Th17 cells in BAFF/CTLA-4 DKO mice were intermediate between BAFF KO and CTLA-4 KO mice. In vivo development of Th17 cells was restored in BAFF KO/Tg mice, suggesting soluble BAFF plays an important role in promoting Th17 cell development. Although there were no significant changes in CD4+CD25+Foxp3+ cells in the thymus, spleen and LN, in vitro generation of Foxp3+ cells was greater in cells from BAFF KO mice than in cells from WT mice. Conversely, Th17 generation in vitro was lesser in cells from BAFF KO mice than in cells from WT mice.

Conclusion: BAFF and CTLA-4 have opposing effects on Th17 cells. Moreover, absence of BAFF impedes Th17 cell generation but promotes Foxp3+ Treg cell generation. Taken together, these results suggest that manipulation of the BAFF and CTLA-4 signaling pathways may have a beneficial role in treating Th17-mediated autoimmune and/or inflammatory diseases.

Disclosure: X. Zhou, None; **W. Stohl**, None; **S. G. Zheng**, None.

2043

Synergy Between IL-32γ and Streptococcus Pyogenes Cell Wall Fragments Results in Destructive Arthritis Which Is IL-1-Dependent. Bas Heinhuis[1], Marije I. Koenders[1], Fons A. van de Loo[1], Peter L.E.M. van Lent[1], Soo-Hyun Kim[2], Charles A. Dinarello[2], Leo A.B. Joosten[1] and Wim B. van den Berg[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University of Colorado Health Sciences Center, Denver, CO

Purpose: IL-32 might play an important role in the pathogenesis of RA by inducing cytokines, and chemokines. IL-32 is highly expressed in RA synovial tissue and strongly correlates with synovial inflammation, TNFα and IL-1 expression. IL-32 alone is not that potent, but it appears to enhance sensitivity of synovial cells to proinflammatory stimuli. Here, we investigated potential synergistic effects of IL-32γ with *Streptococcus pyogenes* cell wall (SCW) fragments, which contain predominantly TLR2/NOD2 ligands, in human fibroblast like synoviocytes (FLS). In addition, we explored the synergistic arthritogenicity of IL-32γ and SCW fragments in wildtype and IL-1 deficient mice.

Method: FLS from 4 arthritis patients were isolated and transduced with an adenoviral vector encoding for IL-32γ (AdIL-32γ) followed by SCW stimulation. To investigate *in vivo* synergy, we injected AdIL-32γ virus together with SCW fragments intraarticularly into knee joints of wildtype and IL-1 deficient mice.

Results: In human FLS synergistic upregulation of the proinflammatory cytokines IL-1β, IL-6, and TNFα was found and similar observation was made for the chemokines CCL2, CCL20, and CXCL8. Of great importance, we also identified synergistic upregulation of matrix degrading enzymes, including MMP1 and MMP3, linking the IL-32 synergy to erosive processes. Part of the synergy may be related to the marked increase of the pattern recognition receptors TLR2 and NOD2. In wildtype mice we observed a prolonged and severe arthritis injected with AdIL-32γ/SCW compared to AdControl/SCW. Furthermore, histological analysis showed apart from enhanced numbers of inflammatory cells, severe cartilage proteoglycan depletion, and irreversible chondrocyte death in mice exposed to IL-32γ and TLR2/NOD2 ligands. Remarkably, IL-1 deficient mice injected with AdIL-32γ/SCW were completely protected against the destructive arthritis observed in wildtype mice.

Conclusion: The observed synergistic effect between IL-32γ and TLR2/NOD2 ligands identifies an important amplifying pathway in the development of destructive arthritis which is IL-1 dependent. Both IL-32γ and TLR2/NOD2 are potential novel therapeutic targets in RA.

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Pathogenic Role of IL-17 in Atherogenesis: A Cross Link Between Rheumatoid Arthritis and Atherosclerosis. Arnaud Hot, Vanina Lenief, Marie-Angélique Cazalis and Pierre Miossec, Research Unit Immunogenomics and Inflammation, Hôpital Edouard Herriot, Lyon I university, Lyon, France

Purpose: Cardiovascular events remain the leading cause of death in Rheumatoid Arthritis (RA). RA and atherosclerosis share common pathway and cytokines involved in RA could play a role in atherogenesis. To better understand the mechanisms involved in atherogenesis during the course of RA, we investigated if IL-17, now seen as a key player in RA, had an effect in endothelial dysfunction, a critical step of atherosclerosis.

Method: Primary endothelial cells (EC) were treated with IL-17 (100ng/ml) alone or combined to TNF-α (1ng/ml). mRNA expression was quantified by qRT PCR and by Affymetrix microarrays HG133 A+2. The role of IL-17 was assessed using functional assays. EC migration and invasion was evaluated using a chemoinvasion assay through BM Matrigel in Boyden chambers. The ability of IL-17 to promote thrombosis through platelet aggregation was evaluated using Platelet rich Plasma (PRP). Hundred microliters of supernatant from IL-17, TNF-α or both -treated EC were added to 1 mL of PRP and platelet aggregation was measured with a Lumi-Aggregometer. Coagulation activation was assessed by the expression of tissue factor and plasminogen activator.

Results: IL-17 alone induced pro-inflammatory changes in EC, inducing changes of 248 genes. A clear synergistic effect was seen with TNF-α and their combination enhanced the expression of 9803 genes. Among the critical genes induced, IL-17 plus TNF-α induced synergistically the expression of chemokine genes such as CCL20, IL-8 and cytokine genes such as IL-6 and IL-15. In contrast, IL-17 decreased the expression of genes involved in the regulation of inflammation such as IL-4-Receptor and IL-33. Regarding invasion, IL-17 alone induced the expression of genes of metalloproteases such as MMP2 and MMP 9, known to be involved in atherosclerosis. The effect of

IL-17 was tested in a chemo invasion assay with the use of Matrigel as a matrix to study not only cell motility, but also their ability to cross tissue barriers. IL-17 not only induced migration, but also induced the same level of EC invasion that induced by TNF-α alone. Furthermore, treatment with the combination of IL-17 with TNF-α resulted in a 5-fold increase in invasive activity. IL-17 inhibited the endothelial CD39/ATPDase expression, which is critical in the inhibition of platelet activation by keeping adenosine nucleotide levels low. Indeed, CD39 mRNA expression was reduced in IL-17 treated EC. Supernatants of IL-17-treated EC induced a strong platelet aggregation (61.25±1.25%), as for TNF-α treated EC (58, 5% ±1.2%). Finally, IL-17 was able to enhance the expression of genes critical for coagulation such as tissue factor and plasminogen activator, leading to a thrombotic state.

Conclusion: Our data show the effects of IL-17 on EC. IL-17 induced a pro-inflammatory phenotype in EC and enhanced their migration, with extra cellular matrix destruction. Finally, IL-17 induced a prothrombotic phenotype.

Disclosure: A. Hot, None; **V. Lenief**, None; **M. A. Cazalis**, None; **P. Miossec**, None.

ACR Concurrent Abstract Sessions

Pathogenesis of the Antiphospholipid Syndrome
Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

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Lupus Susceptible Gene Polymorphisms in Patients with Antiphospholipid Syndrome. Tetsuya Horita, Hisako Nakagawa, Kenji Oku, Hiroshi Kataoka, Shinsuke Yasuda, Tatsuya Atsumi and Takao Koike, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: Genetic factors are hypothesized to play a role in the susceptibility to antiphospholipid syndrome (APS) based on several family studies. However, genetic background of APS is not well known. APS can occur alone (primary APS) or in conjunction with systemic lupus erythematosus (SLE). Therefore, APS and SLE may, in part, share a common mechanism for disease onset or progression. Recent genome wide association studies in patients with SLE in Caucasian population revealed several novel lupus susceptible genes in addition to previously reported genes such as human leukocyte antigen (HLA), interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription 4 (STAT4) and so forth. In this study, we investigated the possible association between novel lupus susceptible gene polymorphisms and APS in Japanese population.

Method: We enrolled 341 SLE patients, 90 APS patients (41 primary APS and 49 secondary APS complicated with SLE), and 428 ethnically matched healthy controls. Written informed consent was obtained from each participant. All the SLE patients fulfilled the American College of Rheumatology classification criteria for SLE and all the APS patients fulfilled the Sydney-revised Sapporo criteria for APS. Genomic DNA samples were extracted from peripheral blood. Single nucleotide polymorphisms (SNPs) of B-cell scaffold protein with ankyrin repeats 1 (BANK1), B lymphocyte specific tyrosine kinase (BLK), Phox homology domain containing serine/threonine kinase (PXK), tumor necrosis factor alpha induced protein 3 (TNFAIP3), tumor necrosis factor ligand superfamily member 4 (TNFSF4) and rs10798269 in 1q25.1 region were genotyped using TaqMan Genotyping Assay kit. Allele frequencies in each group were compared using chi-square test and the related risk was approximated by the odds ratios.

Results: The allele frequencies of each SNP in SLE and APS groups were presented in the Table. BANK1 (rs10516487), BLK (13277113) and rs10798269 in 1q25.1 region were associated with not only SLE but also APS in Japanese population. TNFSF4 (rs844644) association were found only in APS population whereas TNFAIP3 (rs2230926) association was found only in SLE. PXK (rs6445975) was associated with neither SLE nor APS in Japanese population.

Conclusion: Our results suggest that APS and SLE, in part, share a common genetic background.

Table. Allele frequencies of novel lupus susceptible gene polymorphisms in Japanese SLE and APS patients

Gene	SNP ID	disease	risk allele frequency		OR	95%CI	p value
			case	control			

BANK1	rs10516487	SLE	0.92	0.89	**1.48**	**1.04-2.11**	**0.03**
		APS	0.94	0.89	**2.07**	**1.06-4.06**	**0.03**
BLK	rs13277113	SLE	0.75	0.70	**1.30**	**1.04-1.63**	**0.02**
		APS	0.79	0.70	**1.70**	**1.15-2.50**	**0.007**
(1q25.1)	rs10798269	SLE	0.75	0.70	**1.28**	**1.02-1.61**	**0.03**
		APS	0.80	0.70	**1.74**	**1.18-2.59**	**0.005**
PXK	rs6445975	SLE	0.26	0.23	1.19	0.94-1.50	0.15
		APS	0.21	0.23	0.91	0.61-1.34	0.63
TNFAIP3	rs2230926	SLE	0.12	0.06	**1.91**	**1.33-2.73**	**$3.7x10^{-4}$**
		APS	0.09	0.06	1.52	0.86-2.68	0.15
TNFSF4	rs844644	SLE	0.35	0.32	1.16	0.94-1.44	0.17
		APS	0.41	0.32	**1.47**	**1.06-2.05**	**0.02**

The p value and odds ratio (OR) (95% CI) for each group were obtained by the comparison with healthy controls.

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Up-Regulated Expression of Phospholipid Scramblase 1 On Monocytes in Patients with Antiphospholipid Syndrome. Olga Amengual, Tatsuya Atsumi, Eriko Suzuki, Kenji Oku, Toko Hashimoto, Masaru Kato, Kotaro Otomo, Yuichiro Fujieda, Hiroshi Kataoka, Tetsuya Horita, Shinsuke Yasuda and Takao Koike, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: It is worldwide accepted that the interaction between phospholipid (PL)-binding proteins and antiphospholipid antibodies (aPL) triggers tissue factor expression, leading to thrombotic events in patients with antiphospholipid syndrome (APS), but the precise mechanisms underlying thrombosis in APS are not yet clarified. Normal circulating cells show an asymmetric distribution of PL in the membranes with amino-PL, such as phosphatidylserine (PS), restricted to the cytoplasmic leaflets. Externalization of PS occurs in activated cells and is crucial for the activation of the coagulation cascade, as PS serves as an assembly site for coagulation factors. Moreover, PS exposure is essential for the binding of PL-binding protein-aPL complexes to pro-coagulant cells, favoring aPL-mediated cell activation and thrombosis. One of the key molecules involved in the regulation of PS externalization is phospholipid scramblase 1 (PLSCR1) which catalyzes rapid transbilayer movement of PL between membrane leaflets. PLSCR1 was reported to be up-regulated by interferon alpha, but its role in APS pathogenesis is unknown. In this study, we examined the expression of PLSCR1 on pro-coagulant cells in patients with APS.

Method: The study includes 40 patients with APS (35 women, mean age 50 yrs, [range 26-76 yrs]). 17 patients had primary APS and 23 were diagnosis as having systemic lupus erythematosus (SLE). Forty-three healthy individuals were included as a control group. Heparinized venous blood was collected from all the subjects. PBMC were isolated and monocytes purified using CD14 micro beads (Miltenyi Biotec). Total RNA was isolated and reverse- transcribed using SuperScript™ First-Strand Synthesis System (Invitrogen). Quantitative Real-Time PCR was performed using gene-specific PLSCR1 Taq Man MGB Probe and the ABI PRISM 7000 Sequence Detection System. PS exposure on monocyte surface was evaluated by flow-cytometry using the Annexin-V Fluos labeling kit (Roche).

Results: Monocytes from APS patients had higher levels of PLSCR1 mRNA expression than those from healthy controls (mean ± SD; 2.4 ± 1.2 vs. 1.3 ± 0.4, $p < 0.00001$). Levels of PLSCR1 mRNA were significantly elevated in both group of APS patients compared to controls (2.2 ± 0.9, 2.6 ± 1.4, $p= 0.001$, $p= 0.0003$, primary APS and APS/SLE, respectively). However, the increased PS expression in patients with APS was minor compared to controls (20.6 ± 8.2 vs. 17.8 ± 5.8).

Conclusion: Patients with APS have enhanced expression of PLSCR1 on monocytes. Even though the presence of PS on monocytes may be related not only to PLSCR1 expression but to several mechanisms, the up-regulation of PLSCR1 expression in APS might represent a contributing factor in the hypercoagulability in APS.

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Interaction Between Nicked β2-Glycoprotein I and Angiostatin 4.5: Novel Role of Nicked β2-Glycoprotein I in Angiogenesis *in Vitro* and *In Vivo*. Hisako Nakagawa[1], Shinsuke Yasuda[1], Eiji Matsuura[2], Kazuko Kobayashi[2], Masahiro Ieko[3], Hiroshi Kataoka[1], Tetsuya Horita[1], Tatsuya Atsumi[1] and Takao Koike[1], [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Okayama University Graduate School of Medicine, Denstry, and Pharmaceutical Sciences, Okayama, Japan, [3]School of Dentistry, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Japan

Purpose: β2-glycoprotein I (β2GPI) is a major target of pathogenic antiphospholipid antibodies detected in patients with antiphospholipid syndrome. β2GPI is proteolytically cleaved by plasmin in its domain V (nicked β2GPI), which results in binding to plasminogen Kringle 5 via cleaved domain V of β2GPI. Recently, anti-angiogenic properties have been reported in nicked β2GPI as well as in intact β2GPI at relatively high concentrations. Angiostatin was first discovered as a plasminogen fragment with anti-tumor/anti-angiogenic property. Although several isoforms have been known, angiostatin 4.5 (AS4.5) that consists of kringle 1-4 and ~ 85% of kringle 5, is produced by autoproteolysis and is present in human plasma. In the present study, we intended to clarify the interaction between nicked β2GPI and AS4.5 and its property in angiogenesis.

Method: Binding between nicked β2GPI and AS4.5 was tested using BIACORE X. Proliferations of human aortic endothelial cells (HAECs) and human umbilical venous cells (HUVECs) ware evaluated using formazan assay in the presence or absence of 50 nM of AS4.5 and various concentrations of intact/nicked β2GPI. Matrigel-invasion assay and tube-formation assay were done using HUVECs. Finally, *in vivo* angiogenesis assay using directed *in vivo* angiogenesis assay was performed using athymic nude mice. In this assay, semi-closed plugs fulfilled with extracellular matrices including various combinations of AS4.5 (0.2 μM) and nicked β2GPI were inserted subcutaneously and blood vessels formed into these plugs were evaluated and quantified after 11 days.

Results: Significant binding of nicked β2GPI to AS4.5 ($K_D = 3.27 \times 10^6 M^{-1}$) was observed. At concentrations from 0.1 to .04 μM, nicked β2GPI attenuates the anti-angiogenic functions of AS4.5 in the proliferation of HAECs/HUVECs, in the extracellular matrix invasion and the tube-formation of HUVECs, and in our *in vivo* angiogenesis assay. In contrast, intact β2GPI neither binds to AS4.5 nor inhibits its anti-angiogenic activity. At higher concentrations (1-4 μM), both intact and nicked β2GPI inhibited angiogenesis in Matrigel-invasion assay and tube-formation assay.

Conclusion: Nicked β2GPI exerts dual effects on angiogenesis, i.e., nicked β2GPI promotes angiogenesis in the presence of AS4.5, whereas nicked β2GPI inhibits angiogenesis at concentrations high enough to neutralize AS4.5. Once thrombus is formed in a blood vessel, collateral blood flow needs to be generated. At sites of thrombus, both nicked β2GPI and AS4.5 become abundant by fibrinolysis. Plasmin-nicked β2GPI is likely to up-regulate angiogenesis by interacting with AS4.5 at sites of thrombosis.

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Autoantibodies to Heat Shock Protein 60 Are Associated with Arterial Vascular Events in Patients with Anti-Phospholipid Antibodies. Mélanie Dieudé[1], José A. Correa[1], Carolyn Neville[1], Christian A. Pineau[1], Jerrold S. Levine[2], Rebecca Subang[1], C. Landolt-Marticorena[3], Jiandong Su[3], Jeannine Kassis[4], Susan Solymoss[1], Paul. R. Fortin[3] and Joyce Rauch[1], [1]McGill University, Montreal, QC, [2]University of Illinois at Chicago, Chicago, IL, [3]University of Toronto, Toronto, ON, [4]Université de Montréal, Montreal, QC

Purpose: Anti-heat shock protein 60 autoantibodies (anti-HSP60) are associated with coronary artery disease and atherosclerosis, and are known to affect endothelial cells *in vitro*. However, their association with other vascular events (VE) remains unclear. We have recently shown that anti-HSP60 promote thrombosis in a murine model of arterial injury. Based on these findings, we hypothesized that the presence of anti-HSP60 autoantibodies, alone or in combination with other thrombogenic risk factors (e.g., anti-phospholipid antibodies [aPL]), would be associated with an elevated risk of VE.

Method: The study population was derived from the databases of three ongoing cohort studies: two systemic lupus erythematosus (SLE) registries and one cohort of individuals with aPL. Only individuals with aPL testing performed on at least two occasions were included. aPL positivity was defined as: anti-cardiolipin (aCL) IgG/IgM >40 APL units, and/or lupus anticoagulant (LA) positive, and/or anti-β2-glycoprotein I (aβ2GPI) IgG/IgM positive, each on ≥ 2 occasions ≥ 12 weeks apart. Data from a total of 406 participants was captured and four groups were identified: (1) aPL-positive with VE (n=85); (2) aPL-positive without VE (n=83); (3) aPL-negative with VE (n=119); and (4) aPL-negative without VE (n=119). Arterial VE (VE-A) (n=123) or venous VE (VE-V]) (n=97) were confirmed from medical records. Serum anti-HSP60 were determined by enzyme-linked immunoassay and values exceeding the 75th percentile of the healthy controls (n=25) were considered to be high-titer positive. Clinical and demographic variables captured included age, race, gender, family history of cardiovascular disease, smoking, SLE, hypertension, and diabetes mellitus.

Results: Multivariate analyses revealed that total VE were associated solely with age or hypertension. However, analysis of the VE according to their origin showed an association of VE-A, but not VE-V, with anti-HSP60 (OR=2.326 [95% CI=1.157-4.673]). Furthermore, the concomitant presence of aPL with anti-HSP60 increased the risk of VE-A (OR=6.19 [95% CI=2.02-18.91]), but not VE-V (OR=1.09 [95% CI=0.36-3.28]). Finally, the presence of individual aPL (i.e., aCL, LA, or aβ2GPI) with anti-HSP60 also increased the risk of VE-A, with the strongest association observed for aCL (OR=8.67 [95%CI=1.97-38.08]).

Conclusion: Our results demonstrate that anti-HSP60 are associated with VE-A, and that the concomitant presence of aPL (particularly aCL) with anti-HSP60 further enhances the risk of these events.

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ß2 Glycoprotein I (ß2GPI) Binds Platelet Factor 4 (PF4): Implications for the Pathogenesis of Antiphospholipid Syndrome. MP Sikara[1], J G. Routsias[2], M. Samiotaki[3], G. Panayotou[3], HM Moutsopoulos[1] and P G. Vlachoyiannopoulos[2], [1]School of Medicine,National University of Athens, Athens, Greece, [2]School of Medicine, National University of Athens, Athens, Greece, [3]Al. Fleming, Greece

Purpose: Antiphospholipid syndrome (APS) is an autoimmune thrombophilia. It has been suggested that antiβ2GPI antibodies, in the presence of β2GPI, activate platelets. This study aims to reveal platelet proteins that can act as receptors of β2GPI.

Method: Platelets from 3 healthy donors and 7 APS patient were isolated and membrane proteins were extracted. Affinity chromatography using CNBr-Sepharose-β2GPI was performed and captured proteins from different platelet preparations were analyzed with Mass Spectrometry. Since PF4 appeared as the dominant protein bound to β2GPI-affinity column, in vitro and in silico methods were used. The interaction between β2GPI and PF4 was defined using saturation binding assays. The specificity of the interaction was confirmed with homologous inhibition assay and co-precipitation study. The antigenicity of β2GPI-PF4 complex was examined using a modified anti-β2GPI ELISA.

In silico docking was evaluated using the crystal structures of β2GPI and PF4 tetramer. Finally, the activation of platelets, induced by anti-β2GPI-β2GPI-PF4 complexes, was examined by the production of thromboxane A2 (TXB2).

Results: β2GPI-coupled to CNBr-Sepharose selectively binds PF4 from all the platelet protein extracts; in patients' membrane protein extracts (n=7), PF4 was the only protein bound to β2GPI, while in healthy controls' extracts (n=3) several non specific cytoskeletal proteins along with PF4 were bound. Saturation binding assays revealed that PF4 directly binds to β2GPI, in a dose dependent manner with a KD of 105.3±9.8nM, and this binding was abrogated up to 80% in the inhibition experiments.

Docking simulations revealed that positively charged surface of PF4 tetramer interacts with negatively charged regions in domains III – V of β2GPI. Hydrogen bonds were also formed. PF4 tetramer tends to bind 2 β2GPI molecules, leading to the dimerization of the latter. Our

attempt to study the β2GPI-PF4 antigenicity showed that the reactivity of APS sera was higher against PF4-β2GPI complex, than against β2GPI alone. APS patients' sera recognized PF4-β2GPI with a mean of OD increase ~32%, comparing to β2GPI alone ($p<0.0001$).

Finally, platelets exposed to immobilized anti-β2GPI+β2GPI+PF4, display significantly more TXB2 metabolite production (6.6 ± 1.45 pg/μl,) compared to platelets exposed either to anti-β2GPI+BSA+PF4 (0.9±0.16pg/μl) or to isotype control+β2GPI+PF4 (0.87±0.20pg/μl) ($p<0.005$). This demonstrates that antiβ2GPI-β2GPI-PF4 complex exhibits the optimum condition for platelet activation.

Conclusion: This study demonstrates the binding of β2GPI with PF4, both in solid phase and in solution, as well as the *in vitro* sensitization of platelets by anti- β2GPI-β2GPI-PF4. A potential interaction in vivo between PF4 and β2GPI leading to the dimerization of the latter, could mediate platelet activation in the APS.

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A C5a Receptor Antagonist Ameliorates In Vivo Effects of Antiphospholipid Antibodies. Ana Laura Carrera-Marin[1], Zurina Romay-Penabad[1], HongChang Qu[2], Elizabeth Papalardo[1], John Lambris[2], Elba Reyes-Maldonado[3], Ethel Garcia-Latorre[4] and Silvia S. Pierangeli[1], [1]University of Texas Medical Branch, Galveston, TX, [2]Univeristy of Pennsylvania, Philadelphia, PA, [3]Instituto Politecnico Nacional/ ENCB, Mexico D.F., Mexico, [4]Instituto Politecnico Nacional, Mexico D.F., Mexico

Purpose: Studies in mouse models have shown involvement of C3 and C5 on antiphospholipid (aPL)-mediated thrombosis and endothelial cell (EC) activation. It has been proposed that in addition to their direct effects on target cells, aPL antibodies may further enhance endothelial cell activation and a pro-infllammatory/procoagulant state [upregulation of tissue factor (TF)] by activation of complement and interaction of complement split products (i.e. C3a and C5a), with specific receptors on the cell surface. The aim of this study was to examine the effects of a specific C5a receptor antagonist peptide (C5aR-AP) on aPL-mediated thrombosis and upregulation of TF in vivo.

Method: C57BL/6J mice were injected i.p. twice with 500 μg of IgG isolated from a patient with Antiphospholipid Syndrome (APS) or with control IgG (IgG-NHS) preceded by i.p. injection of 25 μg of C5aR-AP (Ac-Phe-c[Orn-Pro-DCha-Trp-Arg] or control peptide (CP) (Ac-Phe-c[ORn-Pro-DCha-Ala-DARg]). Seventy-two hours after the first injection, the size of an induced thrombus was measured in the treated and control mice. TF activity in pM/mg/ml protein was determined in carotid artery homogenates and in lysates of peritoneal macrophages. Anticardiolipin (aCL) and anti-β2glycoprotein (anti-β2GPI) activity was determined by ELISA in the sera of the animals.

Results:

Treatment	Thrombus size (μm^2)	TF carotid (pM/mg/ml)	TF Macrophages (pM/mg/ml)	aCL (GPL)	anti-β_2GPI (SGU)
IgG-APS + CP	3236.0 ± 1729.8	69.3 ±13.8	16.6 ± 3.0	57.8 ± 29.7	57.9 ±16.1
IgG-APS + C5aR-AP	802.8 ± 271.2	33.8 ± 4.1	6.7 ± 2.1	51.2 ± 8.7	61.0 ± 27.3
IgG-NHS + CP	604.7 ± 94.0	39.1 ± 5.0	11.0 ± 1.0	1.2 ± 0.19	4.9 ± 0.3
IgG-NHS + C5aR-AP	623.2 ± 117.4	25.3 ± 8.2	7.2 ± 1.1	0.9 ± 0.1	5.1 ± 0.6

Treatment of the mice with IgG-APS + CP induced significantly larger thrombi, TF in carotids and macrophages when compared to IgG-NHS + CP treated mice (p values=0.027, 0.045, 0.063, respectively). Mice treated with IgG-APS and C5aR-AP had significantly smaller

thrombi and lower TF activity in carotid arteries and macrophages when compared to IgG-APS + CP-injected animals (p values= 0.034,0.036,0.045, respectively).

Conclusion: The data provide relevant information on the involvement of complement activation in aPL-mediated pathogenic effects and underscore the possibility of utilizing complement inhibitors to ameliorate APS clinical manifestations.

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ACR Concurrent Abstract Sessions

Pediatric Rheumatology - Advances in Therapy

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

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Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (A-CUTE-JIA): A Multicenter Randomized Clinical Trial. Pirjo Tynjälä[1], Paula Vähäsalo[2], Maarit Tarkiainen[1], Kristiina Aalto[1], Liisa Kröger[3], Merja Malin[4], Anne Putto-Laurila[5], Visa Honkanen[6] and Pekka Lahdenne[1], [1]Helsinki University Central Hospital, Helsinki, Finland, [2]Oulu University Hospital, [3]Kuopio University Hospital, [4]Tampere University Hospital, [5]Turku University Hospital, [6]Rheumatism Foundation Hospital, Heinola

Purpose: We compared the efficacy of two combination treatment strategies, methotrexate with infliximab (TNF) and synthetic DMARD combination therapy with methotrexate, sulfasalazine and hydroxychloroquine (COMBO) on methotrexate alone (MTX) in early polyarticular juvenile idiopathic arthritis (JIA). The protocol did not include the use of systemic steroids.

Methods: We performed multicenter randomized clinical trial in 60 patients with polyarticular JIA aged 4-16 years with the duration of JIA less than 6 months. Primary endpoint was American College of Rheumatology Pediatric (ACR Pedi) 75 response at 54 weeks. Secondary endpoints included inactive disease at 54 weeks and the time spent in the state of an inactive disease. Outcome was illustrated by Kaplan-Meier analysis and comparison of therapies was performed by Mantel-Cox test, or Kruskall-Wallis and Dunn's test.

Results: Of the 60 patients, 59 completed the trial (64% females). Twenty-two (37%) had ANA, 13 (22%) were HLA-B27 positive, and one (2%) RF positive. At baseline their mean (± SE) duration of JIA was 0.10 ± 0.02 years, age 9.6 ± 0.4 years, ESR 36 ± 4 mm/hr, active joints 18 ± 1, physician's global 55 ± 2 mm, and CHAQ 0.763 ± 0.082.

Primary endpoint: 42 patients (71%) had ACR Pedi 75 response; 19 (100%) receiving TNF, 13 (65%) COMBO and 10 (50%) MTX ($p<0.0001$). The difference was significant between TNF and MTX ($p<0.0001$), and TNF and COMBO ($p=0.0005$), but not between COMBO and MTX.

Secondary endpoint: At 54 weeks, 13 patients (68%) receiving TNF, 8 (40%) receiving COMBO and 5 (25%) receiving MTX ($p=0.002$) had inactive state of the disease. Those on TNF reached inactive disease more often than those on MTX ($p=0.02$), but the response between COMBO and TNF ($p=0.050$), or COMBO and MTX ($p=0.220$) was not significant. During the 54-week follow-up, those on TNF spent a mean of 26 weeks (95% CI 18-34) in inactive state of disease. This was longer than those on COMBO (13 weeks, 95% CI 6-20; $p=0.044$ compared with TNF), or those on MTX (6 weeks, 95% CI 2-10; $p=0.001$ compared with TNF), but the difference between COMBO and MTX was not statistically significant.

Conclusion: When the target was ACR Pedi 75 response within the first year of therapy in early polyarticular JIA, infliximab plus methotrexate turned out to be superior to synthetic DMARD combination, and even more clearly, superior to MTX monotherapy.

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Abatacept IN Refractory ANTI-TNF Resistant Juvenile Idiopathic ARTHRITIS-RELATED Uveitis. Francesco Zulian[1], Marta Balzarin[1], F. Falcini[2], Ginevra Fiori[3], Maria Alessio[4], Rolando Cimaz[5] and Maria Elisabetta Zannin[1], [1]University of Padua, Padua, Italy, [2]Italy, Italy, Italy, [3]University of Florence, Italy, Florence, Italy, [4]Dpt of Pediatrics, Rheumatology Unit, University of Naples Federico II, Naples, Italy, [5]University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy

Purpose: Anterior uveitis is a serious complication of Juvenile Idiopathic Arthritis (JIA) with the potential for significant ocular damage and eventually blindness. Recently, Abatacept, a selective T-cell co-stimulation modulator, has been used in children with JIA who had failed previous treatments, including anti-TNF agents.

We report the short-term results on safety and efficacy of Abatacept in a cohort of patients with severe JIA-related uveitis refractory or intolerant to other anti-TNF agents.

Method: Patients with JIA-related uveitis refractory to previous immunosuppressive treatments (MTX, CyA, MMF) and to anti-TNF agents, Infliximab (IFX) and Adalimumab (ADM), have been treated with Abatacept (ABT) at a monthly dosage of 10 mg/kg (up to 750 mg), administered intravenously. Uveitis course and side effects have been carefully monitored. Absolute frequencies of flares before and after ABT treatment and/or new ocular complications have been reported.

Results: Six patients (5 female, 1 male), aged 9-24 years, have been treated, with a mean follow-up of 7.2 months (range: 6-9 months). The mean uveitis duration, at the beginning of Abatacept treatment, was 11 years (range: 3-17 years). All patients failed previous immunosuppressive (MTX, CyA, MMF) and anti-TNF agents (Infliximab and Adalimumab) treatment. Two patients shifted from IFX to ABT for systemic reactions. Four patients shifted from IFX and ADM for inefficacy. No side effects were reported in all but one patient, who developed serious oral mucous reaction after 3 months of treatment. The mean frequency of uveitis flares went down from 3.3 (range: 2-5) during the six months before ABT to 0.6 (range: 0-2) post ABT. At the end of the follow-up no new ocular complications appeared and the pre-existing ones remained stable in all patients.

Conclusion: Abatacept induced a rapid and sustained improvement of refractory JIA-related uveitis and was well tolerated in 5/6 patients. Abatacept represents a treatment of choice for patients failing both immunosuppressive and anti-TNF agents and a possible candidate for the early treatment of severe course JIA-related uveitis.

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Long-Term Safety and Efficacy of Rilonacept in Patients with Systemic Juvenile Idiopathic Arthritis (SJIA). Daniel J. Lovell[1], Edward H. Giannini[1], Yukiko Kimura[2], Suzanne C. Li[2], Philip J. Hashkes[3], Andreas O. Reiff[4], Carol A. Wallace[5], Karen Onel[6], Dirk Foell[7], Douglas R. Nadler[8], Stephanie Biedermann[8], Jennifer D. Hamilton[8] and Allen R. Radin[8], [1]Children's Hospital Medical Center, Cincinnati, OH, [2]Hackensack Univ Medical Ctr, Hackensack, NJ, [3]Cleveland Clinic, Cleveland, OH, [4]Childrens Hosp LA MS60, Los Angeles, CA, [5]Seattle Children's Hospital, Seattle, WA, [6]Univ of Chicago, Chicago, IL, [7]University of Muenster, Muenster, Germany, [8]Regeneron Pharmaceuticals, Inc., Tarrytown

Purpose: To obtain long-term data following a double-blind (DB) placebo (PBO)-controlled study of rilonacept, a long-acting soluble receptor-based IL-1 blocker, in patients with active SJIA during an open label (OL) 24 month extension phase.

Methods: 23 subjects aged, 5-20 yrs old with a mean disease duration of 3.1 yrs, with both active articular and systemic features, were randomized to receive once weekly 2.2 mg/kg (max. 160 mg), 4.4 mg/kg (max. 320 mg) rilonacept or PBO SC for 4 wks in the DB phase. After 4 wks in the DB or a min. of 2 wks, if rescue in DB was clinically warranted, rilonacept and PBO treated patients were eligible to receive OL treatment at their DB cohort allocated dose. Patients receiving the 2.2 mg/kg dose could escalate after a min. of 4 wks in the OL to the 4.4 mg/kg dose at the investigator's judgment. Data from the OL are presented for all 23 pts.

Results:

Variables	Baseline	6 Months (n = 19)	12 Months (n = 21)	24 Months (n = 12)

	(n = 23)			
ACR Pedi30 (% of n)		87	91	70
ACR Pedi50 (% of n)		78	87	70
ACR Pedi70 (% of n)		61	83	57
Prednisone (mean mg/day)	10.0	5.5	2.5	0
Fever and/or rash (% of n)	100.0	0	0	0
Hb (g/dL)	11.0	9	13	11
MRP8/14 (pg/mL)	5600	n/a	*-80**	*-67**
WBC (K/mm3)	9.2	*-34**	*-32**	*-40**
Platelets (K/mm3)	480	*-31**	*-25**	*-36**
D-dimer (ng/mL)	1936	*-37**	*-73**	*-86**
Fibrinogen (g/L)	468	*-34**	*-31**	*-33**
PhyVAS (0-10)	5.5	*-71**	*-67**	*-80**
ParVAS (0-10)	6.0	*-63**	*-57**	*-29**
No. active jts.	10.5	*-100**	*-100**	*-82**
No. jts. with LOM	7.0	*-74**	*-81**	*-69**
CHAQ (0-3)	1.5	*-70**	*-89**	*-86**
hs-CRP (mg/L)	72	*-91**	*-88**	*-96**

* Median % change

Improvement in median scores was seen in all 6 ACR Pedi core variables upon OL treatment. At 6 mos, OL ACR Pedi 30/50/70 responses were seen in 87%/78%/61%, respectively and at 24 mos, were seen in 70%/70%/57%, respectively. Fever and/or rash observed in all pts at baseline completely resolved. WBC, platelet, Hb and fibrinogen improved substantially. D-dimer and MRP 8/14 were dramatically reduced; elevated CRP was nearly normalized. By 24 mos, steroids were able to be stopped in all pts. Three patients were reported with a total of 6 SAEs including MAS (2), pulmonary fibrosis (1), anemia (1) and arthritis flare (2). AEs were ISRs (30%) and URIs (22%). No deaths, malignancies, or serious infections occurred. Withdrawals were due to AEs and L.O.E.

Conclusion: In this long-term OL extension study sustained responses were observed in clinical and laboratory assessments in over 50% of patients with SJIA at 2 years. There was a significant reduction in daily prednisone dose. Chronic IL-1 blockade was generally safe and well-tolerated.

Disclosure: D. J. Lovell, Regeneron, 5, Novartis Pharmaceutical Corporation, 5, Xoma Corporation , 5, Centocor, Inc., 5, Abbott Laboratories, 5, Pfizer Inc, 5, Hoffmann-La Roche, Inc., 5, Amgen, 5, Bristol-Myers Squibb, 5, Editorial Board - Multiple Journals, 9 ; **E. H. Giannini**, Centocor, Inc., 2, Bristol-Myers Squibb, 5, Abbott Laboratories, 5, Pfizer Inc, 5, Hoffmann-La Roche, Inc., 5, Novartis Pharmaceutical Corporation, 5, Xoma Corporation , 5, Amgen, 5, Regeneron, 5, Genzyme Corporation, 5, Clin Exp Rheum Editorial Board, 9 ; **Y. Kimura**, NIH, 2, Regeneron, 2 ; **S. C. Li**, NexMed, Inc., 5, Amgen, 9, Arthritis Foundation, 2 ; **P. J. Hashkes**, FDA, 2 ; **A. O. Reiff**, Amgen, 5, Abbott Laboratories, 5, Wyeth, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Regeneron, 5 ; **C. A. Wallace**, Pfizer Inc, 2, Centocor, 2, Amgen, 2 ; **K. Onel**, None; **D. Foell**, Regeneron, 5, Wyeth Pharmaceuticals, 5, Rheumatology

Editorial Board, 9 ; **D. R. Nadler**, Regeneron, 1, Regeneron, 3 ; **S. Biedermann**, Regeneron, 1, Regeneron, 3 ; **J. D. Hamilton**, Regeneron, 1, Regeneron, 3 ; **A. R. Radin**, Regeneron, 1, Regeneron, 3 .

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Drug-Free Remission of Patients with Systemic Juvenile Idiopathic Arthritis Receiving Tocilizumab for Treatment. Shumpei Yokota[1], Takuma Hara[1], Masako Kikuchi[2], Takayuki Kishi[2], Ryoki Hara[1], Rumiko Kurosawa, Remi Ozawa[2], Takako Miyamae[1], Tomoyuki Imagawa[1] and Masaaki Mori[1], [1]Yokohama City University, Yokohama, Japan, [2]Yokohama City University Hospital, Yokohama, Japan

Purpose: In patients with systemic juvenile idiopathic arthritis (sJIA) who received long-term treatment with tocilizumab, the possibility of complete withdrawal from drug therapy was studied.

Method: Among 67 patients with sJIA, 11 participating in a phase II study of tocilizumab and 56 participating in a phase III study, 24 patients, who had been monitored at our hospital for 3 year or longer, were analyzed. Of the 24 patients, those who maintained remission and were successfully withdrawn from steroid therapy, and whose interleukin-6 (IL-6) level continued to be at low levels for 1 year or longer were identified to study the possibility of complete withdrawal from drug therapy by discontinuing tocilizumab.

Results: The age of the 24 patients was 2 to 18 years, and 10 of these were boys. The follow-up period was 3.2 to 6.2 years, the duration of sJIA was 0.4 to 8.2 years. The IL-6 level was 0.4 to 102 pg/mL, the CRP level was 0.3 to 29 mg/dL, and the steroid dose administered was 3.8 to 40 mg/body. Among the 24 patients, 8 were successfully withdrawn from tocilizumab during the follow-up period. In these 8 patients, the age was 3 to 10 years, and 4 of these were boys. The duration of sJIA was 0.5 to 8.2 years, the IL-6 level was 1.7 to 96 pg/mL, the CRP level was 0.3 to 15 mg/dL and the steroid dose administered was 3.8 to 30 mg/body. These 8 patients discontinued treatment with tocilizumab 2.6 to 4.9 years after the initiation of treatment. Two of them maintained withdrawal from tocilizumab for 3 years or longer, without recurrence, while the remaining 6 patients resumed treatment with tocilizumab due to recurrent symptoms. The period from discontinuation to resumption of treatment with tocilizumab in the 6 patients was 46 to 571 days. At recurrence, 1 patient resumed both steroid and tocilizumab, but the other 5 patients resumed only tocilizumab and succeeded in achieving ACR pedi 90 within 7 to 66 days. During the tocilizumab-free period, 22 adverse events including upper respiratory tract infection occurred in 8 patients. Most of these were mild in severity and resolved without medical intervention. However, in 2 patients upper respiratory infection was suspected to lead the recurrence of sJIA.

Conclusion: Long-term withdrawal from drug therapy was successful in some patients receiving tocilizumab for 3 years or longer and maintaining remission. In addition, the recurrent symptoms could be controlled properly by the resumption of treatment with tocilizumab in such patients. Further studies to monitor patients who fail to achieve remission and cannot be free from drug therapy despite long-term medication are needed.

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Evaluation of Safety and Preliminary Efficacy of Canakinumab (ACZ885), A New IL-1-Beta Blocking Monoclonal Antibody, in Children with Systemic Juvenile Idiopathic Arthritis (sJIA). N. Ruperto[1], P. Quartier[2], N. Wulffraat[3], P. Woo[4], A. Loy[1], R. Mouy[2], B. Bader-Meunier[2], B. Prakken[3], E. Noseda[5], R. Belleli[5], J. Lecot[5], C. Rordorf[5] and A. Martini for PRINTO[1], [1]Pediatria-II PRINTO, IRCCS G.Gaslini, Genova, Italy, [2]Hopital Necker-Enfants Malades, Paris, France, [3]University Medical Center, Utrecht, Netherlands, [4]Pediatric & Adolescent Rheumatology, London, United Kingdom, [5]Novartis, Basel, Switzerland

Purpose: Canakinumab provides potent, rapid, and sustained blockade of IL-1β. Here we report interim results of a Phase II dose-range finding study including efficacy, safety and tolerability in sJIA patients.

Method: This was an open-label, staggered dose-escalation study. Patients received a single canakinumab sc injection (dose range 0.5–9 mg/kg), followed by an observation period and re-dosing upon relapse. Response was measured using adapted ACR ped criteria (ACR ped criteria+absence of fever). Relapse: reappearance of fever and/or systemic manifestations of disease with elevated CRP or as per ACR ped criteria for flare.

Results: 23 children (4–19 y) with active disease were enrolled (median baseline physician's and parent/patient's global assessment of disease activity–68.5 and 67.0 mm [VAS], respectively; CHAQ disability index–2.1; number of joints with active arthritis–20.6; number of joints with limitation of motion–23.7; CRP–136 mg/L; median prednisone equivalent dose–0.33 mg/kg [n=18]. 13/22 (59%) patients responded to canakinumab, all these achieved ACRped50 or better at Day 15. In 4 cases (18%) inactive disease status was reached. In 1 patient, responder status was not evaluated due to bolus steroids injections to treat an SAE. 17/23 patients were previously treated with anakinra. 6/11 anakinra non-responders achieved at least ACR50 at Day 15 after a single dose of canakinumab (4 ACR50, 2 ACR70). The best baseline parameter to predict response was the number of active joints (median: 33.5: non-responders, 9: responders). All responders could be correctly identified with 100% sensitivity and 70% specificity using 26 joint counts. The observed time to relapse varied from 1–12 weeks. Median time to relapse was 56 (95% CI: 32–100), 60 (38–95) and 90 (45–181) days for doses <3, 3, >3 mg/kg, with a 19 (95% CI: 6–41), 17 (6–34) and 7% (1–23) probability of relapse in 1 month, respectively. Steroid was tapered in 70% of responders, in 10/13 patients on steroids at baseline. On average steroid dose was decreased by 0.054 mg/kg (95% CI: 0.013–0.121) per month in the first 5 months. 1 patient completely discontinued steroids at end of month 5. Injections were well tolerated, no anti-canakinumab antibodies were detected. Adverse events (AEs) based on the 18 months interim analysis were mild–moderate in severity and mainly infections and gastrointestinal disorders. 3 patients experienced drug related serious AEs (resolved during treatment). No patients discontinued due to AEs.

Conclusion: Canakinumab provides rapid improvement of signs and symptoms in sJIA patients with efficacy in more than 50% of anakinra non-responders and allows steroid reduction in the majority of responders. Canakinumab was well tolerated.

Disclosure: N. Ruperto, Novartis , 2 ; **P. Quartier**, Novartis , 2 ; **N. Wulffraat**, Novartis , 2 ; **P. Woo**, Novartis , 2 ; **A. Loy**, Novartis , 2 ; **R. Mouy**, Novartis , 2 ; **B. Bader-Meunier**, Novartis , 2 ; **B. Prakken**, Novartis , 2 ; **E. Noseda**, Novartis , 1, Novartis , 3 ; **R. Belleli**, Novartis , 1, Novartis , 3 ; **J. Lecot**, Novartis , 1, Novartis , 5 ; **C. Rordorf**, Novartis , 1, Novartis , 3 ; **A. Martini for PRINTO**, Novartis , 2 .

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Safety and Efficacy of Canakinumab (Ilaris) in Children Across Different Disease Severity Phenotypes of Cryopyrin Associated Periodic Syndrome (CAPS): Interim Results of An Ongoing Study. J.B. Kuemmerle Deschner[1], R. Cartwright[2], M. Gattorno[3], F. Zulian[4], P. Quartier[5], J. Hoyer[6], I. Foeldvari[7], E. Ramos[8], P.N. Hawkins[9], K. Leslie[10], G. Krammer[11], S. Malfait[11], R. Preiss[12], A. Widmer[11] and E. Hachulla[13], [1]Universitätsklinikum, Tübingen, Germany, [2]Allergy Center at Brookstone, Columbus, [3]Istituto Giannina Gaslini, Genova, Italy, [4]University of Padova School of Medicine, Padova, Italy, [5]Hopital Necker-Enfants Malades, Paris, France, [6]Univ.-Klinikum Gießen und Marburg, Marburg, Germany, [7]Hamburger Zentrum füer Kinder- und Jugendrheumatologie, Hamburg, Germany, [8]Hospital Central de Asturias, Oviedo, Spain, [9]Royal Free and University College Medical School, London, England, [10]UCSF, School of Medicine, San Francisco, [11]Novartis, Basal, Switzerland, [12]Novartis, East Hanover, [13]Hôpital Claude Huriez CHRU, Lille, France

Purpose: Canakinumab provides sustained interleukin 1-beta (IL-1β) blockade and is effective in the treatment of CAPS (comprising of FCAS, MWS, CINCA/NOMID). We report the interim results of pediatric patients enrolled in an ongoing open-label, single-treatment arm study to evaluate long-term safety, tolerability and efficacy of canakinumab in CAPS.

Method: Pediatric patients (n=19; 5–17 years; ≥15 kg) were canakinumab naïve (n=11) or rolled over (n=8) from earlier conducted Phase II/III studies. Patients received canakinumab 150 mg s.c. or 2 mg/kg s.c. (≤40 kg) every 8 weeks. Complete response was defined as physician's global assessment of disease activity and assessment of skin disease ≤minimal with normal serum inflammatory markers (C-reactive protein or Serum Amyloid A <10 mg/L). Complete response was assessed for canakinumab naïve patients, while roll-over patients entered the study allowing continuous treatment every 8 weeks. In case of incomplete response patients received an additional dose of canakinumab 300 mg s.c. or 4 mg/kg s.c. (≤40 kg).

Results: Of 19 patients (11 children; 8 adolescents [≥12 years]), 2 were diagnosed with FCAS, 13 with MWS, 3 with MWS/NOMID overlap and 1 with cold urticaria (discontinued as protocol violator). Complete response was achieved in most (n=9, 81.8%) of canakinumab naïve patients by Day 8. The median duration of exposure to study drug was 86 (29–176) days at the data cut off for this interim analysis. Majority of canakinumab treated pediatric patients were relapse free (11 out of 18), 3 MWS patients experienced one relapse, 3 had missing relapse assessments and 1 MWS/NOMID patient did not achieve complete response and dose was up-titrated. 7 patients (36.8%) received at least one protocol-defined dose adjustment (first dose doubled) or at least one frequency adjustment. The most frequent adverse events were headache, joint sprain and pyrexia. One SAE was reported at the interim data cut off: 1 child was hospitalized due to appendicitis (recovered and continued in the study). Most patients (94.7%) had no injection site reactions. No anti-canakinumab antibodies were detected.

Conclusion: Canakinumab every 8 weeks induced rapid and sustained clinical and biochemical remission in pediatric patients across all severity of CAPS phenotypes. Canakinumab was well tolerated and no differences in safety and efficacy compared to adult patients were observed.

Disclosure: J. B. Kuemmerle Deschner, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5 ; **R. Cartwright**, GlaxoSmithKline, 8, Allergy, Asthma, and Immunology Society of Georgia , 6, Novartis Pharmaceutical Corporation, 5, Dey Pharmaceuticals, 5, Allergy Center at Brookstone, 4, Allergy Center at Brookstone, 3, Sanofi Aventis, 8, Pfizer Inc, 8, UCB Pharma, 8 ; **M. Gattorno**, None; **F. Zulian**, None; **P. Quartier**, None; **J. Hoyer**, None; **I. Foeldvari**, Novartis Pharmaceutical Corporation, 5 ; **E. Ramos**, Private practice, 9, Pension, 9 ; **P. N. Hawkins**, Novartis Pharmaceutical Corporation, 5 ; **K. Leslie**, None; **G. Krammer**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **S. Malfait**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **R. Preiss**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **A. Widmer**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3 ; **E. Hachulla**, Novartis Pharmaceutical Corporation, 5 .

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis Clinical Aspects: Treatment Outcomes

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

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Hydroxychloroquine (HCQ) Eye Examination Frequency, Risk Categories, and the Risk of HCQ Toxicity. Frederick Wolfe[1], Michael F. Marmor[2] and Kaleb D. Michaud[3], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Stanford University, Stanford, CA, [3]University of Nebraska Medical Center and NDB, Omaha, NE

Purpose: HCQ toxicity is of clinical concern because of the seriousness of visual loss and possible medico-legal consequences. The ACR and American Academy of Ophthalmology (AAO) currently recommend a baseline examination and no other examinations in the first 5 years of therapy for patients in low risk categories, and annual examination for those in higher risk categories. In this report we examined the prevalence of self-reported toxicity and eye doctor confirmation in a large cohort of HCQ users, relative to risk factors and screening frequency.

Methods: We studied 3,738 patients with rheumatoid arthritis or systemic lupus erythematosus who had used HCQ, including 1,432 current users. We screened for self-reported toxicity, and followed-up on positive cases with detailed interviews and ophthalmologist/optometrist confirmation. We defined toxicities as specialist designated HCQ toxicity and Bull's eye lesions. We extrapolated from these results to incomplete cases. Risk categories were defined according to published risk recommendations for dosage, duration or use, and complicating medical factors.

Results: 8% of patients reported any HCQ visual toxicity, but only1.8% retinal toxicity. Follow-up confirmation found 1.7% toxicity and 0.7% bull's eye lesions. 7.7% of patients were in the low risk category, 57.7% in high risk, and 36.5% in the very high-risk category. Overall, eye examinations were obtained every 6 months by 40.4%, with almost all of the remaining examinations occurring yearly. There was no statistical relation between risk category (or the individual components of risk) and examination frequency. However, a 10-year reduction in age was associated with the probability of more frequent eye examinations (odds ratio (OR) 1.2 (95% CI 1.1, 1.3), and males were more likely to have a less frequent examinations (OR 1.4 (95% CI 1.1,1.9). Using median regression, adjusted for age, sex, and RA diagnosis, patients with a bull's eye lesion used hydroxychloroquine 4 (95% CI 0.3, 7.7) years longer that patients without self-reported hydroxychloroquine toxicity (p= 0.034). For specialist reported toxicity, there was a non-significant increase in duration of hydroxychloroquine use, 2 (95% CI -2.0, 6.0) years, p = 0.333. Adjusted for age, sex, and RA diagnosis, the median duration of therapy was: specialist bull's eye lesion 7.5 (95% CI 3.8, 11.2) years, specialist toxicity 5.5 (95% CI 1.1, 9.6) years, and patients not reporting hydroxychloroquine toxicity 3.5 (95% CI 3.3, 3.7) years.

Conclusion: We identified HCQ in toxicity 1.7 % and bull's eye lesions in 0.7% .92.3% of patients are in high or very high-risk categories. Risk categories appeared to be weakly related to observed toxicity. There was no relation between risk categories and screening examination frequency.

Disclosure: F. Wolfe, None; **M. F. Marmor**, None; **K. D. Michaud**, None.

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Risk of Infection in Rheumatoid Arthritis Associated with Use of Anti-TNF Agents, Dmards and/or Prednisone. Eduardo Bonilla Trejos[1], Michael J. Hannon[2], Melissa Skanderson[1], Chester Good[1] and C. Kent Kwoh[2], [1]Pittsburgh VA Healthcare System, Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Purpose: To compare the risk of infection associated with different treatment options for RA taking into account the potential combinations of DMARDs, anti-TNF agents and corticosteroids

Method: Data from both the VA National Patient Care Database and the Pharmacy Benefits Management Database dating from Oct. 1, 2000 to Sept. 30, 2007 were utilized to identify cases of RA. The definition of RA was based on ICD-9 codes 714* (either two outpatient codes at least 30 days apart or one inpatient code) and having ever had at least one prescription for a DMARD. A nested case-control study design was utilized to examine 3457 cases of RA patients with a serious infection that were identified based on their corresponding ICD-9 codes from an inpatient admission. Controls with RA but without a serious infection were matched 2:1 by year of initial RA visit, an inpatient or outpatient visit in the same month and year as the inpatient visit for RA case, and location in the same VA region (VISN). Conditional logistic regression was used to examine the risk of serious infection based on DMARD exposure in the 100 days prior to the inpatient admission while controlling for age, gender and the Deyo modification of the Charlson Comorbidity score. The exposures were DMARD1 (i.e., methotrexate/leuflonomide), DMARD2 (i.e., sulfasalazine/hydroxychloroquine/azathiprine), TNF (i.e., infliximab/etanerecept/adalimumab) and Prednisone equivalents (PRED, i.e., categorized as none, low dose (mean of 1-10mg/day) or high dose (mean of >10mg/day)). The reference group consisted of RA patients not on any TNF, DMARDs or PRED.

Results: The results are summarized in the table below.

RA treatment	aOR*	95% CI
TNF and DMARD1 and high PRED	5.18	3.66-7.33
TNF and DMARD2 and any PRED	4.80	3.01-7.66
TNF and DMARD1 and low PRED	4.23	2.95-6.08
TNF and DMARD1 and DMARD2 and any PRED	4.00	2.70-5.92
DMARD1 and high PRED	3.69	2.97-4.58
DMARD2 and high PRED	3.63	2.88-4.57
TNF and any PRED	3.42	2.44-4.81
DMARD1 and DMARD2 and high PRED	3.25	2.52-4.19
TNF alone	3.06	2.03-4.60
DMARD2 and low PRED	3.02	2.40-3.80

DMARD1 and low PRED	2.96	2.40-3.67
Any PRED alone	2.36	1.85-3.00
TNF and DMARD1	2.33	1.60-3.38
DMARD2 alone	2.13	1.71-2.64
TNF and DMARD2	2.06	1.10-3.85
DMARD1 alone	2.02	1.64-2.50
DMARD1 and DMARD2	2.01	1.64-2.50

*adjusted for age, gender and Charlson Comorbidity score

Conclusion: The use of any PRED, especially high dose PRED, is associated with an increased odds of infection in RA when added to a TNF or DMARD. The risk of serious infection with TNF alone is similar to that of DMARD1 or DMARD2 combined with low dose PRED. The combination of TNF, any DMARD and any PRED is associated with the highest odds of serious infection and should be used with special caution.

Disclosure: E. Bonilla Trejos, None; **M. J. Hannon**, None; **M. Skanderson**, None; **C. Good**, None; **C. K. Kwoh**, Abbott Immunology Pharmaceuticals, 5, Centocor, Inc., 5, Wyeth Pharmaceuticals, 5, Centocor, Inc., 2 .

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The Risk for Hospitalized and Outpatient Infections Related to Anti-TNF Therapy and Newer Biologics. Jeffrey R. Curtis[1], Lang Chen[1], John J. Cush[2], Kathryn H. Dao[3], Elizabeth Delzell[1], D. E. Furst[4], J. Greenberg[5], Marc C. Hochberg[6], Archana Jain[1], Joel M. Kremer[7], Nivedita Patkar[1] and Daniel H. Solomon[8], [1]UAB, Birmingham, AL, [2]Baylor Research Institute, Dallas, TX, [3]Texas Health, Dallas, TX, [4]UCLA, Los Angeles, CA, [5]NYU, New York, NY, [6]University of Maryland School of Medicine, Baltimore, MD, [7]Albany Medical College, Albany, NY, [8]Brigham & Women's Hospital, Boston, MA

Purpose: There have been inconsistent results regarding the association between anti-TNF therapies and the risk of serious infection. Several prior studies had relatively poor adjustment for RA disease severity, while other analyses may have had biased ascertainment of infectious outcomes. We compared the risk of infection associated with anti-TNF therapies and other biologics to non-biologic DMARDs in a cohort with substantial information about disease severity.

Method: Data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry was used to identify a cohort of rheumatoid arthritis (RA) patients, RA disease factors, and their relevant DMARD exposures. For patients with reported hospitalized infections, medical records were requested. Cox proportional hazards models estimated the risk for hospitalized infections associated with current use of various biologic DMARDs compared to non-biologic DMARDs. Disease activity (CDAI), functional status (mHAQ), duration of RA, diabetes, lung disease, prior infection, prednisone dose, and number of previous infections were included in adjusted analyses. Sensitivity analysis considered how recently each of the drugs was initiated (< 1 year, ≥ 1 year), and also restricted eligible participants to new users of various medications. Additional analyses using Poisson regression evaluated the risk for all infections (hospitalized and outpatient).

Results: Among 18,305 RA patients with 32,911 years of observation, 586 hospitalized infections and 21,258 outpatient infections were reported. A total of 91% of the hospitalized infections had hospital record evidence to confirm the event; the remaining 9% were not counted as cases. In adjusted analyses, no significant increase in serious infection risk associated was observed for anti-TNF therapy or other biologics compared to non-biologic DMARDs. Factors that were associated with infections included age, RA clinical disease activity index (CDAI), mHAQ, duration of RA, lung disease, prior infection, prednisone dose, and number of previous non-biologic DMARDs. Consistent with the hospitalized infection results, there was no significant difference in the rate associated with the various biologics for the endpoint of all infections.

Conclusion: In an observational cohort of RA patients, we found no significant increase in the adjusted risk for hospitalized or outpatient infections associated with anti-TNF therapy or other biologics compared to MTX and other non-biologic DMARDs. The

infection-related safety profiles of the various biologic agents appear to be similar.

Disclosure: J. R. Curtis, Roche Pharmaceuticals, 5, UCB, 5, Proctor & Gamble Pharmaceuticals, 5, Amgen, 5, Centocor, Inc., 5, Corrona, 5, Novartis Pharmaceutical Corporation, 2, Amgen, 2, Merck Pharmaceuticals, 2, Eli Lilly, 2, Proctor & Gamble Pharmaceuticals, 2, Roche Pharmaceuticals, 2, Centocor, Inc., 2, Corrona, 2, Novartis Pharmaceutical Corporation, 8, Proctor & Gamble Pharmaceuticals, 8, Eli Lilly and Company, 8, Roche Pharmaceuticals, 8, Merck Pharmaceuticals, 8 ; **L. Chen**, None; **J. J. Cush**, Centocor, Inc., 2, Celegene, 2, Roche, 2, Genentech, 5, Pfizer Inc, 2, UCB, 5, Abbott Laboratories, 2, Centocor, 5, Amgen, 5, UCB, 2, Genentech , 2 ; **K. H. Dao**, None; **E. Delzell**, Amgen, Inc, 2 ; **D. E. Furst**, None; **J. Greenberg**, Corrona, 5, Centocor, Inc., 5, Bristol-Myers Squibb, 2, Genentech and Biogen IDEC Inc., 5, Roche Pharmaceuticals, 5 ; **M. C. Hochberg**, None; **A. Jain**, None; **J. M. Kremer**, Abbott Immunology Pharmaceuticals, Amgen, Centocor, BMS, 2, Abbott, Amgen, Centocor, BMS, 5 ; **N. Patkar**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2 .

2060

Risk of Septic Arthritis in Patients with Rheumatoid Arthritis Treated with Anti-TNF Therapy: Results From the BSR Biologics Register (BSRBR). J. B. Galloway[1], K. L. Hyrich[1], L. K. Mercer[1], W. G. Dixon[1], A. P. Ustianowski[2], K. D. Watson[1], M. Lunt[1], D. P. Symmons[1] and On behalf of the BSRBR[1], [1]arc Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]North Manchester General Hospital, Manchester, United Kingdom

Purpose: Rheumatoid arthritis (RA) is associated with an increased risk of septic arthritis (SA). Clinical trials of anti-TNF therapy have not suggested an increased risk of SA, but there have been case reports suggesting a potential association.

Method: Consecutive RA patients treated with anti-TNF therapy recruited between 10/01 and 5/08 by the BSRBR were followed 6 monthly via consultant and patient questionnaires until 12/31/08, end of follow up or death. A comparison cohort with active RA on disease modifying anti-rheumatic drugs (DMARD) was recruited and followed up in the same way. Incident cases of SA were identified from follow-up questionnaires and verified via medical records. SA was attributed to anti-TNF if it was diagnosed while on anti-TNF or within 90 days of the last dose. SA event rates in the anti-TNF and DMARD cohorts were compared using Cox proportional hazard ratio estimates adjusted for age, gender, disease severity, prior joint replacement, co-morbidity and steroid use. Missing baseline data were replaced using multiple imputations.

Results: 246 cases of SA were reported during the follow up period: 229/11757 in the anti-TNF cohort and 17/3515 in the comparison cohort. 179 cases could be attributed to anti-TNF using the “on drug plus 90 day” model. Incident rates were 5.0/1000 pyrs (95% CI 4.3, 5.8) in the anti-TNF cohort and 1.9/1000 pyrs (1.1, 3.0) in the controls. At least 51% of the SA in patients on anti-TNF occurred in native joints (Table). Patients on anti-TNF therapy were twice as likely to develop SA as controls (adjusted HR 2.0, 95% CI 1.1, 3.5). The individual anti-TNF drug adjusted results were etanercept HR 2.3, (CI 1.2, 4.4), infliximab HR 1.6, (CI 0.8, 3.2), and adalimumab HR 1.8, (CI 1.0, 3.5). Staphylococci were the most common organisms in both cohorts (DMARD 50%; anti-TNF 75%). 5 cases of intracellular infection (2 *Listeria*, 3 *Salmonella*) and 11 cases of Streptococcal SA (including 4 *Streptococcus pyogenes*) were reported (all in the anti-TNF cohort).

Conclusion: Exposure to TNF inhibitor therapy is associated with an increased risk of SA in patients with RA. Careful vigilance for joint infections remains important with awareness of the potential range of pathogens. Antibiotic guidelines should incorporate this information.

Table

	DMARD **n=3513**	**Anti-TNF** **On drug + 90 days**

		n=11757
Pyrs follow up	9094	35932
Total joint infections	17	179
Native joint infections, n(%)	11 (65)	91 (51)
Prosthetic joint infections, n(%)	6 (35)	54 (30)
Not stated, n(%)	0	34 (19)
Unadjusted HR SA infections (95% CI)	Ref	2.7 (1.6 – 4.4)
Fully adjusted HR (95% CI)	Ref	2.0 (1.1 – 3.6)
Limited to native joints, fully adjusted HR (95% CI)	Ref	2.5 (1.2 – 5.0)
Limited to culture positive cases, fully adjusted HR (95% CI)	Ref	2.0 (1.1 – 3.6)

Disclosure: J. B. Galloway, None; **K. L. Hyrich**, British Society for Rheumatology, 2 ; **L. K. Mercer**, None; **W. G. Dixon**, None; **A. P. Ustianowski**, None; **K. D. Watson**, None; **M. Lunt**, None; **D. P. Symmons**, British Society for Rheumatology, 2 ; **O. behalf of the BSRBR**, BSR BR, 2 .

2061

Clinical Synovitis Is Associated with Progression of Erosions and Joint Space Narrowing in Individual Joints, but Not in Patients Treated with Initial Infliximab. N.B. Klarenbeek[1], M. Güler-Yüksel[1], W.M. de Beus[2], Désirée M.F.M. van der Heijde[3], H.M.J. Hulsmans[4], P.J.S.M. Kerstens[5], T.W.J. Huizinga[1], B. A. C. Dijkmans[6] and C.F. Allaart[1], [1]LUMC, Leiden, Netherlands, [2]MC Haaglanden, The Hague, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Haga Hospital, The Hague, Netherlands, [5]JBI, Amsterdam, Netherlands, [6]VUMC, Amsterdam, Netherlands

Purpose: To assess for individual joints the relationship between joint tenderness and swelling and progression of erosions and joint space narrowing and to evaluate the influence of initial treatment

Methods: In the BeSt study, recently diagnosed active RA patients were randomized to treatment with: 1. sequential monotherapy, 2. step up combination therapy, 3. initial combination with prednisone, or 4. initial combination with infliximab. X-rays of baseline and year 1 were scored in random order by two readers using the Sharp-van der Heijde score. Using Generalised Estimating Equations (GEE), threemonthly tender and swollen joint counts (44) of year 1 were related to Sharp-van der Heijde progression at the individual joint level (ever/never swollen and ever/never tender vs erosion and joint space narrowing (JSN) progression (yes/no) in year 1, corrected for SHS baseline, age, gender, BMI, treatment, and accounting for within patient correlation for multiple joints per patient).

Results: In total, 13895 joints were analyzed. During year 1, 59% of all joints were ever tender, 45% swollen, 2% showed erosion progression (>0.5 SHS units) and 2% JSN progression (>0.5 SHS units). In treatment groups 1, 2 and 3 but not in 4 both swelling and tenderness were independently associated with erosion progression with a ‘dose effect’ and with ORs comparable for swelling and tenderness. Similar results were found for JSN progression (table). There was no interaction between swelling and tenderness. Odds ratios were higher in the hands than in the feet (ORs for erosion progression: 15.5 for swelling and 8.1 for tenderness in hands vs 1.5 and 1.3 in feet, ORs for JSN progression: 3.6 and 3.3 for swelling and tenderness hands vs 2.2 and 1.6 for feet).

Conclusion: Clinical signs of synovitis are associated with both erosion and joint space narrowing progression in the same joint after 1 year treatment in recent onset RA patients. These associations are stronger in hands than in feet, possibly due to difficult joint evaluations in the feet. We found a disconnect between clinical signs of synovitis and damage progression in patients who received infliximab as initial treatment, confirming the disconnect between synovitis and the development of joint damage in TNF-blockers.

Table: GEE results with ORs for erosion and JSN progression

		Erosions		**JSN**	
		OR	**95% CI**	**OR**	**95% CI**
All patients	Swelling 1x	1.4	0.98 -1.9	1.7	1.2 – 2.4
	Swelling ≥2x	3.1	2.1 – 4.6	3.5	2.4 – 5.2
	Tender 1x	1.5	1.0 – 2.3	1.5	1.0 – 2.2
	Tender ≥2x	4.0	2.7 – 5.9	3.7	2.4 – 5.7
Group 1	Swelling ever	3.0	1.8 – 4.9	3.8	2.5 – 5.9
	Tender ever	3.5	1.9 – 6.7	2.2	1.1 – 4.4
Group 2	Swelling ever	1.6	0.86 – 3.0	1.7	0.97 – 3.1
	Tender ever	2.9	1.3 – 6.5	3.4	1.6 – 6.9
Group 3	Swelling ever	4.4	1.8 – 10.6	3.3	1.7 – 6.4
	Tender ever	2.4	0.97 – 6.1	2.6	1.3 – 5.1
Group 4	Swelling ever	0.94	0.47 – 1.9	1.2	0.5 – 2 9
	Tender ever	1.5	0.89 – 2.8	2.3	0.78 – 6.6

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2062

The Influence of Anti-TNF Therapy Upon Incidence of Non-Melanoma Skin Cancer (NMSC) in Patients with Rheumatoid Arthritis (RA): Results From the BSR Biologics Register (BSRBR). L. K. Mercer[1], J. B. Galloway[1], M. Lunt[1], W. G. Dixon[1], K. D. Watson[1], BSRBR Control Centre Consortium, D. P. Symmons[1], K. L. Hyrich[1] and On behalf of the BSRBR[1], [1]arc Epidemiology Unit, University of Manchester, Manchester, United Kingdom

Purpose: RA is associated with an increased risk of NMSC. Anti-TNF therapy may intensify this risk, although evidence to date is conflicting. Our aim was to explore the influence of anti-TNF therapy on the incidence of NMSC using data from the BSRBR, a prospective cohort study set up in 2001 to monitor the long-term safety of anti-TNF therapy in the UK.

Method: 11757 consecutive anti-TNF treated patients with RA were followed 6 monthly and compared to 3515 biologic-naïve subjects with active RA receiving traditional disease modifying therapy (DMARD). Patients were followed until 12/31/2008 or death, whichever came first. Incident NMSC were identified from consultant and patient questionnaires and record linkage with the UK national register for cancer. Local recurrence was included but carcinoma-in-situ (Bowen's disease) excluded as an incident NMSC. NMSC occurring after stopping anti-TNF was attributed to the most recently received anti-TNF drug. The rates of NMSC in the anti-TNF and DMARD cohorts were compared using multivariate Cox proportional hazards models adjusted for age, gender, disease duration, disease activity, HAQ, baseline steroid use, number of prior DMARDs, smoking and year of registration.

Results: 221 NMSC were verified: 175 in 149 anti-TNF patients (4.2/1000 pyrs) and 46 in 40 DMARD patients (5.1/1000 pyrs). Histology data were received for 135 NMSC in the anti-TNF patients of which 122 (90%) were basal cell carcinoma (BCC) and 12 (9%) squamous cell carcinoma (SCC). A similar ratio of BCC:SCC was seen in the DMARD cohort. The strongest predictor for NMSC was prior NMSC (HR 9.8 (95% CI 5.6, 17.0)), with other known risk factors (age, male gender and steroids) also associated with increased risk. Limiting the analysis to patients with no prior NMSC the fully adjusted hazard ratio (aHR) for anti-TNF vs. DMARD was 1.7 (0.9, 3.4). The aHR was 1.7 (0.8, 3.4) for etanercept (ETA), 2.9 (1.4, 6.1) for infliximab (INF) and 1.1 (0.5, 2.5) for adalimumab (ADA).

Conclusion: In patients with no prior NMSC, the risk of NMSC was increased by 70% in patients with RA treated with anti-TNF therapy, although this was not significant. INF was associated with an almost 3 fold increase in risk of NMSC in this group. Vigilance for NMSC should be maintained in all patients with RA, especially when treated with anti-TNF therapy.

Table:

No of patients ever received the drug	**DMARD N=3515**	**All Anti-TNF N=11757**	**ETA**	**INF**	**ADA**
Person years follow up	9058	41716	18133	11212	12371
No of patients with prior NMSC (%)	83 (2.4)*	159 (1.4)*	64 (1.6)	38 (1.1)	57 (1.4)
Rate / 1000 pyrs (95% CI) in patients with no prior NMSC	2.4 (1.5, 3.6)	3.5 (2.9, 4.1)	3.0 (2.2, 3.9)	5.5 (4.2, 7.1)	2.4 (1.6, 3.4)
Crude HR in patients with no prior NMSC (95% CI)	Ref	1.0 (0.6, 1.6)	0.8 (0.5, 1.4)	1.8 (1.0, 3.1)	0.7 (0.4, 1.2)
Fully adjusted, limited to patients without prior NMSC (95% CI)	Ref	1.7 (0.9, 3.4)	1.7 (0.8, 3.4)	2.9 (1.4, 6.1)	1.1 (0.5, 2.5)

*p <0.001

Disclosure: L. K. Mercer, None; **J. B. Galloway**, None; **M. Lunt**, None; **W. G. Dixon**, None; **K. D. Watson**, None; **D. P. Symmons**, The British Society for Rheumatology, 2 ; **K. L. Hyrich**, The British Society for Rheumatology, 2 ; **O. behalf of the BSRBR**, The British Society for Rheumatology, 2 .

ACR Concurrent Abstract Sessions

Rheumatoid Arthritis - Human Etiology And Pathogenesis

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

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Increased Proportions of CD4+CD25+CD127-FoxP3+ T Cells with Superior Suppressive Capacity Are Present in the Peripheral Blood of Early RA Patients. Y. García-Carmona, M. Benito-Miguel, Alejandro Balsa, C.P. de Ayala, E. Martin-Mola and M. E. Miranda-Carús, Hospital La Paz, Madrid, Spain

Purpose: To assess the frequency and function of CD4+CD25+CD127-FoxP3+ T cells in the peripheral blood of early RA patients.

Method: Peripheral blood was drawn from 30 healthy controls (HCPB) and 30 early RA patients who had not received treatment with steroids or DMARDs (RAPB). In addition, 10 patients donated blood for a second time, after remission had been achieved with treatment (RAPB-R). The frequency of CD4+CD25+CD127-FoxP3+ T cells was assessed by flow cytometry. CD4+CD25+CD127- T reg and CD4+CD25- Tresp cells were isolated by Ficoll-Hypaque gradient, followed by sorting. Treg cell function was assessed using two different approaches: A.The regulatory function of natural proportions of Tregs was inferred by comparing the proliferative and cytokine responses of total CD4+ T cells (TCD4T) versus CD25+ depleted CD4+ T cells (CD4+CD25-T cells); B. The per cell suppressor potency of Tregs was

assessed in cocultures of isolated Tregs with Tresp, established at different Treg/Tresp ratios. Proliferation was determined by 3Hthymidine incorporation and CFSE dilution; cytokine secretion was measured by ELISA of culture supernatants.

Results: When compared with HCPB, the proportion of CD25+CD127- T cells was significantly increased among RAPB CD4+ T cells (mean + SD, 6.4+2.1 vs 9.8+2.7, p<0,05; range 4.1-8.6 vs 8.9-16.3). These RAPB CD4+CD25+CD127- T cells expressed FoxP3 but did not express CD69. We then tested the suppressive function of the naturally increased proportion of Treg cells in RAPB. When compared with HCPB, TCD4 T cells from RAPB showed a lower proliferative response. In contrast, RAPB CD4+CD25-Tresp cells demonstrated higher proliferation rates. Subsequently, the calculated inhibitory potency of RAPBTreg on Tresp proliferation resulted significantly increased. This suggests that the low proliferative response of RAPB TCD4T cells is attributable to the superior suppressive potency of RA Tregs. In parallel, IFN-γ and TNF-α secretion were higher for TCD4T and also for Tresp cells from RAPB, when compared with HCPB. That is, despite their low proliferative response, RAPB TCD4 T cells secrete more IFN-γ and TNF-α. At the same time, the potency of inhibition of RATreg on RATresp cytokine secretion was significantly increased. That is, the increased suppressive potency of RA Treg cells is not able to overcome the increased Tresp IFN-γ and TNF-α secretion in these patients. We next sought to determine the per cell suppressive potency of RA Tregs. On a per cell basis, RAPB Tregs were significantly more potent suppressors of proliferation, TNFα and IFNγ secretion when compared with HCPB Tregs. The frequency and function of RAPB-R Treg cells were not different from HCPB Tregs.

Conclusion: Increased proportions of CD4+CD25+CD127-FoxP3+ T cells with superior suppressive capacity are present in the peripheral blood of early RA patients. However, this higher suppressive action is not able to overcome the increased Tresp IFN-γ and TNF-α secretion.

Disclosure: Y. García-Carmona, None; **M. Benito-Miguel**, None; **A. Balsa**, None; **C. P. D. Ayala**, None; **E. Martin-Mola**, None; **M. E. Miranda-Carús**, None.

2064

Dendritic Cell-Derived Dopamine Induces IL-6-Th17 Axis in Rheumatoid Arthritis. Kazuhisa Nakano, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Purpose: It is emerging that Th17 cells among various T cell subsets play important roles in the inflammatory processes including rheumatoid arthritis (RA). Although certain factors and immune cells such as dendritic cells (DCs) are known to be involved in the induction of Th17 cells in murine system, precise mechanisms in human diseases remain unclear. The neuron system is supposed to affect the immune system by releasing neurotransmitters and among them dopamine is a major one in the brain and the first catecholamine synthesized there. We found that DCs secrete dopamine and assessed the role of dopaminergic-signaling in the T cell differentiation and its involvement in the pathogenesis of RA using SCID mice co-implanted with synovium and cartilage from RA patients (SCID-HuRAg mice).

Method: T-cell response to dopamine was assessed by the levels of intracellular cAMP and IFN-g, IL-4, IL-5, IL-17, IL-1b, IL-6 and TGF-b production. Catecholamine concentrations in synovial fluid were analyzed by *HPLC*. Expression of dopamine in synovium from patients with RA was analyzed by immunostaining. Antagonists of either D1-like or D2-like dopamine-receptor were administered subcutaneously twice a week into SCID-HuRAg mice. The implants were removed after 30 days and histologically evaluated.

Results: Dopamine increased cAMP levels via D1-like dopamine receptors in human naïve $CD4^+$ T cells and production of induced IL-6 and IL-17 from T cells under the presence of anti-CD3 and anti-CD28 antibody stimulation in a concentration-dependent manner. This dopamine-mediated IL-17 production was completely inhibited by pretreatment with human IL-6 receptor (IL-6R) mAb tocilizumab. D2-like receptor antagonists significantly induced DC-mediated Th17 differentiation in a mixed lymphocyte reaction with human Mo-DCs and allogenic naïve $CD4^+$ T cells. On the other hand, dopamine concentration was significantly higher in synovial fluid from RA patients compared with osteoarthritis patients. In RA synovium, large amount of dopamine was detectable in DC cytoplasm, whereas dopamine-receptors could be detected on $CD4^+$ T cells, but not on synovial fibroblasts. In SCID-HuRAg mice, all mice treated with SCH-23390, a D1-like receptor antagonist, showed protective effects on cartilage destruction. In contrast, all mice treated with haloperidol, a D2-like receptor antagonist, showed accumulation of IL-6 and IL-17 positive cells, proliferation of synovium, remarkable neo-vasculization and exacerbated cartilage destruction in the SCID-HuRAg mice.

Conclusion: These findings indicate that DC is a major source of dopamine in RA synovium and that DC-derived dopamine induces IL-6 – Th17 axis, resulting in aggravation of RA.

Disclosure: K. Nakano, None.

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Gene Signatures That Predict Development of Arthritis. Lisa G.M. Van Baarsen[1], Wouter H. Bos[2], Francois Rustenburg[1], Tineke C.T.M. van der Pouw Kraan[1], Gertjan. Wolbink[2], Ben A.C. Dijkmans[3], Dirkjan van Schaardenburg[2] and Cornelis L. Verweij[1], [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Institute, Amsterdam, Netherlands, [3]VU Medical Centre, Amsterdam, Netherlands

Purpose: Recognition of the preclinical phase of rheumatoid arthritis (RA) allows a timely start of treatment with the ultimate goal of primary prevention. We aimed to identify molecular features that are associated with the development of RA in order to understand the pathophysiology of preclinical development and to assign predictive biomarkers.

Methods: In total, 25 RA patients and 109 ACPA and/or RF positive arthralgia patients at risk for RA and with definitive absence of arthritis (swollen joint count [SJC] =0) in 44 joints at physical examination at the baseline visit determined by two experienced rheumatologists, were included in this study. Exclusion criteria for the arthralgia group were: the presence of recent infections, autoimmune rheumatic diseases, cancer, arthritis revealed by chart review or baseline physical examination, erosions on hand or feet X-ray examination and previous treatment with DMARD or corticosteroids. Gene expression profiles of blood samples were determined by DNA microarray analysis and qPCR. Significance Analysis of Microarrays (SAM) was used to determine significantly differential expressed genes. PANTHER Classification System was used to interpret our data. Cox-regression hazard analysis assessed the relative risk for arthritis development in subgroups of autoantibody positive arthralgia patients.

Results: Gene expression profiling of peripheral blood cells revealed molecular heterogeneity among autoantibody positive arthralgia patients at risk for arthritis development based on differential expression of genes that are involved in diverse arms of the immune response. Interim analysis revealed that 20 at risk patients have developed arthritis after a median of 7 months (IQR 4-15; median follow-up of all patients is 30 [IQR 22-39] months) in a median of 3 joints (IQR 3-5). Here, we report for the first time gene signatures relevant to development of arthritis. Signatures significantly associated with arthritis development (HR 4.5; 95% C.I. 1.3-15.4; P=0.016) involved IFN-mediated immunity, hematopoiesis and cytokine activity. These processes were reminiscent of those present in RA patients, implying that the preclinical phase of disease already carries features of established disease. Genes involved in B-cell immunology were associated with protection from progression to arthritis.

Conclusion: Our results imply that, IFN-mediated immunity, hematopoiesis and cell trafficking specify the processes relevant to progression to arthritis besides autoantibody positivity. These findings strongly suggest that gene signatures have predictive value for progression to arthritis, which will pave the way to preventive medicine.

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CXCR3 Regulates the Invasive Properties of Synovial Fibroblasts Via Akt Signaling, Collagenase Activation and Actin Reorganization. Teresina Laragione, Adriana Mello, Max Brenner, Barbara Sherry and Percio S. Gulko, Feinstein Institute for Medical Research, Manhasset, NY

Purpose: The in vitro invasive properties of fibroblast-like synoviocytes (FLS) in a Matrigel assay correlate with joint damage and erosions in pristane-induced arthritis (PIA) in rats and in rheumatoid arthritis (RA) in humans. We have identified a unique mRNA gene expression signature associated with highly invasive FLS obtained from PIA-susceptible DA rats. This signature includes genes implicated in cancer phenotypes such as cell invasion and metastasis. Among the genes up-regulated in DA FLS, as compared with minimally invasive FLS obtained from the arthritis-protected Cia5d strain, is the chemokine CXCL10. Therefore, we hypothesized that the interaction between CXCL10 and CXCR3 plays a role in the regulation of FLS invasion and joint damage.

Method: FLS were obtained from DA and Cia5d synovium 21 days after the induction of PIA, and cultured for at least three passages. Supernatants were used to measure CXCL10 protein levels. FLS were also isolated from synovial tissues from RA patients. FLS invasion

was studied in a 24h Matrigel assay in the presence or absence of recombinant CXCL10 (1µg/mL), anti-CXCR3 blocking antibody, isotype control antibody, or the small molecule CXCR3 inhibitor AMG487. Supernatants were collected for quantification of matrix metalloproteinase (MMP) activity (MMP-1, 2, 3, 9 and 13). Total cell lysates were tested for Erk and Akt phosphorylation by western blot. Actin filament organization was detected by immunofluorescence in presence or absence of AMG487.

Results: Supernatants from DA FLS had 30% higher levels of CXCL10, compared with Cia5d FLS, confirming the previous mRNA data. DA and Cia5d FLS had similar levels of CXCR3 protein and also similar CXCR3-CXCL10 binding. The addition of CXCL10 to 24h Cia5d FLS cultures significantly increased invasion by nearly 2.5-fold, and was specifically blocked by anti-CXCR3 antibodies. Both anti-CXCR3 antibodies and the small molecule CXCR3 inhibitor AMG487 reduced DA FLS invasion by as much as 85%. AMG487 also significantly reduced the invasion of RA FLS (n=6) by 60%. Anti-CXCR3 antibody and AMG487 reduced levels of active MMP-1, and levels of phospho-Akt both in rat and RA FLS. AMG487 treatment prevented actin cytoskeleton reorganization and the polarized formation of lamellipodia, which is required for cell invasion, both in rat and RA FLS.

Conclusion: We describe for the first time a new autocrine/paracrine role for CXCL10 in the regulation of FLS invasion in arthritis, including RA. Antibody neutralization and a small molecule inhibitor of the CXCL10 receptor, CXCR3, both in rats and human cells significantly reduced FLS invasion as well as key processes known to regulate cell invasion such as levels of phospho-Akt and MMP-1, and the polarized formation of lamellipodia. These observations suggest that the CXCL10-CXCR3 pathway is a promising new target for therapies aimed at reducing joint damage and pannus invasion and destruction in RA.

Disclosure: T. Laragione, None; **A. Mello**, None; **M. Brenner**, None; **B. Sherry**, None; **P. S. Gulko**, None.

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mTOR Regulates the Invasive Properties of Synovial Fibroblast. Teresina Laragione, Adriana Mello, Keren Amir and Percio S. Gulko, Feinstein Institute for Medical Research, Manhasset, NY

Purpose: The invasive properties of fibroblast-like synoviocytes (FLS) correlate with disease severity and radiographic damage in rheumatoid arthritis (RA), and with histological articular damage in pristane-induced arthritis (PIA). We have recently determined that highly invasive FLS obtained from PIA-susceptible DA rats have a gene expression signature similar to that detected in highly invasive and metastatic cancers. Among the genes up-regulated in DA FLS, is ezrin, a member of ERM (ezrin-radixin-moesin) family. Ezrin promotes cancer cell invasion and metastasis via the mammalian target of rapamycin (mTOR) pathway. In the present study we used Rapamycin, an inhibitor of mTOR, to assess the role of the ezrin-mTOR pathway on the invasive properties of FLS from DA rats with PIA and patients with RA.

Methods: FLS were collected from DA rat synovial tissues 21 days after the induction of PIA. Human FLS were isolated from synovial tissues obtained from RA patients. After the third passage, cells were treated with Rapamycin for 24 hours and tested on the Matrigel invasion assay. Supernatants were assayed for matrix metalloproteinase (MMP) activity. Cell lysates from Rapamycin or DMSO-treated FLS were used for detection and quantification of mTOR, p70S6K1, 4EBP1, FAK, and their respective phosphorylated subsets by western blot. Actin filament organization and FAK localization were determined by immunofluorescence 20 minutes and 24 hours after incubation with rapamycin or control.

Results: Rapamycin decreased both DA (10 µM) and RA (0.1 µM) FLS invasion through Matrigel. Rapamycin treatment reduced mTOR, p70S6K1 and 4EBP1 phosphorylation confirming the inhibition of the mTOR pathway. The activity of MMP-1, MMP-2, MMP-3 and MMP-13 was not significantly affected by rapamycin. Rapamycin prevented actin reorganization in both DA and RA FLS and inhibited the formation of directional lamellipodia protrusion, compared with DMSO. Phosphorylation and polarization of the lamellipodia marker FAK was also reduced by rapamycin.

Conclusion: Rapamycin significantly reduced FLS invasion in rat and human RA FLS through the suppression of ezrin-mediated mTOR signaling pathway. This is the first time that mTOR is implicated in the invasive properties of FLS. These observations suggest that rapamycin could have a role in RA therapy aimed at reducing the articular damage and erosive changes mediated by FLS.

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2068

Expression of Ang-1 and Engagement of Tie2 Is Related to Development of Persistent and Erosive Disease in Early Arthritis Patients. Marleen G.H. van de Sande[1], Daphne deLaunay[1], Gijs P.M. van de Sande[1], Paul P. Tak[2] and Kris A. Reedquist[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands

Purpose: Angiopoietin (Ang) -1 and -2, and their receptor Tie2, are important mediators of angiogenesis, a process which promotes inflammation, supplies nutrients, and contributes to tissue destruction and remodeling in synovial tissue. Previous reports have indicated that Ang-1 and Ang-2 are differentially expressed in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). In vitro, Ang-1 can promote fibroblast-like synoviocyte production of matrix metalloproteinases, and under certain experimental conditions, Ang-2 can antagonize Ang-1 signaling. Therefore, differential expression of Ang-1 and Ang-2, and engagement of Tie2, in an early phase of the disease might play a role in the development of persistent (erosive) disease.

We investigated the value of synovial tissue expression of Ang-1, Ang-2, Tie2 and active phosphorylated Tie2 (pTie2) in predicting outcome in early arthritis patients.

Methods: We analyzed synovial tissue biopsies of 48 disease-modifying antirheumatic drug (DMARD) -naïve early arthritis patients. Patients were selected from our early arthritis cohort based on diagnosis of RA or undifferentiated arthritis (UA) at baseline. Patients were prospectively followed and diagnosed after 2 years according to established classification criteria and according to outcome (self-limiting, persistent or persistent erosive disease). Baseline synovial tissue expression and activation of the angiogenic markers was examined by immunohistochemical analysis, using quantitative computer-assisted digital imaging. Predictors of outcome were identified by logistic regression analysis.

Results: 21 patients fulfilled ACR criteria of RA at baseline, 8 patients had undifferentiated arthritis (UA) at baseline and fulfilled ACR criteria of RA after 2 years of follow-up, and 19 patients had UA after 2 years of follow-up. The relative activation of Tie2 (pTie2/Tie2) was significantly related to development of erosions in the RA patients (all RA patients at 2 years follow-up) (P=0.01) with an explained variance of 50% (Nagelkerke R^2 =0.502). Tie2 (P=0.03), pTie2 (P=0.03) and Ang1 (P=0.03) were all significantly related to development of persistent disease compared to self-limiting disease in the patients with UA at baseline, with a combined explained variance of 69% (Nagelkerke R2 =0.69).

Conclusion: Our study provides the first evidence that engagement of the Ang-1/Tie2 axis in synovial tissue is related to development of persistent and erosive disease. Therefore, targeting Ang-1 and Tie2 therapeutically may be useful in improving outcome in arthritis. Furthermore, these markers might be of use as a biomarker for predicting outcome.

Disclosure: M. G. H. van de Sande, None; **D. deLaunay**, None; **G. P. M. van de Sande**, None; **P. P. Tak**, None; **K. A. Reedquist**, None.

ACR Concurrent Abstract Sessions

Systemic Lupus Erythematosus Therapy

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

2069

Four-Year Experience of Belimumab, a BLyS-Specific Inhibitor, in Systemic Lupus Erythematosus (SLE) Patients. Michelle Petri[1], R. Furie[2], Joan Merrill[3], D. J. Wallace[4], E. M. Ginzler[5], W. Stohl[6], W. Chatham[7], J. McCune[8], A. Weinstein[9], L. Pineda[10], Z. J. Zhong[10], J. Klein[10], D. Hough[10], W. Freimuth[10] and LBSL02/99 Study Grp, [1]JHU, Baltimore, MD, [2]NSLIJHS, Lake Success, NY, [3]OK Med Research Foundation, OKklahoma City, OK, [4]Cedars-Sinai UCLA, West Hollywood, CA, [5]SUNY-Downstate, Brooklyn, NY, [6]USC, Los Angeles, CA, [7]UAB, Birmingham, AL, [8]Univ of Mich, Ann Arbor, MI, [9]Wash Hosp Ctr, Washington, DC, [10]HGS, Rockville, MD

Purpose: Provide 4-yr safety and efficacy data in SLE patients (pts) treated with belimumab.

Methods: 449 SLE pts with SELENA SLEDAI (SS) ≥4 enrolled in a phase 2, 52-week (wk), double-blind trial of belimumab (1, 4 or 10 mg/kg,

q28d) vs placebo (plc) plus background SLE therapy. At wk 56, plc pts received belimumab 10 mg/kg; belimumab pts could remain on their current dose or receive 10 mg/kg (investigator's discretion). At wk 80, all remaining pts (296) received belimumab 10 mg/kg in a continuation trial. The 4-yr dataset was divided into eight 6-mo intervals for reporting adverse event (AE) and flare rates. Interval 1 includes the initial belimumab treatment which for plc pts began at wk 56. Analyses of disease activity included the SS SLE Flare Index (SFI) and a post-hoc SLE Responder Index (SRI): improvement in SS (≥4 pt decrease), no new BILAG A or 2 new B flares, and no Physician's Global Assessment (PGA) worsening (< 0.3 pt increase) vs baseline. Post-hoc analyses identified a serologically active (ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL) pt subgroup (321) for whom belimumab demonstrated increased response.

Results: By 4 yrs, overall belimumab exposure was 1,192 pt yrs. The incidence rates (per 100 pt-yrs) of AEs remained the same or decreased over 4 yrs (Table 1). In serologically active pts, SRI rate was 46% at wk 52 (vs plc 29%, $p<0.05$) which increased to 55% by wk 76 and was maintained through wk 208 (original belimumab pts); the frequency of new BILAG A or 2 B flares decreased from 30% at 6 mo to 23% at 1 yr (vs plc 33% and 25%, respectively) and declined to 5% at 4 yrs; the frequency of flares by SFI decreased from 72% at 6 mo to 62% at 1 yr (vs plc 76% and 73%, respectively) and declined to 16% at 4 yrs. Flare data included plc-to-belimumab pts after yr 1.

Table 1: AE Incidence (rate per 100 pt-yrs)

	All belimumab-treated pts							
Interval / Yrs	**1** (0 – 0.5 yr)	**2** (0.5 – 1yr)	**3** (1 – 1.5 yr)	**4** (1.5 – 2 yr)	**5** (2 – 2.5 yr)	**6** (2.5 – 3 yr)	**7** (3 – 3.5 yr)	**8** (3.5 – 4 yr)
No. pts [pt-yrs]	424 [206]	398 [183]	353 [166]	314 [147]	284 [136]	261 [128]	252 [122]	237 [103]
Overall AEs	400 (194)	337 (184)	304 (184)	271 (184)	244 (179)	226 (177)	203 (166)	179 (173)
Serious AEs	43 (20.8)	33 (18.0)	28 (16.9)	25 (17.0)	24 (17.6)	26 (20.4)	13 (10.6)	17 (16.5)
Overall Infections	246 (119)	197 (108)	170 (103)	165 (112)	145 (107)	131 (103)	106 (87)	105 (102)
Serious Infections	14 (6.8)	10 (5.5)	6 (3.6)	8 (5.4)	4 (2.9)	5 (3.9)	2 (1.6)	5 (4.8)
Malignant Neoplasms	0 (0)	1 (0.5)	3 (1.8)	2 (1.4)	0 (0)	1 (0.8)	1 (0.9)	2 (2.1)

Conclusion: Belimumab added to standard of care therapy was generally well tolerated over 4 yrs. Serologically active pts treated with belimumab showed sustained improvement in disease activity and a decline in BILAG and SFI flares over 4 yrs.

Disclosure: M. Petri, HGS, 5, HGS, 2 ; **R. Furie**, Human Genome Sciences, Inc., 5 ; **J. Merrill**, None; **D. J. Wallace**, None; **E. M. Ginzler**, Aspreva, 5, Aspreva, 2, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2, Human Genome Sciences, Inc., 9, Human Genome Sciences, Inc, 2, La Jolla Pharmaceutical, 5, MedImmune, 5, Merck/Serono, 2, Novo Nordisk, 5, Zymogenetics, 5, UCB, 2 ; **W. Stohl**, Human Genome Sciences, 2, Human Genome Sciences, 9 ; **W. Chatham**, HGS, 2, Bristol-Myers Squibb, 2, Genentech and Biogen IDEC Inc., 2, UCB Pharma, 2, Merck-Serono, 2 ; **J. McCune**, Genentech/Roche, 5, Johnson and Johnson, 5, HGS, 2 ; **A. Weinstein**, Human Genome Sciences, Inc., 2 ; **L. Pineda**, HGS, 1, HGS, 3 ; **Z. J. Zhong**, HGS, 1, HGS, 3 ; **J. Klein**, HGS, 1, HGS, 3 ; **D. Hough**, Johnson & Johnson, Bristol-Myers Squibb, Roche, Human Genome Sciences, 1, Human Genome Sciences, 3 ; **W. Freimuth**, HGS, 1, HGS, 3 .

2070

Treatment of Systemic Lupus Erythematosus (SLE) with Rituximab: 78-Week Safety Data From the Phase II/II EXPLORER Trial.

Joan T. Merrill[1], D.J. Wallace[2], K.M. Latinis[3], T.O. Utset[4], R. Furie[5], C. Michael Neuwelt[6], Richard J. Looney[7], H. Hsieh[8], B. Wagner[9] and P. Brunetta[8], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Cedars-Sinai Medical Center/UCLA, West Hollywood, CA, [3]Kansas University Medical Center, Kansas City, KS, [4]University of Chicago, Chicago, IL, [5]North Shore-LIJ Health System, Lake Success, NY, [6]Alameda County Medical Center, Oakland, CA, [7]University of Rochester, Rochester, NY, [8]Genentech, Inc., South San Francisco, CA, [9]Genentech, Inc., South San Francisco

Purpose: In RA patients (pts), multiple courses of rituximab (RTX) are well tolerated. Analysis of safety for 12 months after receipt of the 2nd course of RTX in SLE has not yet been performed. Our objectives were to highlight the safety data obtained in EXPLORER through 78 wks.

Methods: Pts on background immunosuppressants and corticosteroids were randomized to placebo (PLA) or RTX (1000 mg IV on days 1, 15, 168, and 182). Adverse events (AEs), serious AEs (SAEs), deaths, and antibodies to RTX (HACAs) were recorded from screening to wk 78, or to termination visits. HACA responses were measured at baseline and every 3 mo. Immunoglobulin (Ig) levels were measured at baseline and days 112, 168, 308, 364, 455, and 546.

Results: Eighty-eight PLA and 169 RTX pts were included in the safety-evaluable populations. AEs and SAEs were comparable between PLA and RTX groups. Infection and infestation treatment-emergent SAEs were higher in the PLA than in the RTX group (18.2% vs 11.2%). Rates of infections were 227 and 224 events/100 pt-yr (patient-years) for PLA and RTX. Rates of serious infections were 16.7 and 13.6 events/100 pt-yr for PLA and RTX. Herpes virus infection-related AEs occurred in 8 (9.1%) pts in the PLA group vs 26 (15.4%) in the RTX group. The % of pts with infusion-related AEs during course 1 was comparable between groups, but during course 2 a higher % of RTX-treated pts had infusion-related AEs. HACAs were present in 3 (3.4%) and 48 (28.4%) pts in the PLA and RTX groups. At the 4th infusion, 11 (22.9%) of the 48 HACA+ RTX-treated pts experienced an infusion-related AE (1 SAE), vs 14 (11.0%) of the HACA- RTX-treated pts. Neutropenia occurred in 6 RTX pts. Four cases of serum sickness (1 serious) occurred in the RTX group. At any time during the study, IgG levels were below the lower limit of normal (LLN) in 8.5% of PLA, and 6.3% of RTX pts. IgM levels were below the LLN in 9.7% of the PLA group, and 28.7% of the RTX group. Mean IgG levels did not significantly change in the RTX group during the trial. Low Ig levels did not correlate with serious infectious AEs.

Conclusion: The numbers of pts who developed AEs and SAEs were comparable between the PLA and RTX groups. Whereas overall infection rates were also comparable, infectious SAEs were higher in PLA. The percent of pts with infusion reactions was similar between groups after the 1st and 2nd infusions, however, more pts experienced infusion reactions in the RTX group after the 3rd and 4th infusions. No clear associations were observed between HACAs and safety. Herpes viral infections, neutropenia, and serum sickness occurred more frequently in the RTX group.

Disclosure: J. T. Merrill, Genentech , 2, Genentech , 5 ; **D. J. Wallace**, None; **K. M. Latinis**, Genentech , 2, Genentech , 5, Genentech, Centocor , 6 ; **T. O. Utset**, Genentech , 5 ; **R. Furie**, Genentech, Roche, Biogen Idec, 2, Genentech, Roche, Biogen Idec, 5, Genentech, Roche, Biogen Idec, 6 ; **C. M. Neuwelt**, Genentech and Biogen IDEC Inc., 8, Genentech, Biogen IDEC, Roche, 2 ; **R. J. Looney**, Genentech, Biogen IDEC, Roche, 5 ; **H. Hsieh**, Genentech , 3 ; **B. Wagner**, Genentech , 3 ; **P. Brunetta**, Genentech , 3 .

2071

Evaluation of CD4+ Lymphopenia and Infection Risk in Systemic Lupus Erythematosus (SLE) Patients: Data From Rituximab Clinical Trials. K.M. Latinis[1], E.F. Chakravarty[2], P. Brunetta[3], H. Hsieh[3], J. Garg[3], R. Maciuca[3] and B. Wagner[3], [1]Univ. Kansas Medical Center, Kansas City, KS, [2]Stanford Health Services/Blake Wilbur Clinic, Palo Alto, CA, [3]Genentech, Inc., South San Francisco, CA

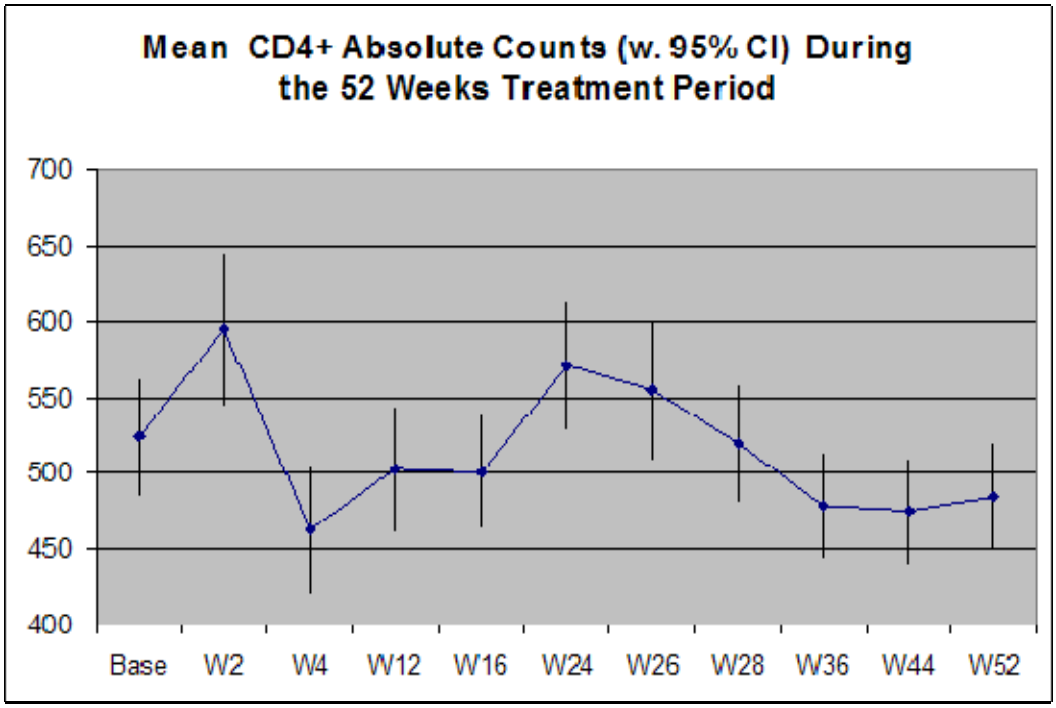
Purpose: Previous reports have suggested that a substantial portion of SLE patients (pts) have CD4+ lymphopenia. We evaluated the proportion of SLE pts with CD4+ lymphopenia enrolled in EXPLORER (extra-renal SLE) and LUNAR (lupus nephritis) and the relationship of sustained CD4+ lymphopenia (CD4+ T cell counts < 200/uL) to serious infections.

Methods: All pts enrolled in EXPLORER and LUNAR had moderate-to-severe disease activity, were treated with a background immunosuppressant (mycophenolate mofetil, azathioprine, or methotrexate) plus corticosteroids, and were randomized to either placebo or rituximab (1000 mg) given on days 1, 15, 168, and 182. The levels of CD4+ T cells at baseline and over 1 year were evaluated on days 1, 15, 28, 84,112, 168, 182, 196, 252, 308 and 364. Pts with sustained lymphopenia over 2 consecutive visits, at least 4 weeks apart, were evaluated for serious infection rates.

Results: At baseline, the mean level of CD4+ T cells for the combined cohort (n=401) was 524±387 cells/uL. Sixty-four (16.3%) pts had CD4+ counts < 200 cells/uL. Although CD4+ counts initially decreased to a mean level of 456.9 cells/uL at Day 28, likely due to protocol-mandated steroid administration, they were not significantly different from baseline at week 52 (figure). The mean percentage change from baseline to week 52 was -16.2±4.6%. During the trial, 100 (24.9%) pts experienced sustained lymphopenia. The mean duration of lymphopenia was 111.3 +/- 83.7 days. There was no significant difference in rate of serious infections between sustained lymphopenia pts,

who had 22 events over 103.2 patient-years (p-y) (21.3/100 p-y, 95% CI: 14.0, 32.4) of follow-up, and those without sustained lymphopenia, who had 438 events over 299.5 p-y (16.0/100 p-y, 95% CI: 12.1, 21.3; p=0.27) of follow-up.

Conclusion: Sixteen percent of SLE pts had CD4+ counts < 200 cells/uL at baseline. Although CD4+ counts fluctuated over time, likely due to concomitant therapy, levels stabilized near baseline values by the end of the treatment period. Sustained CD4+ lymphopenia occurred in a quarter of pts but did not appear to significantly increase the risk of serious infections. Further analysis by treatment group will be conducted.



Disclosure: K. M. Latinis, Genentech , 2, Genentech , 5, Genentech, Centocor , 6 ; **E. F. Chakravarty**, Genentech , 5 ; **P. Brunetta**, Genentech , 3 ; **H. Hsieh**, Genentech , 3 ; **J. Garg**, Genentech , 3 ; **R. Maciuca**, Genentech , 3 ; **B. Wagner**, Genentech , 3 .

2072

Dose-Dependent Modulation of Interferon Regulated Genes with Administration of Single and Repeat Doses of Rontalizumab in a Phase I, Placebo Controlled, Double Blind, Dose Escalation Study in SLE. Jacqueline M McBride[1], Daniel J Wallace[2], Zhenling Yao[1], Alyssa Morimoto[1], Jenny Jiang[1], Romeo Maciuca[1], Iain McLean[1], Jorn Drappa[1] [1] Genentech Inc, 1 DNA Way, South San Francisco, CA, [2]Cedars-Sinai / David Geffen School of Medicine, UCLA, CA.

Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by diverse autoantibodies and inflammation in multiple organ systems. Elevated mRNA levels of interferon-regulated genes (IRGs) have been identified in the peripheral blood of the majority of SLE patients and are thought to be associated with disease pathogenesis.

Method: The safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of rontalizumab, a humanized IgG1 monoclonal antibody that neutralizes human interferon alpha, was assessed in a Phase I dose escalation study of single and repeat doses in adults with mild-moderate SLE. Dose levels ranged from 0.3 mg/kg to 10 mg/kg administered by the intravenous (IV) and subcutaneous (SC) routes. Expression levels of seven IFN-regulated genes (IRGs) were measured by quantitative RT-PCR throughout the dosing and follow up periods for all patients.

Results: The PK profiles of rontalizumab at all dose levels exhibited apparent biphasic distribution and appeared dose proportional following both single dose IV and SC administrations. The clearance, volume of distribution and terminal half-life were 2.8 mL/day/kg, 64 mL/kg and 18 days, respectively, similar to other humanized monoclonal IgG1 antibodies that bind soluble ligands. The bioavailability was approximately 40% in the SC cohorts. Interim analysis identified elevated IRGs in approximately 50% of patients as compared to normal healthy donors. There was a rapid decline in expression of all seven IRGs in the majority of patients after dosing with 3 mg/kg and 10 mg/kg IV cohorts. In general, the reduction was sustained for one month following a single dose; a similar trend was observed during the repeat dose phase. PK/PD correlations were performed with available single dose data and using an Emax model to describe the dose response curve. The integrated gene expression reduction over time (AUEC) started to deviate from placebo at 1-3 mg/kg and appeared to reach maximum at 10 mg/kg.

Conclusion: Rontalizumab has PK properties favorable for use in further SLE studies. The PD results demonstrate a dose-dependent reduction in the IRGs consistent with the expected down-modulation of the IFN signaling pathway, suggesting the possibility of clinical benefit in SLE.

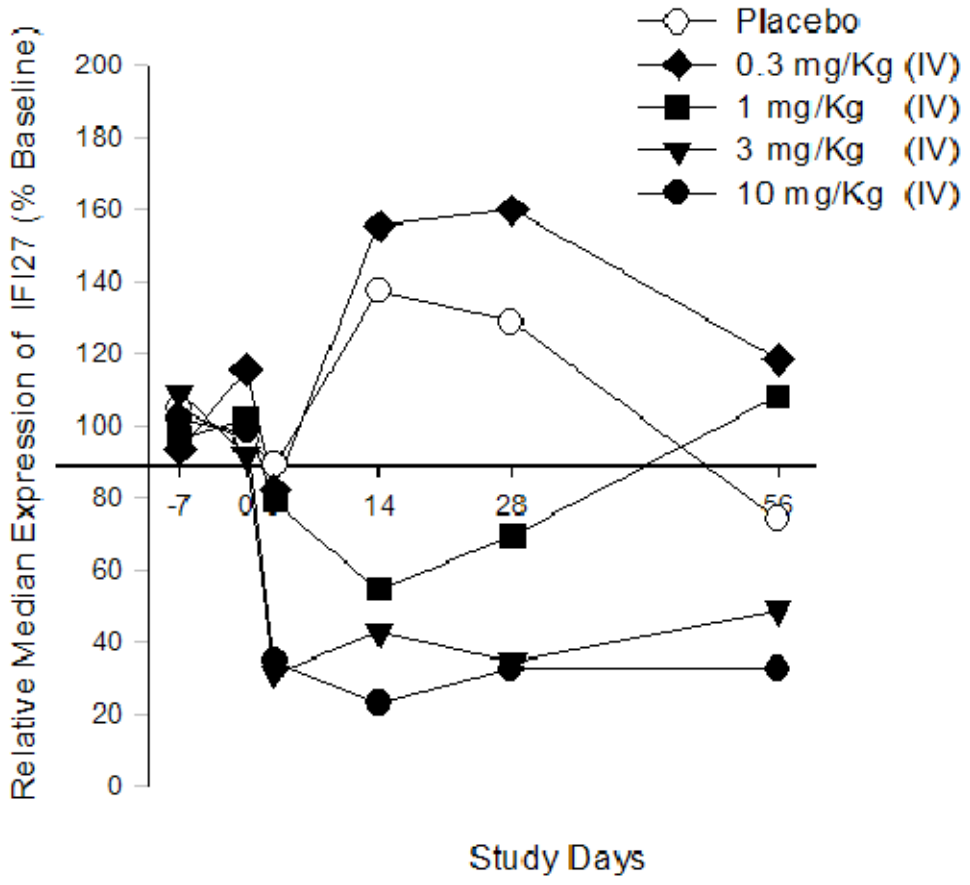


Figure 1. Single dose IV administration of rontalizumab induces a dose-dependent reduction in expression of IFI27, a representative interferon regulated gene (IRG). All patients from each cohort are shown; placebo (n=12) and all other dose groups (n=8).

Disclosure: J. M. McBride, None.

2073

Identification of Biomarkers That Predict Response to Treatment of Lupus Nephritis with Mycophenolate Mofetil (MMF) or Pulse Cyclophosphamide (IVC). David H. Stone[1], Maria Dall'Era[1], Victoria Levesque[2], Miriam G. Cisternas[3] and David Wofsy[1], [1]UCSF, San Francisco, CA, [2]Vifor Pharma, Victoria, BC, [3]MGC Data Services, Carlsbad, CA

Purpose: There is a great need to identify clinical characteristics and/or biomarkers that can serve as predictors of treatment outcome in patients with SLE. Toward this end, we used data from the Aspreva Lupus Management Study (ALMS) to identify possible baseline and early clinical predictors of renal response to MMF or IVC among patients with lupus nephritis.

Method: In the ALMS trial, patients with Class III-V lupus nephritis were randomized to MMF or IVC in addition to prednisone starting at 60mg/d. Renal response was defined as a decrease in urine prot:creat ratio to <3 in patients with baseline nephrotic range proteinuria, or by ≥50% in patients with subnephrotic range proteinuria, and stabilization or improvement in serum creatinine at 24 weeks. Univariate predictors of renal response were assessed retrospectively and included baseline demographic, clinical, serological and histological characteristics as well as early clinical and serological data obtained within the first two months of therapy. Odds ratios and 95% confidence intervals (CI) for renal response were calculated for each putative predictor in the overall study population and within each treatment group.

Results: A total of 370 patients were randomized in this trial. Among patients with low baseline complement in the overall study population (n=285), normalization of C3, C4, or both by week 8 was strongly predictive of meeting the renal response criteria at 24 weeks (odds ratio=2.5, 95% CI 1.4-4.2; odds ratio= 2.6, 95% CI 1.5-4.5; odds ratio=2.9, 95% CI 1.7-5.2, respectively). The response rate was 76% among subjects with early normalization of C3 and C4, vs 51% in patients without early normalization. Similarly, reduction in proteinuria by at least 25% by week 8 was predictive of a renal response at 24 weeks (68% response rate vs 40% response rate in those without early improvement; odds ratio=3.2, 95% CI 2.1-5.1). Among patients with elevated anti-dsDNA at baseline, a reduction in anti-dsDNA by week 8 was not predictive of renal response (odds ratio=1.2, 95% CI 0.8-2.0). There were no significant differences between treatment arms in these outcomes.

We previously reported that baseline levels of C3 and anti-dsDNA were not predictive of response. We now add that age, age of lupus onset, sex, biopsy class, presence of anti-cardiolipin IgG, and baseline use of an angiotensin converting enzyme inhibitor, a statin, and/or hydroxychloroquine did not predict response.

Conclusion: The ALMS trial, the largest trial to date for the treatment of lupus nephritis, determined that the induction renal response rate was similar for MMF and IVC. A retrospective review of the data has shown that normalization of complement and reduction of proteinuria by 8 weeks were both predictive of renal response at 24 weeks whereas reduction in anti-dsDNA levels by 8 weeks was not predictive of renal response.

Disclosure: D. H. Stone, None; **M. Dall'Era**, None; **V. Levesque**, None; **M. G. Cisternas**, None; **D. Wofsy**, Bristol-Myers Squibb , 5, Genentech and Biogen IDEC Inc., 5 .

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Allogenic Mesenchymal Stem Cells Transplantation for Patients with Systemic Lupus Erythematosus: One-Year Fellowup. Lingyun Sun[1], Huayong Zhang[1], Xuebing Feng[1], Dandan Wang[1], GS Gilkeson[2] and Richard M. Silver[2], [1]the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Medical University of South Carolina, Charleston, SC

Purpose: To assess the efficacy and safety of allogenic bone marrow or umbilical cord derived mesenchymal stem cell transplantation (MSCT) for patients with refractory systemic lupus erythematosus (SLE).

Method: 13 patients with SLE refractory to immunosuppressive therapies were enrolled from March 2007 through May 2009, 11 female and 2 male, aged 16~42(mean 28±8.8 years). All the patients fulfilled the 1997 American Collage Rheumatology (ACR) SLE criteria and 12 had lupus nephritis (LN). Disease duration was from 12 to 192 months.The study was approved by the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School. Bone marrow derived mesenchymal stem cells (MSCs) were aspirated from related healthy donors and expanded in vitro, and umbilical cord derived MSCs were obtained from National Engineering Research Center of Cell

Products, Tianjing, China (NECCP). 12 patients were given cyclophosphamide (CTX) 0.6~2.2g divided by two to four times except for one patient with severe myelosuppression and poor health condition, then MSCs were administered 1.0×10^6/kg body weight intravenously, for 11 patients with bone marrow derived MSCs and 2 patients with umbilical cord derived MSCs. The clinical manifestations and laboratory parameters were compared before and after MSCT with a follow-up of 12 to 25 months(mean19 months).

Results: Remission of disease activity (Systemic Lupus Erythematosus Disease Activity Index, SLEDAI less than 3 and prednisone dose less than 10mg/d) was seen in 7/13 (54%) evaluable patients at 1 year and 3/5 (60%) at 2 year after MSCT . Two patients with drug withdrawal relapsed at 1 year post MSCs transplantation. Amelioration of LN was found for the 12 patients, including significant decline of 24-hour proteinuria at 1 year (2162.5±796.0 *vs* 724.3±313.5mg, $P<0.01$), and at 2 years (281.5±120.5mg , n=4) after transplantation. The high serum creatinine levels of three patients also returned to normal at 6 months after transplantation. A significant improvement of glomerular filtration rate (GFR) was found in two patients at 4 months after MSCT. In addition, serum albumin and complement 3 (C3) increased combined with the significant decline of autoantibodies as well as normalization hematological disorder. One relapsed patients has been given a second MSCT and remission of lupus has been also found. No transplant related mortality or any significant toxicity was observed and overall survival was 100%.

Conclusion: This study demonstrates that allogenic MSCT has a potential effect and safety for refractory SLE.

Disclosure: L. Sun, None; **H. Zhang**, None; **X. Feng**, None; **D. Wang**, None; **G. Gilkeson**, None; **R. M. Silver**, None.

ARHP Concurrent Abstract Sessions

Community Resources and Participation

Wednesday, October 21, 2009, 11:00 AM - 12:30 PM

2075

Health-Related Quality of Life Among US Adults Aged 65+ with Arthritis. Sylvia E. Furner[1], Jennifer M. Hootman[2], C. G. Helmick[3] and Matthew A. Zack[3], [1]University of Illinois Chicago School of Public Health/Centers for Disease Control and Prevention, Chicago, IL, [2]Arthritis Program, Atlanta, GA, [3]Centers for Disease Control an, Atlanta, GA

Purpose: To determine how demographics, social or healthcare factors, health behaviors, and health conditions are associated with health-related quality of life (HRQOL) among persons aged 65+ years with arthritis.

Methods: Data came from the 2003, 2005, & 2007 Behavioral Risk Factor Surveillance System, a state-based, random-digit dialed telephone survey of U.S. adults. Analysis was restricted to persons aged 65+ (n=254,311). Persons were classified as having arthritis if they reported ever being told by a doctor or other health care professional they had arthritis, rheumatoid arthritis, gout, lupus or fibromyalgia. Three *healthy days* measures (past 30 days) were evaluated to assess HRQOL: physically unhealthy days (PUD), mentally unhealthy days (MUD), and activity limitation days (LIMDAY), each categorized in groups of 0, 1-13, or 14+ days. Fair or poor self-rated health status was the fourth HRQOL outcome assessed. Independent variables included demographics (age, sex, race/ethnicity); social factors (marital status, education, employment, income); healthcare factors (health insurance, cost a barrier to care); health behaviors (smoking, drinking, physical activity); and health conditions (diabetes, hypertension, obesity). Means, proportions and ordinal logistic regression analyses were conducted using sampling weights and SUDAAN to account for the complex sample design. Factors were included in final models based on statistical significance ($\alpha=0.05$) in domain-specific models or the literature.

Results: The median prevalence of arthritis among persons 65+ for the 50 states and District of Columbia was 56% for the 3 years. Compared to those without arthritis, those with arthritis reported more PUD (7.0 ± 0.12 vs. 3.5 ± 0.10), MUD (2.6 ± 0.08 vs. 1.5 ± 0.06), LIMDAY (3.5 ± 0.08 vs. 1.7 ± 0.0.8), and fair or poor self-rated health (33.2% ± 1.6% vs. 19.2% ± 1.0). Lower income, being out of/unable to work, ever smoking, cost being a barrier to care, and diabetes or hypertension were associated with poor HRQOL across all HRQOL. Women with arthritis reported more MUD and PUD but better self-rated health than men. Compared to non-Hispanic whites, Hispanics reported poorer self-rated health, and black non-Hispanics, fewer PUD. Compared to normal weight, those underweight had more PUD, LIMDAY and poorer self-rated health, and obese persons had more MUD, PUD, and LIMDAY but better self-rated health. Being physically

active resulted in fewer PUD and LIMDAY and better self-rated health. Alcohol consumers had fewer PUD and LIMDAY and better self-rated health.

Conclusion: Those factors consistently associated with poor HRQOL in persons 65+ with arthritis are modifiable. Social, health education, and public health policies targeted to this population may help reduce the HRQOL burden associated with arthritis. Increasing physical activity in this population is associated with many health benefits and may also positively influence HRQOL.

Disclosure: S. E. Furner, None; **J. M. Hootman**, None; **C. G. Helmick**, None; **M. A. Zack**, None.

2076

Shut in? Impact of Arthritis and Other Chronic Conditions On Community Participation Among Older Adults. Sylvia E. Furner[1] and Kristina A. Theis[2], [1]University of Illinois Chicago School of Public Health/Centers for Disease Control and Prevention, Chicago, IL, [2]Centers for Disease Control and Prevention, Atlanta, GA

Statement of Purpose: To estimate the prevalence of participation restriction (PR) in community activities due to physical environmental barriers among older adults and to compare the impact among those with arthritis versus other chronic conditions.

Methods: Data were obtained from the 2002 National Health Interview Survey, an annual interview-administered survey representative of the US civilian, noninstitutionalized population. Respondents ≥50 years were included (n=12, 376). Information on condition status was obtained for: arthritis, depression/anxiety, diabetes, hearing impairments, heart conditions, hypertension, neurological conditions, respiratory conditions, stroke, vision impairments, and psychological distress. PR due to 6 environmental barriers from 2 categories ("built environment" [building design, lighting, sound]; "walkability" [crowds, sidewalks/curbs, transportation]) was examined in the community setting for adults ≥50 years by chronic conditions and sex. Weighted frequencies and standard errors, taking into consideration the complex sampling design, were obtained with SUDAAN software.

Results: Across conditions, prevalence of PR due to environmental barriers ranged from 5%-20%. Building design was the most commonly reported built environment barrier overall and for women, with the exception of those with hearing impairments who most often reported sound as a barrier. The same exception was true for men with hearing impairments and psychological distress. Men who reported stroke identified lighting as the most common built environment barrier. Women with arthritis or diabetes reported sidewalks/curbs as the most common walkability barrier; transportation was the biggest barrier for women with stroke. Women with all other conditions and men regardless of condition reported crowds as the most frequent walkability barrier. Hypertension and arthritis were the most prevalent conditions overall (44% and 40%, respectively), representing 34 and 30 million adults ≥50 years; however, respondents with these conditions reported the lowest prevalence of any community barrier, 5% and 6%. In absolute numbers, PR has the greatest impact among people with arthritis, affecting 1.9 million adults ≥50 years.

Conclusion: Arthritis prevalence is projected to increase by ~19 million Americans by 2030 and is already most common among older adults. These findings suggest that increasing numbers of adults ≥50 years with arthritis will experience PR due to modifiable environmental characteristics. Moreover, many of these built environment and walkability features are barriers to older adults with other chronic conditions and are expected to be exponentially limiting in people with comorbid conditions. Promising targets for interventions to reduce community PR among adults ≥50 years with chronic conditions, particularly arthritis, are building design, sidewalks/curbs, and crowd control.

Disclosure: S. E. Furner, None; **K. A. Theis**, None.

2077

Quality of Non-Pharmacological Care for People with Osteoarthritis in the Community. Linda C. Li[1], Eric C. Sayre[2], Jacek Kopec[1], John Esdaile[3], Sherry Bar[4] and Jolanda Cibere[5], [1]University of British Columbia, Vancouver, BC, [2]Simon Fraser University, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC, [4]BC Ministry of Health Services, Vancouver, BC, [5]University of British Columbia and ARC, Vancouver

Purpose: To describe the quality of non-pharmacological care received by people with knee and/or hip osteoarthritis (OA) in the community and to assess the associated factors.

Method: We evaluated four OA quality-of-care indicators for knee and/or hip OA[1]: 1) advice to exercise; 2) advice to lose weight (for body mass index ›27); 3) assessment for ambulatory function; 4.) assessment for non-ambulatory function, using a postal survey. Eligible participants were those identified from the provincial administrative database between 1992 and 2006 as meeting the case definitions for OA, and had two or more medical visits or one hospitalization for OA within a 365-day period. From 1,713 participants, we collected information on the WOMAC, demographics and quality of care. The passing rate for a quality indicator was calculated by dividing the number of people who received the care with those who were eligible for the care. Logistic regression models were developed to explore the associations between quality of care (yes/no to passing a quality indicator) and the functional/demographic variables (WOMAC, age, sex, education, employment status).

Results: Participants were majority females (61.8%) with a mean age of 67.2 (SD=11.1) years. 66.0% were diagnosed six years ago or more. 16.3% had a university degree, and 30.6% were employed in the previous year. 1,088 participants (63.5%) had knee OA and 648 (37.8%) had hip OA. The mean normalized WOMAC aggregate score was 66.9 (SD=20.2), indicating a moderate level of disability. Overall the quality of non-pharmacological care for OA was poor: exercise (needed advice: n=1,165, received advice: n=294; passing rate=25.2%); weight loss (needed advice: n=660, received advice: n=165; passing rate=25.0%); ambulatory activities (needed assessment: n=120, received assessment: n=35; passing rate=29.2%); non-ambulatory activities (needed assessment: n=403, received assessment: n=28; passing rate=7.0%). Logistic regression revealed that receiving exercise advice was associated with having a university degree (versus high school diploma; OR=2.6, 95% CI=1.6, 4.2) and higher WOMAC scores (for every 10-point increment; OR=1.1, 95% CI=1.0, 1.2). Receiving weight loss advice was associated with being female (OR=2.7, 95% CI=1.7, 4.3) and higher WOMAC scores (for every 10-point increment; OR=1.2, 95% C=1.0, 1.3).

Conclusion: Quality of non-pharmacological care for people with knee/hip OA in the community is suboptimal. Further, inequity may exist in providing advice on exercise and weight management. Given the evidence supporting the use of these interventions to improve OA symptoms and function, and the potential to reduce the progression of joint damage, investment in future research to enhance the provision of OA care is warranted.

[1]Pencharz & MacLean. *Arthritis Rheum* 2004, 51: 538-548

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Participant Perception of the Importance of Social and Built Environmental Resources for Osteoarthritis Management (OA): Formative Work in a Rural, Southeastern County. Kathryn Remmes Martin, Britta Schoster and Leigh F. Callahan, University of North Carolina at Chapel Hill, Chapel Hill, NC

Purpose: Community social and built environment resources have been shown to influence health outcomes, yet little research has examined these resources for an arthritis population living in a rural area. The purpose of our study was to query African Americans (AA) and Whites with OA about community resources for OA management.

Method: We conducted 6 focus groups with thirty-six community dwelling adults with self-reported OA residing in a rural county in a southeastern state. Groups were stratified by race (AA/White). Participants discussed the aspects of the social and built environments of their communities that helped or hindered their ability to manage their OA. They also marked their social, medical, physical activity, and shopping activity areas on a map of the county. Descriptive analyses of participant characteristics were conducted (Stata v8), and verbatim transcripts of the focus groups were reviewed for key themes.

Results: The sample had a mean age of 71 years (range 50-90), was 83% female, 55% White, and 66% had greater than a high school education . Nearly 78% reported knee OA and 80% reported hip OA; with 53% reporting both knee and hip OA. The majority, 67% reported moderate/severe arthritis, and 43% reported fair or poor general health. The map activity indicated that participants used community resources and had social interactions within and beyond county boundaries. Four themes emerged from the focus group discussions, with no differences by race. The two primary themes most often discussed as important for OA management were *community*

resources for physical activity and *social resources.* Participants cited the availability of community parks, a local health facility and senior centers for providing space and programs for physical activity, yet some of these physical activity opportunities (e.g. aquatics) had high fees. Participants listed family, friends, neighbors, and community members, who assisted with transportation, chores, food preparation, and provided emotional support, as primary facilitators in management of OA. Two secondary themes also emerged: *community services* (e.g., churches, pharmacies, food banks, and senior centers) and elements of the *built environment* (e.g., sufficient lighting, sidewalk condition and availability, access ramps, curb-cuts, traffic, automatic doors, availability of store motorized scooters and community handicapped parking). These secondary themes highlighted resources that enabled or hindered participants' ability to navigate built and social environments to manage their OA.

Conclusion: A greater understanding of the community environmental resources and social support structures that may facilitate arthritis management can assist city and regional planners, public health programmers, and policy makers in developing context appropriate interventions to improve arthritis outcomes.

Disclosure: K. R. Martin, None; **B. Schoster**, None; **L. F. Callahan**, None.

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The Effect of Adherence Support From Social Network Members On Depression and Patient Medication Adherence. Delesha M. Carpenter[1], Robert F. DeVellis[1] and Jm Jordan[2], [1]University of North Carolina, Chapel Hill, NC, [2]UNC, Chapel Hill, NC

Purpose: Relatively little is known about how different sources of support affect depression and medication adherence in rheumatic populations. Our goal was to determine whether adherence support from vasculitis patients' physicians, partners/spouses, other family members, and other vasculitis patients influences depressive symptoms and medication adherence.

Method: We used data from the Accessing Social Support in Symptom Treatment (ASSIST) Study, in which vasculitis patients (n=232) completed baseline and 3-month follow-up online surveys. Demographic variables and adherence support were measured at baseline while medication adherence (Morisky adherence scale: α=.60 and .63) and depressive symptoms (CES-D: α=.93 and .92) were measured at baseline and follow-up. We conducted regression analyses cross-sectionally and longitudinally controlling for age, gender, education, race, disease duration, health insurance status, and disease status. Depressive symptoms and medication adherence were modeled separately.

Results: Physician and partner adherence support were negatively associated with depressive symptoms cross-sectionally (B: -4.18 and -3.66, $p<.05$) and longitudinally (B: -4.03 and -3.83, $p<.05$). However, when we controlled for baseline levels of depression, only gender and health insurance were predictive of depression at follow-up. For medication adherence, partner adherence support (B=0.12) was associated with greater adherence cross-sectionally, whereas family support (B=0.08) was positively associated with adherence longitudinally controlling for baseline levels of adherence.

Conclusion: Adherence support from physicians and partners may act as a protective factor against depressive symptoms. Partners and family members appear to positively affect patient medication adherence.

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Perceived Restrictions in Participation in Life Situations Among Patients with Rheumatoid Arthritis. Erik Taal[1], Petra Hagens[1], Louise Braakman-Jansen[1] and Martin A.F.J. van de Laar[2], [1]University of Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente & University Twente, Enschede, Netherlands

Purpose: Social consequences of rheumatoid arthritis (RA) can be classified along the lines of the International Classification of Functioning, Disability and Health (ICF), in terms of participation restrictions. Previous research on participation has focused primarily on the impact of RA on paid employment and recreation and leisure, and many measures of participation do not address the evaluative aspects of participation. Purpose of this study was to examine the impact of RA on the patient's perceived participation in life situations and analyse associations between impairments, activity limitations, coping styles (a contextual factor) and participation restrictions within the framework of the ICF.

Method: Cross-sectional data were collected from 143 outpatients with RA who participated in the ongoing Dutch Rheumatoid Arthritis Anti-TNF Monitoring (DREAM) cohort (mean age 55 years, 64% female) and from 119 subjects without RA (mean age 52 years, 67% female). The Impact on Participation and Autonomy (IPA) questionnaire was used to assess person-perceived restrictions in five participation domains: autonomy indoors, family role, autonomy outdoors, social relations, and work and education. Impairments were measured by a pain score (NRS 0-10), disease activity score (DAS28), and fatigue score (SF-36 vitality scale). Activity limitations were measured with the HAQ-DI. Coping was measured by two higher-order coping styles: "active, problem-oriented", and "passive-avoidant" with the Utrecht Coping List (UCL).

Results: Patients experienced more restrictions in all participation domains compared to non-RA subjects ($P<0.001$). Hierarchical regression analyses revealed that the impairment variables accounted for 42-59% of the variance in participation domain scores. Fatigue and pain were more important predictors of participation restrictions than disease activity. Disease activity was not a significant predictor of restrictions in autonomy outdoors, social relations, and work and education. Activity limitations explained up to 13% of the variance in participation scores and partially mediated the relationships of pain and disease activity with restrictions in participation. Together the coping styles accounted for a significant proportion (3-6%) of the explained variance in participation scores. Higher use of active, problem-oriented coping was related to less participation restrictions with regard to autonomy indoors, family role, social relations, and work and education. Higher use of passive coping was related to more restrictions in social relations.

Conclusion: RA patients experienced more restrictions in participation compared to people without RA. This study highlights the importance of fatigue as an independent predictor of participation restrictions next to pain and disease activity, and suggests that activity limitations act as a pathway to explain the association between impairments and participation in life situations. Finally, coping styles (a contextual factor in the ICF model) are independent predictors of participation.

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